Maternal, obstetric, biochemical and ultrasonic associations of normal and abnormal human pregnancy

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Summary

The work in this thesis describes a series of studies utilising diverse data sources which were analysed using a number of regression methods (logistic, linear, Cox, Poisson), to address the factors associated with normal and abnormal pregnancy outcome. A series of maternal characteristics were related to adverse pregnancy outcome. Teenage pregnancy was not associated with an increased risk of any adverse outcome among first births, but was strongly associated with adverse outcome among second births [8]. Parity also interacted with body mass index: maternal obesity was associated with an increased risk of preterm birth among nulliparous but not multiparous women. This was explained by higher rates of elective preterm deliveries among obese nullipara [31]. There was a linear relationship between maternal age and the duration of labour, and the risk of operative vaginal and caesarean delivery [37]. It was hypothesised that age-related deterioration in obstetric performance was due to prolonged hormonal stimulation prior to the first birth. This hypothesis was supported by the observation that later menarche was independently associated with a decreased risk of operative delivery [38]. A short inter-pregnancy interval was associated with an increased risk of spontaneous preterm birth, but not stillbirth or intra-uterine growth restriction [16]. The risk of unexplained stillbirth at term was increased among nulliparous women [5] and nulliparous women also had slightly longer pregnancies [7]. A U-shaped relationship between birth weight and caesarean risk was observed at term. There was an interaction between fetal sex and caesarean risk: small boys were at increased risk of emergency caesarean [3]. The same interaction was observed for antepartum stillbirth [4]. Previous pregnancy outcome was

predictive of the outcome of subsequent pregnancies. Women who were delivered by caesarean section in their first pregnancy had an increased risk of unexplained stillbirth in their second [17]. This finding was confirmed in a separate cohort and associations were also observed between previous complicated livebirths and the subsequent risk of unexplained stillbirth [32]. Some specific situations were also studied (vaginal birth after caesarean section (VBAC) and twins). Among women attempting VBAC, the absolute risk of delivery-related perinatal death was comparable to primiparous women but was significantly higher than women delivered by elective caesarean section [11]. The risk of perinatal death associated with uterine rupture was increased in low throughput obstetric units and among women induced with prostaglandins [19]. Using simple maternal characteristics, approximately 50% of women attempting VBAC could be classified into having a high (>40%) or low (<10%) risk of emergency caesarean [24]. This was better discrimination than could be achieved using similar characteristics among nulliparous women being induced at term [21]. The risk of delivery related perinatal death was increased among second twins, although this was only evident among births at term [13]. The association was observed among sex discordant twins, but was not observed among twins delivered by elective caesarean section [23]. The association between birth order and the risk of death due to anoxia was confirmed in data from England and Wales [33]. Ultrasonic measurements of the fetus were related to eventual birth weight. The range of error associated with such estimates was quantified and abdominal circumference on its own was as predictive as models using abdominal circumference and femur length [1]. Estimating fetal weight using ultrasound was not found to be a better

measure of human fetal blood volume than simply using gestational age [10]. A series of ultrasonic measurements in the first and second trimester were predictive of pregnancy outcome, including smaller than expected crown rump length and intra-uterine growth restriction, preterm birth and low birth weight [2]; a long cervix in mid gestation and caesarean section [36]; and, high resistance patterns of uterine artery Doppler flow velocimetry and stillbirth [30]. Biochemical measurements performed in early pregnancy were also predictive of later adverse outcome: low maternal levels of pregnancy-associated plasma protein A (PAPP-A) were associated with an increased of pre-eclampsia, preterm birth and growth restriction [9]; low PAPP-A prior to 13 weeks was associated with birth weight at term in healthy pregnancies [12] and with a dramatically increased risk of stillbirth due to placental dysfunction [22]. Low first trimester levels of placenta growth factor were associated with increased risks of pre-eclampsia and growth restriction, whereas there was no association between elevated levels of the soluble fms-like receptor and adverse outcome [35]. Measurements of biochemical variables in the second trimester were also predictive of outcome, with elevated maternal serum alpha-fetoprotein (AFP) being associated with an increased risk of stillbirth [34] and spontaneous preterm birth [29]. Women with the combination of low first trimester PAPP-A and high second trimester AFP were at particularly high risk of complications, reflecting the synergistic predictive ability of the two measures [27]. Given proposed similarities between stillbirth and sudden infant death syndrome (SIDS), this outcome was also studied. Elevated second trimester levels of AFP were also associated with an increased subsequent risk of SIDS [20]. Women with a pregnancy resulting ultimately in SIDS were found

to be more likely to have had complications in past and future pregnancies [25]. The risk of SIDS declined with advancing gestational age at term following spontaneous, but not elective birth [15]. Obstetric characteristics were used to generate a predictive model for SIDS [26]. Pregnancy outcome was also predictive of other aspects of child health, specifically, respiratory morbidity following birth at term was associated with an increased risk of hospital admission for asthma [18]. Pregnancy complications were also related to long term maternal health. Elective caesarean delivery for breech presentation did not appear to have an independent effect on fertility [28]. However, pregnancy complications were associated with the mother's subsequent experience of cardiovascular disease. Women experiencing growth restriction, preterm birth or pre-eclampsia were at increased risk of subsequent ischaemic heart disease (IHD) [6] and the risk of this was also related to the number of miscarriages experienced prior to the first birth [14]. The parents of women who had experienced pregnancy complications or recurrent miscarriage had an increased incidence of IHD [39 & 40, respectively].

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List of abbreviations

AFP	Alpha-fetoprotein
ALSPAC	Avon Longitudinal Study of Parents and Children
CEMACH	Confidential Enquiry into Maternal and Child Health
CI	Confidence Interval
CUBS	Combined Ultrasound and Biochemical Screening
hCG	Human Chorionic Gonadotrophin
ICD	International Classification of Disease
IHD	Ischaemic Heart Disease
ISD	Information and Statistics Division
MRC	Medical Research Council
NICHD	National Institutes of Child Health and Development
NICE	National Institute of Clinical Excellence
PAPP-A	Pregnancy-associated Plasma Protein A
PIGF	Placental Growth Factor
RCOG	Royal College of Obstetricians and Gynaecologists
sFlt-1	Soluble fms-like tyrosine-kinase-1
SIDS	Sudden Infant Death Syndrome
SSBIDS	Scottish Stillbirth and Infant Death Survey
VBAC	Vaginal birth after caesarean section

Acknowledgement of contributions from collaborators

In all of the papers described in this thesis I am the first author and the corresponding author. In all cases, the idea for the analysis was my own, I designed the analysis, interpreted the results, drafted the first version of the manuscript, and made final decisions regarding the final format of the manuscript. In all cases I would have the status of guarantor of both the data and its interpretation. However, the co-authors of this work made considerable contributions to it and I acknowledge these now. First, I am extremely grateful to all the individuals who provided access to data. Jim Chalmers, Consultant in Public Health at the Information Services Division at NHS Scotland has been my point of contact for access to Scottish NHS data for more than 10 years and I am extremely grateful to him for his assistance in providing these data. During that time I have interacted with four of the statisticians for the purposes of record linkage and obtaining extracts of data, namely, David Walsh, Richard Dobbie, Michael Fleming and Joanne Hattie.

I have collaborated with Professor Jill Pell for more than 10 years. When we first started collaborating she was a Consultant in Public Health for the NHS in Glasgow and she is now a Professor of Public Health in the University of Glasgow. Jill has provided invaluable support for this work, including a discussion of ideas, plans for analysis, interpretation of results, and in the presentation of data and I am extremely grateful to her for her contribution in all the work that we have published together. Some of the earliest work in the thesis was published from the Queen Mother's Hospital ultrasound database. The data collection was led by Dr Margaret McNay who was a Consultant in Obstetric Ultrasound at that hospital

and Mr John E E Fleming who was a research technologist in the Department of Ultrasonic Technology. I am extremely grateful to both of them for allowing me access to the data and for their comments on the papers arising from that data source.

A number of the papers in the thesis have used data which was sourced from the West of Scotland Regional Genetics Service of the Institute of Medical Genetics in Glasgow. My two main contacts there were Dr Jenny Crossley and Dr David Aitken. Sources of data are two-fold. First, they provide access to the combined ultrasound and biochemical screening (CUBS) study which was a prospective cohort study of women attending for antenatal care in western and central Scotland. Professor Fiona Lyall also significantly contributed to the follow-up analysis of the specimens stored in the CUBS study and suggested the analysis of placental growth factor (PlGF) and soluble fms-like tyrosine-kinase-1 (sFlt-1). The obstetric lead for this work was my clinical mentor in Glasgow, Dr Alan Cameron, who also provided useful input into all the papers arising from this study. Drs Crossley and Aitken also provided access to the routine screening data from the routine data collected for the purposes of Down syndrome screening in the west of Scotland.

A number of papers in the thesis used data collection obtained from Professor Kypros Nicolaides at the Fetal Medicine Foundation and again I am extremely grateful to him for providing access to these data. These were chiefly results obtained by their Fetal Medicine Foundation Second Trimester Screening Group, which involved measurement of both cervical length and uterine artery Doppler for

the purposes of recruiting women into randomised control trials. One paper in the analysis uses data from the Avon Longitudinal Study of Parents and Children and I am grateful to Dr Jon Heron, a statistician on this study, who was instrumental in obtaining access to these data. Finally, a single paper uses data from the Confidential Enquiry into Maternal and Child Health and I am grateful to Kate Fleming, a Senior Data Analyst for the Confidential Enquiry into Maternal and Child Health (CEMACH), for her help in facilitating access to these data.

Co-authors have made other significant contributions to this work. Most important amongst these, who are not mentioned above, are as follows. Dr Yolande Cordeaux, post-doctoral Senior Research Associate working on a grant where I am principal investigator (funded by the Evelyn Trust) performed all the myometrial contractility studies described in the third paper in Section 1 (PLoS Medicine, 2008). I have obtained extremely useful and sophisticated statistical support from two statisticians, Mr Ian White, Senior Scientists at the Medical Research Council Biostatistics Unit in Cambridge, and Dr Angela Wood, Lecturer in Public Health and formerly a Research Associate in the Biostatistics Unit. I have had many discussions with Ian over aspects of statistical analysis of the data. Moreover, Ian has on a number of occasions either facilitated my use of particular statistical methods or actually developed new statistical methods for the analysis and presentation of these results. The details are described in the papers that we have co-authored. I would particularly highlight his development of a novel technique for converting multiple logistic regression models into tables of adjusted likelihood ratios, a method which is employed in a number of papers in this analysis. Angela Wood conducted the statistical analysis in the four papers where she is listed as a

second author and I am very grateful to her for doing this. Angela and I had extensive discussions and had agreed the plan of statistical analysis jointly prior to her performing these. Imran Shah worked as a Research Assistant in this Department funded by a grant from the Foundation for the Study of Infant Death where I was the principal investigator. He was jointly supervised by myself and Ian White over a two-year period. Imran conducted the statistical analysis on all the papers where he is listed as second author. This was done under my direct supervision and the specifics of the statistical analysis in each case were jointly agreed by myself and Ian White. These represent the major contributions by other individuals to the work described in this thesis but I also acknowledge the important, but less substantial contributions made by all the co-authors to the papers included here.

I also acknowledge the agencies that have provided funding which supported this work, specifically, the National Institutes of Health Research, the Evelyn Trust, the Chief Scientists Office of the Scottish Health Executive, the Foundation for the Study of Infant Deaths, and the Royal Hospital for Sick Children Research Fund.

I would also like to acknowledge my PA, Barbara Hall, for her assistance in preparing this thesis.

Finally, I would like to express my sincere thanks to my wife, Nicola, and my daughters, Jessica and Alice, for their constant support over the whole period of time when this work was being produced.

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1. Introduction

1.1 Studying adverse pregnancy outcome

Adverse pregnancy outcome contributes to between 5 and 10% of global morbidity and mortality.[1] The significance of complicated pregnancy in determining global burdens of disease is possibly not proportionately reflected in support by funding agencies for research into the factors determining complicated pregnancy. Better understanding of these factors can potentially lead to better stratification of pregnant women attending for care and therefore more efficient use of resources. Moreover, understanding the mechanisms behind these adverse outcomes could also help develop novel therapies to reduce the burden of morbidity and mortality. The work described in this thesis examines adverse pregnancy outcome from multiple different perspectives.

1. 2 Inter-relationships and overall perspective of the body of published work

The thesis is based on published work. Therefore, the thesis consists of a series of papers, each of which has an introduction which sets the work in context, a methods section which describes the approach, a results section which describes the data and a discussion which puts the findings in context. I have grouped the papers into 6 major thematic areas. At the start of each section, I provide text which shows the inter-relationships between the various studies in the section. I have also included a section where the work is put in the context of the rest of the literature. Each introduction and discussion clearly addresses this for the given paper at the time of its publication. The main approach to further discussion of the relationship between these papers and

the rest of the literature was to identify papers which subsequently cited each of the individual outputs. I did this using a search in the Institute of Scientific Information website at the beginning of August 2010. For some of the papers, particularly those published recently, the introduction and discussion needs very little further development as there has been relatively little change in the literature since the publication. However, many of the papers in the thesis have been extensively cited. Hence, the extent of the discussion around each paper, placing it in the context of the rest of the scientific literature, generally varies in relation to the number of times it was subsequently cited.

1.3 Data sources employed

With the exception of one paper, all work in this thesis is derived from secondary analysis of data collected for some other purpose. The exception is the second paper in Section 3 where I personally retrieved information from case notes to perform the analysis of estimating human fetal blood volume. In total, 16 different data sources were employed for secondary analysis and these are listed in Table 1. A key feature of the approach of many of the studies described in this thesis was to employ record linkage to create novel collections of information on the basis of routinely collected data. Of the 16 data sources used, 12 were employed in some form of record linkage. In total, 11 different combinations of these data sources (Table 2) were utilised in the papers presented in the thesis and the specifics of each linkage are described in the methodology section of each paper. All record linkages were approved by the Privacy Advisory Committee of the Information and Statistics Division (ISD) of NHS Scotland, and all linkages were performed within the ISD.

Table 1. Data sources

Name of Data Source	Abbreviation	Nature of Data
Scottish Morbidity Record 02	SMR02*	National registry of pregnancy data
Scottish Stillbirth and Infant Death Survey	SSBIDS*	National registry of perinatal death
Scottish Morbidity Record 11	SMR11*	Neonatal database
Scottish Morbidity Record 01 - Infant	SMR01*	Hospital admission of infants
Scottish Morbidity Record 01 - mother	SMR01*	Hospital admission of mothers
Scottish Morbidity Record 01 – grandparent	SMR01*	Hospital admission of grandparents of child whose record is stored in SMR02
General Registrar's Office Birth Certificate Database	GRO Birth Certificate*	Details from birth certificate, includes parents' names and dates of birth, child's name and date of birth
General Registrar's Office Death Certificate – infant	GRO Death Certificate – infant*	Death certificate of infant whose record is stored in SMR02
General Registrar's Office Death Certificate – mother	GRO Death Certificate – mother*	Death certificate of woman whose pregnancy is recorded in SMR02
General Registrar's Office Death Certificate – grandparent	GRO Death Certificate – grandparent*	Death certificate of the parent of the woman whose record is recorded in SMR02
West of Scotland Regional Genetics Service Glasgow	No abbreviation*	Database of routine Down's Syndrome biochemical screening data
Combined Ultrasound and Screening Study	CUBS Study*	Prospective cohort study of unselected women evaluating first trimester screening for Down's Syndrome
Queen Mother's Hospital Ultrasound Database	QMH Database	Prospective cohort study of all women attending Queen Mother's Hospital for antenatal care between 1985 and 1995
Avon Longitudinal Study of Parents and Children	ALSPAC	Prospective cohort study of women resident in Avon UK between April 1991 and December 1992
Confidential Enquiry into Maternal and Child Health	CEMACH	Registry of perinatal deaths in England and Wales
Fetal Medicine Foundation Second Trimester Screening Group	FMF	Prospective cohort study of women attending for antenatal care in seven hospitals in London

*Used in 1 or more record linkages

Table 2. Record linkages

Data Sources
SMR02 + SSBIDS
SMR02 + SSBIDS + SMR11
SMR02 + SSBIDS + SMR11 + SMR01-infant
SMR02 + SSBIDS + SMR11 + GRO Death Certificate - infant
SMR02 + SSBIDS + SMR01 + GRO Death Certificate – mother
SMR02 + SSBIDS + GRO Birth Certificate + GRO Death Certificate – infant
SMR02 + SSBIDS + GRO Birth Certificate + GRO Death Certificate – infant + West of Scotland Regional Genetics Service Glasgow
SMR02 + SSBIDS + CUBS Study
SMR02 + SSBIDS + CUBS Study + West of Scotland Regional Genetics Service Glasgow
SMR02 + SSBIDS + SMR01-mother + GRO Death Certificate – mother
SMR02 + SSBIDS + GRO Birth Certificate-mother – SMR01-grandparent + GRO Death Certificate - grandparent

1.4 Key themes in the body of work

In the text below, I address some over-arching themes which highlight common areas in papers across the six sections, focusing on those themes which are most novel and those which encompass multiple papers in different sections of the thesis.

1.4.1 Gestational age and prediction of outcome

An important aspect of a number of the papers described in this thesis is the relationship between when a measurement was made in pregnancy and the risk of subsequent adverse outcome. There is a historical perspective on this, namely the previously proposed phenomenon of 'maternal impression'. For a very substantial proportion of human history, it was believed that congenital abnormalities of the infant may be related to events that happen to a mother in late pregnancy.[2] For example, cleft lip has the colloquial expression 'hare lip'. It was thought that cleft lip in the child may be explained by the mother being frightened by a hare near the time of birth. The term 'maternal impression' referred to the belief that a particular environmental stimulus in the mother would have a related effect on the fetus. It is now appreciated that the vast majority of congenital abnormalities have their origins in the very early stages of pregnancy in the period of embryonic development. A theme which runs through this thesis is that many other complications of pregnancy, such as growth restriction, pre-term birth and pre-eclampsia, also have their origins in the very earliest weeks of gestation. A significant proportion of these complications are related in some way to the dysfunction of the placenta.[3] It is plausible, therefore, that in the same way that the early development of the

fetus is important in determining the final structure of the baby, that the early development of the placenta is important in determining placentally-related complications in later pregnancy. The thesis describes both ultrasonic and biochemical measurements made in the first 10 weeks post-conception which demonstrate striking associations between markers of placentation and the subsequent risk of these outcomes, supporting this hypothesis. Some of these papers represented the first description of early pregnancy markers of such complications and this is an area that has been significantly developed as evidenced by the number of citations for this work.

Another important aspect of the thesis that relates to gestational age is multiple analyses of whether given risk factors for adverse pregnancy outcome are more strongly associated with complications at a particular stage in pregnancy. This question is of immediate practical significance. If a woman has a risk factor for antepartum stillbirth, this can be seen as a rationale for offering early delivery, such as induction of labour at 37 or 38 weeks gestation. This is common practice in women who have pre-existing diabetes mellitus or who have had a previous stillbirth. By extension, therefore, it may be regarded as logical or indicated in women who have other risk factors for stillbirth. However, before considering such interventions, it is important to know whether the risk of stillbirth associated with a given factor varies in relation to the gestational age. The same rationale can be developed for the risk of pre-term birth. There may be an association between a given characteristic or measurement and overall rates of prematurity. However, it could be that this risk differs in relation to whether the pre-term birth was extreme, moderate or mild. Multiple papers in

this thesis perform systematic examination of the gestational age dependence of risk factors. This was conducted by the application of time to event analytic methods and this is discussed in more detail before. This whole area represents a situation where making very practical clinical statements is intertwined with quite sophisticated questions around the appropriate use of statistical methods. These issues underline the importance of a high quality methodological approach when analysing observational data.

1.4.2 Application of novel statistical methods to studying clinical epidemiology of human pregnancy

1.4.2.1 Time to event analysis

The section above introduced the issue of studying gestational age dependence of markers. Specifically, what I did in these analyses was to perform time to event analysis where gestational age was used as the timescale. When studying antepartum stillbirth, the event was taken as antepartum stillbirth and censoring was taken as either intrapartum stillbirth or live birth. In the case of spontaneous pre-term birth, a spontaneous delivery (defined in the details of the papers) was taken as the event and all other births were taken as being censored. In these cases, I then analysed the data using a Cox proportional hazards model. It is an assumption of a Cox model that the hazard ratio associated with a given factor is constant across the range of time of follow-up. This assumption can be formally tested using a statistical test described by Grambsch and Therneau.[4] I used a Cox proportional hazards model in the analysis of the risk of both stillbirth and spontaneous pre-term birth and in both cases employed the test of the proportional hazards

assumption to determine whether there was objective evidence that the strength of association of a given factor did or did not vary across the range of gestation. These analyses provided objective evidence that certain biochemical and ultrasonic markers of risk varied in their predictive ability across the range of gestational age. The general pattern that I found was that measurements made in the second trimester of pregnancy were particularly strongly associated with the risk of adverse outcome at extreme pre-term gestations. This was true for alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) for both pre-term birth and stillbirth. It was also true of high resistance patterns of uterine artery Doppler flow velocimetry and the risk of stillbirth. To my knowledge, I was the first person to employ the use of the proportional hazards model in assessing stillbirth risk in pregnancy. Others may have used time to event analysis to assess the risk of pre-term birth but, to the best of my knowledge, I was the first to use the Grambsch and Therneau test of the proportional hazards assumption to assess the gestational age dependence of risk factors for spontaneous pre-term birth.

1.4.2.2 Using paired statistical methods in twins

Another slightly surprising innovation in this thesis was the use of paired statistical methods to compare the risk of death between the first and second twin. When I reviewed the literature on the association between birth order and the risk of perinatal death in twins, I was extremely surprised to discover that all the major studies that were available had used non-paired statistical tests to compare the outcome of first and second twins. That's not to say that no study had ever used paired statistical methods, but such studies were certainly in the

minority. However, in relation to previous analyses of birth order and the risk of perinatal death, none of the studies which were adequately powered had used paired tests to make this comparison. Therefore, when I examined the relationship between birth order and the risk of perinatal death, I used McNemar's test, which is the appropriate method for the comparison of a dichotomous outcome in paired observations. This is self evidently the appropriate approach to comparing outcome within pairs of twins. The slightly more innovative approach was to use conditional logistic regression to model the effect of birth order and to determine whether the risk of birth order interacted with gestational age. To my knowledge, this was the first application of conditional logistic regression to study the gestational age dependence effects of birth order. As discussed in the specific section, these studies have led to a large-scale randomised trial and the insights of these papers may turn out to be highly clinical relevant.

1.4.2.3 Adjusted likelihood ratios for predicting risk

A number of the papers in the thesis described the conversion of complex multivariate logistic regression models into tables of adjusted likelihood ratios. The method to perform this was developed by Mr Ian White, a Senior Scientist at the MRC Biostatistics Unit in Cambridge, following my specific request. The background to this request was that clinicians are generally comfortable using likelihood ratios when discussing the risk of Down's syndrome with women. I felt that if other predictive models could be converted into likelihood ratios, it may facilitate the clinical uptake of the models. The method is described in detail in its initial description in the American Journal of Obstetrics and

Gynecology (Section 3.4) and then Ian White refined the method further in the paper described in PLoS Medicine (Section 3.3).

1.4.2.4 Using the proportional hazards model for assessing family history of disease

Another relatively innovative approach was a further development of time to event analysis. This is employed in two papers looking at the risk of cardiovascular disease in the parents of women whose pregnancy was recorded in the SMR02. The issue in these analyses was that the age of the parents of the women was highly variable and their risk of experiencing cardiovascular disease would clearly vary in relation to their age. By treating the parents as a cohort and analysing the risk of ischaemic heart disease (IHD) using a Cox proportional hazards model, I was able to estimate the relative risk of IHD in the parents while avoiding confounding through variation in their age. As a given pair of parents are non-independent, this required a model that allowed for multiple levels of clustering within the cohort of parents and this was overseen by Ian White. This is not something that I have seen used elsewhere in the obstetric literature although I am not sufficiently familiar with the cardiology literature to know whether it may have been previously employed.

1.4.2.5 Accounting for non-independence in biological replicates

Finally, I also applied sophisticated statistical methods to address the question of non-independence in studies of uterine smooth muscle (myometrium) contractility. Many studies have described measurement of myometrial

contractility *in vitro* where strips of uterine muscle are obtained at the time of caesarean section and studied in an organ bath. A problem arises when more than one strip of muscle is obtained from the same woman as these cannot be treated as being independent in any subsequent statistical analysis. In practice, the non-independence of different strips from the same woman is generally ignored and statistical methods which do not account for this are employed. However, when I addressed the effect of maternal age on the spontaneous contractile activity of human myometrium, I was aware that I could not simply ignore the violated assumption of independence. Therefore, I applied regression methods employing the generalised estimating equations clustered on a maternal identifier to account for the non-independence of different strips of muscle from the same woman. It is an interesting reflection on the general awareness of the importance of using appropriate statistical methods that this approach was flagged as a problem by one of the reviewers, rather than as a sophisticated solution to an often ignored methodological flaw. However, I was able to convince the Journal's editors, through their statistical reviewer, that the method was appropriate.

Collectively, the above underline the importance, when analysing complex numerical information, of making every effort to use appropriate methods. In the case of twin pregnancy, the failure to use appropriate methods may have resulted in clinical conclusions which were incorrect, misleading and potentially dangerous to individual women and their babies. The scope for- severe consequences in using inappropriate methods to analyse myometrial smooth muscle contractility is less immediately apparent. However, given the

substantial investment of charities and research councils in this work, it would seem reasonable that, if it generates complex numerical information, the information is examined and analysed in a competent and appropriate manner. In conclusion, I feel I that any substantial body of work that makes a significant contribution in the analysis of complex data will generally involve generation of new statistical methods and/or novel application of existing sophisticated statistical methods. I think this is true for the work described in this thesis.

1.4.3 Using epidemiological research methods to study human reproductive biology

Some of the studies could be viewed as describing aspects of human biology using clinical information. Moreover, the biological questions addressed are clinically relevant as they are associated with variation in important clinical outcomes. An example is the analysis of the relationship between age and the risk of emergency caesarean section. This study combined a population analysis of women with a first singleton pregnancy presenting cephalically at term and demonstrated a linear association between the age of the mother and the risk of emergency caesarean section and assisted vaginal delivery. The nature of this association was such that the rise in risk started from age 16 upwards and the proportional increase in risk of caesarean section associated with a given increase in age was the same across the whole of the range of maternal age. This observation led to basic laboratory studies of the contractility of smooth muscle from the uterus, which are also described in the same paper. These experiments demonstrated that the uterine muscle from older women demonstrated reduced spontaneous contractions and greater

numbers of coupled (multi-phasic) contractions. These observations led to a specific hypothesis that the age-related deterioration of the uterus was due to prolonged pre-pregnancy hormonal stimulation by sex steroids. The steroid exposure could either be endogenous, from the ovarian cycle among women who either abstained from intercourse or used barrier methods. Alternatively, it could be due to the effects of exogenous synthetic sex steroids given in the form of the combined pill. This biological explanation for the clinical observation made a specific prediction, namely, that earlier age at menarche would be associated with increased rates of operative delivery. This prediction was tested using data from the ALSPAC cohort and that analysis confirmed the prediction, supporting the biological hypothesis.

Another essentially descriptive biological finding was the estimation of the normal duration of human pregnancy. This was performed using data from women with a very accurate menstrual history and where the gestational age of the baby was confirmed by measurement of the crown-rump length in the first trimester of pregnancy. This cohort was analysed using a statistical method developed for longitudinal epidemiological research studies, namely, time to event analysis. The paper developed the arguments why time to event analysis is well suited to assessing the normal duration of human pregnancy. This study demonstrated an average duration of first human pregnancy of 283 days and of subsequent pregnancies of 281 days. Hence, clinical observations and clinical research methods could be applied to clinical data to make a basic biological description of human reproductive characteristics.

Finally, two papers again used complex statistical methods to test the biological hypothesis that male babies may be more vulnerable to hostile intrauterine environments than female babies. The first paper addressed antepartum stillbirth of normally formed babies in relation to their sex and gestational age-specific birth weight percentiles comparing the risks for male and female babies. This demonstrated that growth restricted males were at increased risk of stillbirth whereas males of normal weight or males which were large for gestational age were not at increased risk of stillbirth compared with similarly sized females. Interestingly, a similar interaction was noted in relation to emergency caesarean section at term. The relative risk of emergency caesarean delivery was compared for male and female babies across a range of birth weights. Again, an interaction was found such that male fetal sex was associated with an increased risk where the baby was small, but not if the baby was of average, or above average, size. Both observations are discussed in the context of basic laboratory studies of the control of the stress responses in relation to the sex of an infant.

1.5 Use of routinely collected data

An interesting feature of the papers included in this thesis is that most of the data were collected for some other purpose. The opportunity for conducting research was based partly on understanding the value of individual data sources which had not been completely exploited. It was also based on understanding the opportunities for record linkage to take individual datasets with less interest and, by combining them with other sources, create extremely powerful datasets to interrogate a specific question. Perhaps the best example

of this in the thesis is the record linkage of the SMR02, the West of Scotland Regional Genetics Service Database of Down Syndrome Screening, the Birth Certificate Database and the General Registrar's Office Death Certificate Database to identify infant deaths. This allowed us to test a specific hypothesis, namely, that raised levels of AFP in early pregnancy would be predictive of an increased risk of sudden infant death syndrome (SIDS). This paper was published in the New England Journal of Medicine and received worldwide press attention.

However, it is equally important that the limitations of these analysis is also recognised, in particular the well recognised problems of poor quality of routinely collected data. Fortunately, in the case of the SMR02, the dataset is subjected to regular quality assurance exercises. It was a deliberate focus in much of this work to concentrate on the fields within the SMR02 which have high levels of quality. Hence, relatively few of the analyses involved the use of the International Classification of Disease (ICD) diagnostic codes included in the SMR02 as these are known to be less than wholly reliable. Most of the analysis was confined to variables which were >90% and indeed >98% free of major or minor errors. Another key aspect of interpreting observational data is to be aware of the possibilities for confounding and bias. As outlined in the hierarchy of evidence, the studies which are least likely to be affected by bias are randomised control trials. The issues with observational data are well recognised and discussed in detail elsewhere.[5] However, the reality is that many important obstetric questions will never be able to be answered by a randomised control trial as women will not consent to being randomly allocated

to treatments which they feel very strongly about. For example, when a trial of mode of delivery was attempted among women with a previous caesarean, very few women were prepared to be randomly allocated to either attempting vaginal birth or having a repeat elective caesarean section. Therefore, the literature on vaginal birth after caesarean section (VBAC) is almost exclusively composed of studies of routinely collected data. In each of the papers, I attempt to identify and discuss the potential sources of bias and to explore how these biases might have led to spurious associations. I have also employed multivariate modelling methods to examine whether associations were dependent or independent of the other maternal characteristics which had been measured. I also systematically examined interactions in many of the papers to see if apparent associations were consistent across sub-groups of individuals. A feature of this work is that many of the papers are published in general journals and I feel that this is an objective testimony to the quality of the analytic approach, despite the limitations of secondary analysis of routinely collected data.

2. Maternal and fetal characteristics and the outcome of pregnancy

The papers included in this section relate a number of outcomes of pregnancy to a mother's characteristics or to fetal characteristics. The significance of each of the analyses varies according to the question addressed. In some, it may seek to inform the consequences of certain choices. Examples would include the analysis of stillbirth risk in the second pregnancy in relation to caesarean in the prior pregnancy. These findings may help inform decision making around performing caesarean section by providing information about the consequences of that decision for future pregnancies. Similarly, inter-pregnancy interval is potentially within the control of parents and modifiable through advice from healthcare providers. Hence, analyses of the outcomes following a short inter-pregnancy interval are potentially informative in decision making. Another example of a potentially modifiable characteristic associated with adverse outcome is maternal obesity. Demonstrating a striking association between obesity and both the risk of neonatal death and an extremely low birth weight long-term survivor provides a rationale and motivation for counselling women about pre-pregnancy weight reduction, where appropriate.

Some of the other publications in this section relate to the classification of women as being at high or low risk of particular events in relation to a number of characteristics. These include analyses of the risk of stillbirth in relation to complications in the previous pregnancy and in relation to gestational age at term. The information in both analyses can be used to inform the use of

investigations to assess fetal wellbeing, as well as potentially informing decisions around elective delivery in women who have a relevant history.

2.1 BMJ 2001;323:476-479

Teenage pregnancy and the risk of adverse perinatal outcomes associated with first and second births: population based retrospective cohort study.

Cited 47 times

Two citations made direct attempts at comparable analyses. A UK based study compared just under 2000 pregnant teenagers with 10,000 women aged 20 to 39 and demonstrated no increased risk of pre-term birth or stillbirth but confirmed reduced rates of operative delivery.[6] These results were consistent with my analysis. A study using US birth certificate data[7], however, found increased rates of complications amongst teenagers having a first birth in the United States. It may be that there is a true difference between outcomes in the UK and the US. For example, there is free access to maternity care in the UK and it is plausible that the different structure of healthcare provision in the United States results in disadvantages to teenagers. It is also possible that ethnic or social differences may explain the different observations between the UK and US studies. However, an important caveat to these points is that the data source employed in the US study was the US birth certificate database, which is known to have profound weaknesses.[8] The data verification, quality and completeness is less well developed than the Scottish Morbidity Record employed in the BMJ paper 2001. As discussed in the paper, there are a number of studies that suggest there is no true increased risk of perinatal

complications in teenagers. Taking the prior work, this paper, and subsequent work, it seems reasonable to say that first teenage pregnancy in the UK is not strongly associated with adverse outcome. However, as the paper makes clear, a second teenage pregnancy is strongly associated with preterm delivery.

2.2 Am J Public Health 2007;97:157-162

***Maternal obesity in early pregnancy and risk of spontaneous and elective preterm deliveries: a retrospective cohort study*.**

Cited 43 times

Maternal obesity is a focus of increasing concern and this is reflected in the fact that this paper is cited 43 times over the interval from publication to August 2010. As described in the paper, the analysis was intended to try and describe the relationship between obesity and preterm birth separately into elective and spontaneous preterm delivery. Of the subsequent papers, one almost perfectly replicated the methodological approach using data from Missouri maternally-linked files.[9] This is a regional dataset within the US which has reasonably high quality pregnancy data. The authors of this paper found essentially the same observation, namely that obesity was associated with a reduced risk of spontaneous preterm birth but an increased risk of elective preterm delivery. Furthermore, they extended the findings by also studying twin pregnancies and they demonstrated very similar findings in multiple pregnancy. The replication of this finding in a separate population strengthens the conclusion that this observation is going to be generally applicable for pregnant women in high income countries. The observation that obesity is associated with premature

birth through elective preterm delivery, often due to pre-eclampsia, indicates potential strategies for ameliorating this risk, such as the use of aspirin in very obese women.

2.3 PLoS Medicine 2008;5:1123-1132

***The effect of delaying childbirth on primary caesarean section rates*.**

Cited 3 times

This paper is discussed together with the study below.

2.4 BJOG 2009;116:1613-1621

***Age at menarche and the risk of operative first delivery*.**

Cited 0 times

This study was published relatively recently and has not yet been cited. The key inter-relationships in the literature are between this study and the study above. In the PLoS Medicine paper of 2008, I made a specific prediction that age at menarche would be associated with caesarean section and operative vaginal delivery. The nature of the relationship is such that earlier menarche was predicted to be associated with increased rates of operative delivery. This was a specific prediction arising from the hypothesis that prolonged hormonal stimulation of the uterus prior to a first pregnancy was harmful to uterine function. The analysis with age at menarche was consistent with this hypothesis in three important ways. First, the effect on the risk of operative delivery was very similar comparing a 5-year decrease in age at menarche and a 5-year increase in age at first birth. The hypothesis is that the interval between menarche and first birth has a major influence on how the uterus

functions during labour, such that longer intervals will result in less effective contraction. Therefore it would be anticipated that increasing this interval at either end of the range would have the same effect for the given number of years. Second, the association between age at menarche and operative delivery disappeared on adjusting for the interval between the age at menarche and birth. This indicates that the interval between menarche and birth is the true underlying association and age at menarche was associated with this outcome by its influence on the duration of this interval. Third, the specificity of this association was confirmed by demonstrating that the association between the age of menarche and other maternal characteristics, such as body mass index, were unaffected by adjusting for the menarche to birth interval. I am currently supervising studies in mice where the animal's hormonal environment is being manipulated and the effect of this on age-related changes in myometrial contractility is being studied.

2.5 BMJ 2003;327:313-318

***Interpregnancy interval and the risk of preterm birth and neonatal death: retrospective cohort study*.**

Cited 34 times

The most relevant subsequent study was a meta-analysis of studies examining the relationship between the inter-pregnancy interval and perinatal outcome.[10] The BMJ paper fulfilled the quality criteria for inclusion in this meta-analysis and was one of the studies incorporated. The meta-analysis confirmed the association with preterm birth which I described in the BMJ paper. There was, however, a significant difference between the BMJ conclusion and the meta-

analysis. The meta-analysis suggested a shortened inter-pregnancy interval (< 6 months) was associated with odds ratio of 1.26 (95% confidence interval (CI) 1.18-1.33) for delivery of a small for gestational age baby. In the BMJ analysis I did not observe this association. However, a critical feature in all meta-analysis, and in particular meta-analysis of observational studies, is the quality of the data which is used for the primary research. In the case of the BMJ paper, I demonstrated that women who had a shorter inter-pregnancy interval were much more likely to have the first pregnancy result in perinatal death or delivery of a growth restricted baby. Therefore, when I performed the analysis of inter-pregnancy interval, I excluded women who had delivered a baby that was stillborn or was delivered pre-term. This exclusion was simply not possible in many of the studies included in the meta-analysis as they lacked the same level of detailed information on the outcome of the first pregnancy. Given the importance of confounding as a source of positive results in observational analyses, I feel that the advantage of including all of these studies in the meta-analysis may be somewhat outweighed by the drawback of many of the individual studies lacking the level of detailed information required to isolate any true biological effect of a short inter-pregnancy interval.

2.6 Am J Obstet Gynecol 2001;184:489-496

***Life-table analysis of the risk of perinatal death at term and post term in singleton pregnancies*.**

Cited 42 times

Many of the citations papers subsequently citing this work attempted to put the observed risk in a context and draw conclusions about clinical care. One of the

citations is from an American College of Obstetrics and Gynecology Practice Bulletin regarding the clinical management of women having a post-dates pregnancy[11]. Similarly, the data in this study are quoted in the National Institute of Clinical Excellence (NICE) guideline on antenatal care.[12] One of the particularly noteworthy features of this paper is that it is the first application of time to event analysis for stillbirth risk. The paper used the simplest form of time to event analysis, namely, life-table analysis. This is comparable to Kaplan-Meier except that the timescale of follow-up is by fixed periods whereas Kaplan-Meier allows calculation of the cumulative probability at varying time intervals. The idea to use time to event analysis to assess stillbirth risk was my own and the rationale was developed in this paper. I subsequently developed this further by using both Kaplan-Meier analysis and Cox proportional hazards models to assess stillbirth risk. In these analyses, the gestational age (in days or weeks) is used as the timescale, the event is taken as stillbirth, and censoring is taken as birth of a live-born infant or birth of a baby that was an intrapartum stillbirth. I wrote a review article in the American Journal of Obstetrics and Gynecology in 2005 summarising the advantages of the time to event approach.[13] In brief, the advantages are that gestational age is used as the time-scale. This means that the denominator for the risk of stillbirth at any given stage of the pregnancy is the number of on-going pregnancies at that given gestational age. It is now generally accepted that relating stillbirth risk at a given week of gestation to the numbers of births at the given week of gestation is methodologically flawed and leads to misleading patterns of risk. However, simply relating the number of births to the number of on-going pregnancies at the start of the week without using time to event methods over-

estimates the denominator. Within any given time interval, a proportion of women will deliver. Therefore, if one uses the total number of women with an on-going pregnancy at the start of the 40th week as the denominator and the number of stillbirths is the numerator, the denominator will be over-estimated as a proportion of the women at this stage in gestation will deliver over the course of that week and therefore not be exposed to a full week's worth of risk. Time to event analysis adjusts the denominator for the effect of women being censored due to delivery. The application of Kaplan-Meier analysis allows stillbirth risk to be demonstrated graphically in relation to the week of gestation. The application of the Cox proportional hazards model allows measures of relative risk to be adjusted for other maternal characteristics. Moreover, the hypothesis that a given characteristic varies in relation to gestational age can be formally tested by a statistical method which tests the hypothesis that the hazard ratio associated with a given factor systematically varies in relation to the time-scale (gestational age).[4] Since pioneering this method, there are many subsequent applications of time to event analytical methods in the analysis of stillbirth risk.

2.7 Human Reproduction 2001;16:1497-1500

Use of time to event analysis to estimate the normal duration of human pregnancy.

Cited 12 times

The majority of the citations were reviews around the management of post-dates pregnancy. A novel part of this paper was again the use of time to event analysis. On this occasion, it was used to estimate the duration of pregnancy

and the probability of labour on any given day of delivery. A major development of this was one of my later papers published in Nature where I used the same analytical approach to determine the association between biochemical measurements in early pregnancy and the duration of pregnancy (discussed in more detail below).

2.8 Am J Epidemiol 2000;151:614-619

***Sex, birth weight, and the risk of stillbirth in Scotland, 1980-1996*.**

Cited 19 times

Many of the subsequent citations were reviews putting the finding in the context of other risk factors for stillbirth. However, as discussed in the introductory comments to this section, the observation in this paper suggest a greater vulnerability of poorly grown male babies. This paper demonstrates this quality for stillbirth and a comparable observation was made for caesarean section. Interestingly, one of the papers citing this made a very similar comparison in relation to cerebral palsy.[14] These authors examined almost 3,500 cases of cerebral palsy and found that male sex was a risk factor but it was much more strongly associated with cerebral palsy when the birth weight was less than the third percentile. Hence, this follow-up study was also consistent with the underlying hypothesis behind this analysis namely, that male babies are more vulnerable to intra-uterine stress than female babies.

2.9 BJOG 2000;107:740-744

***A population study of birthweight and the risk of caesarean section: Scotland 1980-1996*.**

Cited 4 times

As discussed above the most significant context is the differential probability between male and female babies to a hostile intra-uterine environment. The paper has also been cited in relation to understanding rising rates of caesarean section.

2.10 Lancet 2003;362:1779-1784

***Caesarean section and the risk of unexplained stillbirth in subsequent pregnancy*.**

Cited 103 times

This paper attracted worldwide publicity when it was published, as an increased risk of stillbirth in association with caesarean section has major implications for public health given relatively high rates of caesarean delivery. Many of the articles citing this paper put the finding in the context of decision-making around having caesarean section or other modes of delivery. A number of papers analysed the risk of stillbirth in other populations. Crucially, this included an examination of the following three years worth of data from Scotland, which is published in the next paper in this section (Am J Epidemiology 2007;165:194-202). This analysis was performed after publication of the Lancet paper. It demonstrated a virtually identical association between previous caesarean section and the risk of stillbirth in Scotland in the following three years of data. All the inclusion criteria, definitions and analytic

methods were identical to the original Lancet paper. The level of statistical significance in the replication study was P<0.001. This, therefore, essentially dismissed the possibility that the original finding published in the Lancet was observed through the play of chance. It did not, however, exclude the possibility that the association may be explained by some hidden bias. That question will never be adequately resolved, except by a randomised control trial. Realistically, no trial of appropriate size or duration of follow-up would ever be practical.

The analysis of caesarean section risk is a situation where applying the appropriate analytical methods is essential. A significant proportion of women who have a previous caesarean section will have an elective repeat caesarean section around 38-39 weeks. Therefore, these women are not at risk of stillbirth at 40 weeks gestation and beyond. In contrast, women who have not had a previous caesarean section will have a normal distribution of timing of delivery. Therefore, this will include women whose pregnancies are on-going at 40, 41, and 42 weeks. Therefore, women who have not had a previous caesarean section will be exposed to a greater duration of risk of stillbirth due to longer duration of pregnancy. It is essential, therefore, that an analytic method is applied which takes into account the different duration of pregnancy with women with a previous caesarean section and those without. Other key features in the analytic approach are that I confined the original analysis to second pregnancies. The total number of pregnancies will vary systematically according to whether a woman has had a prior experience of caesarean section. In order to remove this source of bias, the original Lancet analysis and

the follow-up analysis were confined to second pregnancies. If other studies failed to confine the analysis to second pregnancies, biases could be introduced which could affect the associations observed. Third, in the analysis of the Scottish data sets, all stillbirths are classified according to a standardised system. Classification is performed by a single medically qualified individual who has a complete description of the case and has access to post-mortem data. It is possible, therefore, to identify stillbirths due to congenital abnormality and pre-existing maternal disease. Failure to exclude these cases could lead to biases both to increase and decrease associations with caesarean section. The results of subsequent studies which sought to test the finding in other populations were inconsistent. Some studies confirmed an association between previous caesarean section and stillbirth[15-18]. A study of a large dataset from the United States did not demonstrate an association between previous caesarean section and stillbirth. However, this study used the US birth certificate database and the weaknesses of this data source are well recognised.[8] Moreover, these authors did not employ a method which took into account the different duration of pregnancy in women with a previous caesarean section. As the study did not replicate the methods of the Lancet paper, it is very hard to make direct comparisons. Another American study using the Missouri maternity linked cohort did demonstrate an association between previous caesarean section and stillbirth. However, this was observed in black, but not white, women.[19] Finally, a study of over 150,000 second births in a Canadian perinatal database concluded that there was no association between previous caesarean section and stillbirth. However, their adjusted hazard ratio for previous caesarean section was 1.36 with 95% Confidence

Interval (CI) between 0.98 and 1.89.[20] The Lancet analysis reported hazard ratios of 1.64 with 95% CI of 1.17 to 2.30. Clearly, these two results are consistent with each other. Moreover, given that the lower 95% CI in this analysis was very close to 1.0, the authors clearly cannot confidently exclude an association between previous caesarean section and stillbirth. In correspondence following their paper, the authors suggested that the relatively modest overall association between previous caesarean section and stillbirth, namely a 60-70% increase in risk, suggests that it was unlikely to be causal in nature. However, this betrays a misunderstanding of the entity of stillbirth. Stillbirth is simply death of a baby prior to birth. This can be the end process of many diverse pathophysiological pathways. If caesarean section has a causal role in stillbirth, such as through increasing rates of severe growth restriction, one would not expect there to be a global increase in all different types of stillbirth. The Lancet paper demonstrated a particular association between structurally normal babies which were growth restricted. These losses only constitute a minority of all stillbirths. Even if caesarean section is strongly associated with this outcome, the overall association with stillbirth will necessarily be relatively weak. I am aware of an Australian group who have performed a meta-analysis of risk factors for stillbirth and they have confirmed that previous caesarean section is statistically associated with this outcome. However, one would have to accept that the association does not equal causation and although the association appears to be true, further work is still required to determine whether this is a true biological effect of caesarean delivery.

Finally, one of the practical consequences of the increased risks of caesarean section is that women who have had a previous caesarean section and who are considering vaginal birth are going to be exposed to the risk of antepartum stillbirth in the interval from 39 weeks until they deliver. That is to say, if a woman chooses to have an elective caesarean section at 39 weeks she is not exposed to the risks of antepartum stillbirth at 40, 41 and 42 weeks. However, if a woman with a previous caesarean section chooses VBAC, she would normally be allowed to go up to 10 days after her due date before induction of labour would be recommended.[21] One of the points raised in the Lancet paper was that the greatest risk of perinatal death among women with a previous caesarean section is not the risk of the baby dying due to uterine rupture but the risk of an antepartum stillbirth while awaiting the onset of labour. The absolute risk estimated in the Lancet paper was approximately one antepartum stillbirth per thousand births. A large scale prospective study in the United States, sponsored by the National Institutes of Health, demonstrated a virtually identical absolute risk of stillbirth from 39 weeks gestation onwards. Moreover, in that analysis of women with previous caesarean section, the greatest risk of perinatal mortality in those attempting vaginal birth was an increased risk of antepartum stillbirth.[22] Hence, this study confirmed both my findings and my interpretation.

2.11 Am J Epidemiol 2007;165:194-202

***Previous pre-eclampsia, preterm delivery, and delivery of a small for gestational age infant and the risk of unexplained stillbirth in the second pregnancy: a retrospective cohort study, Scotland, 1992-2001*.**

Cited 8 times

Most of the citations were related to putting the paper in a clinical context. However, one paper published in 2009[23] reporting a similar analysis of the Medical Birth Registry of Norway, drew almost identical conclusions, such that pre-term birth, growth restriction and pre-eclampsia were all strongly associated with stillbirth in a subsequent pregnancy. The importance of this paper in the context of previous caesarean section is also discussed above. These finding underline the importance of increased surveillance of women who had these complications in previous pregnancies.

3. Delivery-related complications in special situations (multiple pregnancy and among women attempting vaginal birth after caesarean section)

The focus of the papers in this section is to understand the associations between obstetric factors and the risk of adverse events in the context of twin pregnancy and VBAC. The data informing decisions around VBAC are wholly observational in nature[21] due to the difficulty of performing any randomised controlled trial, particularly trials with statistical power to study perinatal death or uterine rupture. These studies all make use of the high quality national audits of perinatal death that take place in the UK. In the case of the studies linking the Scottish registries of pregnancies and perinatal deaths, this combination results in a database with unique strengths internationally. Even some of the Scandinavian databases (which are often regarded as a "gold standard" of routinely collected data) lack detailed information on the cause of stillbirth. Hence, many of these studies represent use of a data resource of international importance.

3.1 JAMA 2002;28:2684-2690

Risk of perinatal death associated with labor after previous caesarean delivery in uncomplicated term pregnancies.

Cited 96 times

Many of the articles citing this paper were reviews and the estimate of absolute risk are quoted both in UK guidelines (NICE and Royal College of Obstetricians and Gynaecologists (RCOG)) and in international guidelines. As discussed in

the paper, a key difference between this study and previous publications is that I confined the estimation of the risk of death to deliveries at term. This meant that the absolute risk of perinatal death for both women attempting vaginal birth and those having repeat caesarean section were much lower than previously reported.[24] A number of follow-up studies took the same approach and drew very similar conclusions. For example Kwee et al[25] quoted an absolute risk of perinatal death of 1.2 per thousand VBAC attempts which was virtually identical to the figure quoted in the JAMA paper. One aspect of the JAMA paper is that the data were from the whole of Scotland. Therefore, this summarised information from hospitals of very different types, from low throughput units to high throughput tertiary centres. One subsequent follow-up study demonstrated an even lower absolute risk of perinatal death associated with VBAC in the region of 1/5000 VBAC attempts.[22] That study reported data from the National Institutes of Child Health and Development (NICHD) Maternal Fetal Medicine network units. These are all tertiary referral centres with well in excess of 3,000 births per annum and with highly sophisticated out of hours and weekend cover on delivery unit. In the following paper, I addressed the size of unit and the risk of death during an attempted vaginal birth amongst women with a previous caesarean section and confirmed that the absolute risk varied inversely with the throughput of the unit. Therefore, I see the data presented in the JAMA paper as representing a summary of the national experience and that international experience was consistent with this when accounting for the type of obstetric facilities. Consistent with this interpretation, a systematic review of VBAC[26] produced an estimate of the risk of death due to uterine rupture associated with VBAC of 1.4/10,000 with CI of

0.00 to 9.8. The JAMA analysis demonstrated an absolute risk of perinatal death amongst women attempting VBAC with just over 10/10,000 with approximately one-third of these due to uterine rupture. Therefore, our results were consistent with the meta-analysis.

3.2 BMJ 2004;329:375-379

Factors predisposing to perinatal death related to uterine rupture during attempted vaginal birth after caesarean section: retrospective cohort study.

Cited 28 times

As discussed above, one of the key issues was the relationship between the risk of perinatal death due to uterine rupture and hospital throughput. A key observation here is that the absolute risk of death due to uterine rupture in large centres was in the region of 1/5000. As discussed above this figure was consistent with that reported in the same year by the NICHD Fetal Medicine Unit network. The other key finding reported in this paper was that the risk of perinatal death due to uterine rupture was increased among women who had a prostaglandin induction of labour. This finding was confirmed by two subsequent studies,[27;28] both of which demonstrated increased rates of uterine rupture amongst women induced with prostaglandin. These, and other studies which demonstrated associations between uterine rupture and prostaglandin, led the American College of Obstetrics and Gynecology to advocate strongly against the use of prostaglandin in women with previous caesarean section. I regard that recommendation as understandable but not necessarily appropriate for all women. One of the major issues for women to consider who have had

one previous caesarean section and are considering mode of delivery in their current pregnancy is how many further pregnancies they will be having in the future. One of the major long-term complications of caesarean section is the increased rate of placental complications in women who have had large numbers of previous caesarean sections. The NICHD Maternal Fetal Medicine Network study, referred to above, demonstrated rates of hysterectomy between 5 and 10% amongst women who have had five or more previous caesarean sections. Therefore, a decision to perform a repeat caesarean section in a second pregnancy could have long-term adverse effects on the woman if she was planning a large family. This is an issue that I discussed in detail as the senior author in the RCOG guideline on VBAC.[21] In the RCOG Guideline, despite the increased risk of perinatal death due to uterine rupture associated with the use of prostaglandins, I recommended that prostaglandin induction should still be considered amongst women who are considering the possibility (or have the potential) for many future pregnancies, where the alternative is to perform a repeat caesarean section. I felt there was a balance between the increased relative risk of uterine rupture in these women in the current pregnancy and the risk of severe placental-related complications in subsequent pregnancies. The relative risk of uterine rupture with prostaglandins is in the region of 3. The absolute risk of uterine rupture is therefore in the region of 1-2%. Moreover, if the induction of labour is taking place in a large centre, many of the infants will have a good outcome even if uterine rupture occurs. Therefore, the decision around induction of labour in these women must reflect a balance between the short-term risks of uterine rupture and the longer-term

risks of placental-related complications in women who were planning to have a large family.

3.3 PLoS Medicine 2005;2:871-878

Predicting caesarean section and uterine rupture among women attempting vaginal birth after prior caesarean section.

Cited 7 times

An editorial accompanied this paper and described the method for predicting caesarean risk as 'a great leap forwards'.[29] A number of other studies have produced predictive models for VBAC and these have variable levels of discrimination. In this analysis I made a conscious decision not to include the birth weight of the baby in the predictive model, as the birth weight cannot be known accurately prior to delivery. We do know, however, that birth weight is associated with a higher rate of emergency caesarean section. Some other predictive models which followed this publication did include birth weight and, unsurprisingly, their models had greater predictive power. However, these models lack clinical utility as they are predicated on a measurement which is not available prior to birth. The NICHD Maternal Fetal Medicine Network group developed a predictive model from their dataset. This had the advantage that the study was prospective and therefore they collected more information than there was available from the Scottish Morbidity Record. For example, they had information on body mass index, which is known to be an important predictor of caesarean section.

A key point in the discussion of the PLoS Medicine paper was that by identifying women at high risk of emergency caesarean section, one might be able to select women who would have a lower composite risk of morbidity if they chose to have an elective caesarean section. The rationale for this is that the highest rates of maternal morbidity are observed among women who attempt VBAC but end up with emergency caesarean section. This hypothesis was tested directly by the NICHD Maternal Fetal Medicine Network group who applied their model in a separate population.[30] They demonstrated that the risk of maternal morbidity became lower as the predicted chance of successful VBAC increased amongst the women who attempted vaginal birth, but not amongst those delivered by elective caesarean section. Hence, the results of that analysis supported the rationale for trying to predict the success or otherwise of VBAC.

3.4 Am J Obstet Gynecol 2004;191:2029-2034

Combined logistic and Bayesian modelling of caesarean section risk.

Cited 10 times

This paper was the first describing our method for converting complex multivariate logistic regression models into adjusted likelihood ratios. Most of the subsequent citations were papers producing other predictive models of emergency caesarean section. One aspect of this analysis was the idea that likelihood ratios were conceptually more straightforward than logistic regression models. A complexity that arises when we consider caesarean section is that this outcome is relatively common. As likelihood ratios deal with odds, all calculations using likelihood ratios require that the prior probability

and the posterior probability are expressed as odds. The odds equate to the probability when the outcome is uncommon, (this is termed the 'rare disease assumption'). However, any outcome which affects >10% of the population is regarded as common and there is a significant difference between the odds and the probability. This introduces the problem that, in order to apply a likelihood ratio-based model, one has to convert the prior probability into odds, multiply by the likelihood ratios and then convert the posterior odds back into probability. This hurdle may have limited the clinical applicability of using a likelihood ration based approach in the context of caesarean delivery.

3.5 BMJ 2002;325:1004-1006

Birth order, gestational age, and risk of delivery related perinatal death in twins: retrospective cohort study.

Cited 30 times

One of the key methodological innovations in this paper was to use McNemar's test and conditional logistic regression for the comparison of outcomes between first and second twins. Both of these methods are appropriate for situations where one is comparing a dichotomous outcome in a matched pair. As discussed in the paper, virtually all previous studies had compared the outcome of first and second twins using statistical tests that involved the assumption that the first and second twins had been selected at random from a general population, i.e. that the twins were not paired. It is extraordinary that this was the case but this reflects a general lack of understanding of the importance of some very basic statistical principles when analysing clinical epidemiological data. A follow-up study replicated the methods with the use of

McNemar's test as I had employed in the BMJ analysis.[31] These authors then observed a very similar finding, namely an increased risk of death of the second twin compared with the first. Moreover, this was observed where the delivery was a planned vaginal birth but it was not observed when the delivery was by planned caesarean section. In the discussion of the BMJ paper, I speculated about the potential protective effect of elective caesarean section for the second twin although I did not have direct evidence that this was beneficial. A second follow-up study compared second twins delivered by caesarean section with second twins delivered following vaginal delivery of the first twin.[32] Moreover, as I had demonstrated that the effect of birth order was particularly marked at term, these authors also confined their analysis to babies with a birth weight >2.5Kg. This would effectively exclude most pre-term deliveries. These authors demonstrated that vaginal birth was associated with an odds ratio for perinatal death (excluding losses due to congenital abnormality) of 4.64, with 95% CI of 1.9 to 13.9.

The BMJ analysis was published at a time when a colleague in Toronto (Dr Jon Barrett) was applying for a grant to perform a randomised controlled trial of elective caesarean section for twins. On the basis of personal communication, I understand that the publication was pivotal in his securing funding and he describes the rationale for the trial and its conduct in a publication.[33] I had the opportunity to look at the protocol for this trial and there is one potential cause for concern in the way that it has been put together. A key aspect of the BMJ analysis was that the difference in birth order was apparent for births at term but not pre-term. The explanation for this is that the absolute risk of death to

the second twin due to delivery complications is relatively low. Amongst pre-term infants, there are high absolute rates of death due to prematurity and clearly this will be the same for the first and the second twin. Therefore, a small additional increased risk of death to the second twin is masked by the very high rates of perinatal death for both twins related to gestational age. Therefore, I found (using conditional logistic regression analysis) an interaction between birth order and gestational age, such that birth order was only associated with an increased risk of adverse outcome at term. A concern that I have regarding the design of the Twin Birth Study is that women are recruited at around 32-weeks gestation and all deliveries thereafter are going to be analysed on the basis of randomisation to caesarean section or planned vaginal birth. The primary outcome for the trial is neonatal morbidity or mortality. The rates of pre-term delivery of twins from 32 weeks onwards will be quite substantial as twins are well recognised as having an increased risk of pre-term birth. I suspect, therefore, that in both groups there will be substantial numbers of babies born in the interval 32 to 36 weeks, i.e. preterm. Hence, both intervention and control groups will have high rates of the primary outcome which are due to preterm birth and are independent of mode of delivery. My concern is, therefore, that a true protective effect of planned caesarean section at term will be obscured by high rates of morbidity in both the elective caesarean section and planned vaginal birth groups due to high rates of prematurity. I have communicated with Dr Barrett on a number of occasions that I think they should set out a pre-specified subgroup analysis, namely, to compare the risk of morbidity in relation to elective caesarean section or planned vaginal birth

confining the analysis to babies born at 37 weeks or beyond. The trial is on-going and should report in the next few years.

3.6 BJOG 2005;112:1139-1144

Mode of delivery and the risk of delivery-related perinatal death among twins at term: a retrospective cohort study of 8073 births.

Cited 26 times

This paper extended the previous publication by increasing the total number of births available for analysis. Moreover, the analysis was confined to births at term. The key difference to the previous paper is that the dataset included almost 1500 deliveries by planned caesarean section and I was able to make a direct comparison of the risk of death of either twin in relation to whether the delivery was by planned caesarean section or by some other means. This demonstrated a 75% lower risk of death amongst twins delivered by planned caesarean section. One study attempted to replicate this analysis to some degree using the Swedish Medical Birth Registry.[34] They compared twin pairs delivered by caesarean section for breech presentation and twin pairs who were delivered vaginally. They included babies of all gestational age, both pre-term and term, although they stratified the analysis by gestational age. Their outcome was neonatal mortality, but it was not sub-divided by cause of death. The rates of neonatal mortality were low for both vaginally born second twins and second twins born by caesarean section from 34 weeks and beyond. There was no statistically significant difference, although the CI were consistent with a 90% reduction in the risk of death of the second twin delivered by caesarean section, compared with vaginal birth. Hence, this study

was under-powered to analyse the difference in risk of death of the second twin in relation to mode of delivery. An important point in the interpretation of that study is that the Swedish Medical Birth Registry has very limited information on causes of perinatal death. Therefore, stillbirth is merely indicated as a dichotomous outcome with no sub-division according to whether the baby died before or after the onset of labour. In contrast, the Scottish Morbidity Record is linked to a national registry of all perinatal deaths. It is possible, therefore, in the Scottish Morbidity Record to identify stillbirths which occurred following death of the baby during labour (intrapartum stillbirth). Moreover, I am able to identify and exclude deaths which are related to congenital abnormality. The Swedish Medical Birth Registry, lacks information on the 30% of neonatal deaths that are related to congenital abnormality. The Swedish Medical Birth Registry is seen as one of the most valuable international resources for population-based research. The comparison of these two analyses demonstrates some of the strengths of the Scottish national data.

3.7 BMJ 2007;334:576-578

Birth order of twins and risk of perinatal death related to delivery in England, Northern Ireland, and Wales, 1994-2003: retrospective cohort study.

Cited 11 times

This paper describes an analysis of the effect of birth order on the risk of perinatal death in England and Wales. This was a useful validation of the findings I made in the Scottish databases and allowed me to determine whether the association between birth order and the risk of death was apparent

in the rest of the UK. A major problem with perinatal data collection in England and Wales is the lack of a national registry. Whereas there is a national registry of all births which is centrally maintained by the Information Services Division of NHS Scotland, there is no equivalent Registry of all births in England and Wales. However, there is a national enquiry of perinatal deaths within England and Wales (called the Confidential Enquiry into Maternal and Child Health (CEMACH)) at the time of this analysis. However, the problem which limits analysis of these data is the lack of any denominator information. All that is available is relatively detailed information on the cause of death (stillbirth and neonatal deaths), but CEMACH lacked information on the babies that survived. This paper represents one of the analytical studies which has been possible using the English and Welsh data. The ability to analyse in this situation relates to the unusual situation of making a comparison in twins. As discussed above, comparison of a first and second twin should be performed using a paired statistical test, i.e. McNemar's test or conditional logistic regression when comparing a dichotomous outcome. The approach of these methods is to ignore all pairs which are concordant for the outcome. Therefore, twin pairs are ignored where either both twins survive or both twins die. This property means that a complete analysis can be performed using a dataset which has information only on perinatal death. So long as all deaths are identified, one would be able to identify all cases where one twin died but the other twin did not. On the basis of this slightly circuitous approach, I was able to perform an analytical study using the CEMACH data. Using this approach, I was able to confirm the key associations observed using the Scottish data. There was no difference between the risk of death in first and second babies born pre-term.

There was a significant interaction with gestational age, and there was an increased risk of death of the second twin due to anoxia at term. Put together, these three papers provide strong evidence regarding a problem with twin mortality within the United Kingdom. This makes it particularly important that the Twin Birth Study is completed and is appropriately analysed so that correct inferences can be made about the potential benefit of elective caesarean section to prevent perinatal morbidity and mortality.

4. Ultrasonic predictors of pregnancy outcome

The papers in this section all relate to ultrasonic measurements made during pregnancy to outcomes for the baby. The main focus of these studies are (1) the way in which measurements of the fetus in a 2 dimensional plane may be associated with the weight of the baby, or associated factors (such as blood volume), (2) the way in which assessment of blood flow using Doppler flow velocimetry can be used to predict adverse outcome. The studies span all three trimesters of pregnancy and use routinely collected and research data. There is a further study which employs measurement of a maternal structure (the cervix) in the prediction of mode of delivery.

4.1 BJOG 1997;204:186-190

The relation between fetal abdominal circumference and birthweight: findings in 3512 pregnancies.

Cited 39 times

The majority of the subsequent citations were review articles where the paper was discussed. One study followed up the suggestion that adding femur length to abdominal circumference for the prediction of birth weight was not of great value by addressing this question in women with a baby with an abnormal umbilical artery Doppler.[35] Whereas the conclusion of the BJOG paper was that femur length added relatively little to the estimation of weight, these authors actually found that adding femur length to the equation reduced the accuracy of ultrasound to estimate birth weight. Hence although the populations were different, similar conclusions were drawn. An important aspect of this paper

was the extent to which ultrasound could rule in or rule out a baby that was macrosomic, namely had a birthweight of >4.5Kg (UK definition) or over 4 Kg (US definition). The paper was cited by the American College of Obstetrics and Gynecology Practice bulletin on shoulder dystocia.[36] Another study followed up the suggestion that an abdominal circumference ≥ 36cm was sensitive for the detection of a macrosomic infant. This study demonstrated that an abdominal circumference ≥ 35cm had 93% sensitivity for babies weighing 4Kg or more. [37] This is consistent with my finding that an abdominal circumference of ≥36cm had 100% sensitivity for macrosomia defined by the UK threshold of 4.5Kg.

Stepping back from the specifics of these analyses, there is a very important question regarding how fetal biometry and estimated fetal weights are employed clinically. For example, as discussed above, there are associations between the baby's birth weight and the risk of emergency caesarean section. However, birth weight is not known prior to delivery and it is difficult to incorporate this information. A key finding in the BJOG paper was that a given abdominal circumference is associated with quite a wide range in birth weight. Therefore, what is currently missing is high quality data that relates the ultrasonic measurement of the fetus, in particular the abdominal circumference, to the likelihood of important clinical outcomes, such as caesarean section. Many studies have addressed this question. However, there is a major issue in relation to bias. In the vast majority of such studies, the ultrasound estimation of fetal weight is known by the clinician who is managing the labour. It is clear, therefore, that the decision-making of an obstetrician looking after a woman in labour may be influenced by whether the baby is suspected to be small or large

for gestational age. Even if there was a poor relationship between predicted and actual birth weight, estimated fetal weight could be associated with increased rates of intervention due to the effect of this knowledge on clinical decision-making. What is currently lacking from the literature is very high quality data on whether ultrasound is independently predictive of mode of delivery. To answer this question, information would be required where the ultrasound scan had been performed but where the clinician was 'blinded' to the result. As one of the follow-ups to the work described in this thesis, I am currently conducting a large-scale prospective cohort study of women in their first pregnancy and one aspect of this is making ultrasonic measurements at 28 and 36-weeks of gestation but concealing the fetal biometry from the attending clinician.[38] Clearly, a proportion of women will end up having a clinically indicated scan but over half of the cohort have not had any further scans in the third trimester. I will, therefore, be able to relate these fetal biometric measurements to the risk of important outcomes in labour and delivery, such as emergency caesarean section.

4.2 BJOG 2002;109:721-722

Estimating human fetal blood volume on the basis of gestational age and fetal abdominal circumference.

No citations

This was a clinical paper which addressed a very specific, rather technical, point in relation to an uncommonly performed treatment. The key finding of this study was that abdominal circumference and gestational age were similarly predictive of the outcome (post-transfusion haematocrit) following intrauterine

blood transfusion. Therefore, the paper has a largely practical and clinical utility such that if a woman attends for intrauterine transfusion where the gestational age is not known, the abdominal circumference can be used in the equation described in this analysis and a similar result can be expected to equations based on gestational age.

4.3 New Eng J Med 1998;339:1817-1822

First trimester growth and the risk of low birth weight.

Cited 113 times

This paper was the first piece of work on a theme which is elaborated in a series of papers in the rest of this thesis, namely, that adverse pregnancy outcome is determined (at least in part) in very early pregnancy. The paper exploited a virtually unique database where highly detailed menstrual history had been collected as part of a prospective cohort study in a single centre. The detailed nature of the menstrual history allowed optimising the accuracy of estimation of the date of conception amongst women having spontaneous conception. Another feature of the hospital, which was unusual at the time, was that all women were dated by first trimester crown-rump length. This partly reflected the fact that the hospital (The Queen Mother's Hospital, Glasgow) was the centre where ultrasound was pioneered by Professor Ian Donald. Moreover, a research technologist who assisted Professor Donald, Mr John Fleming, had made one of the first descriptions of crown-rump length to estimate gestational age.[39] Hence, the data source presented an extremely valuable opportunity to test the hypothesis that growth restriction would be evident in very early pregnancy. The key finding, that smaller than expected

crown-rump length was associated with an increased risk of being delivered small for gestational age, was then replicated in a series of other databases. Importantly, many of these studies did not have the same level of information on the menstrual history and, therefore, could not provide as accurate estimation of the expected size of the baby in the first trimester. The expected size is clearly critical in determining whether the baby was small or large in the first trimester of pregnancy. Nevertheless, the association was sufficiently robust that it was observed in a number of other populations.[40-45] Two of these follow-up studies warrant particular consideration. First, Bukowski et al (2007)[43] were able to identify 1,000 pregnancies where conception was through an assisted reproductive technology method. One of the relative weaknesses of the original analysis was that, despite the fact that the menstrual history was as close to perfect as possible, the estimate of the expected size of the babies still involved certain assumptions. In particular, I assumed that ovulation had taken place on day 14 (where day 1 is the first day of the last menstrual period). It was possible that differences in the observed versus expected size of the embryo or fetus may have been due to differences in the assumed time of ovulation. It is conceivable, therefore, that the true association was between some maternal determinant of the timing of ovulation and intrauterine growth restriction. The major strength of the Bukowski paper is that they were able to remove the uncertainty around the time of conception by studying assisted reproductive technology pregnancies. This analysis confirmed the findings almost perfectly, with a smaller than expected crown-rump length being associated both with earlier delivery and an increased risk of delivering a small for gestational age infant. The second study, Mook-Kanamori et al (2010) also

extended the finding. Like the NEJM paper, these authors relied on the menstrual history. However, in addition to the birth weight, these authors also had data on the growth of the children following birth. They found that where the baby had been small in the first trimester of pregnancy and was subsequently delivered small for gestational age, there was post-natal catch-up growth, i.e. the fetal growth was reduced resulting in reduced birth weight but the baby subsequently established a normal weight in infancy and childhood. This strongly supports the interpretation that the association with first trimester growth genuinely reflects intrauterine growth restriction. Intrauterine growth restriction is essentially a theoretical concept that is defined as a baby that fails to reach its genetically determined growth potential. The lower birth weight percentile compared with the weight percentile achieved in infancy and childhood suggests that these children had a higher genetically determined growth than they achieved in utero, presumably because their growth was restricted by some process. The contrast with this outcome is the situation where a baby simply is constitutionally small. It could have been that a small crown-rump length represented a baby that was genetically determined to be small. Hence, a baby that was small in utero, was small at birth and remained small through infancy and childhood. Therefore, the follow up studies confirmed my observation of the early onset of variation in fetal growth and secondly, support the interpretation that this is due to pathological restriction of growth rather than physiological variation. I also went on to follow-up this study by looking at other pregnancy parameters and in particular biochemical tests (see below). I am currently the principal investigator of a prospective cohort study[38] that is in process is taking measurements in the first trimester and I

have preliminary data that other ultrasonic parameters which can be measured in the first trimester of pregnancy are also associated with the risk of delivering a small for gestational age baby. I wrote an editorial to accompany the Mook-Kanamori paper in JAMA[46] which elaborates on the whole area of the early determination of late complications of pregnancy. It is likely that this field of research will continue to grow over the coming years.

4.4 New Eng J Med 2008;358:1346-1353

Cervical length at mid-pregnancy and the risk of primary caesarean delivery.

Cited 8 times

This paper is in some ways thematically related to papers in the preceding section relating maternal age and age at menarche to the risk of emergency caesarean section. The last 30 years has seen a very dramatic rises in rates of caesarean section and much of the focus of attention has been on variation in medical practice as a determinant of this. These three papers all report studies of primary caesarean section as being something that is, to some extent, biologically determined. The most common indication for emergency intrapartum caesarean section during a first labour is failure to progress. Failure to progress in labour could be regarded as an essentially biological complication: a women presents in labour but progressive dilation and effacement of the cervix fails to occur, often despite medical intervention. Despite the clear physiological basis for this, the concept that caesarean section represents a failure of some underlying biological process is not particularly widely discussed. A key aspect of this paper is that it had parallels

to findings which had been made in a series of animal species, such that preparation for labour and delivery, in terms of uterine biology, are occurring as a continuing process of modelling and remodelling during gestation. This paper, which demonstrated a striking association between the length of the cervix in mid-gestation and the ultimate risk of caesarean section in women in a first labour at term, suggests similar remodelling of the uterus is occurring during human pregnancy. Again, with our prospective cohort study,[38] a key focus is to try and identify other early pregnancy ultrasonic and biochemical predictors of caesarean section risk.

4.5 Obstet Gynecol 2007;109:144-151

Maternal uterine artery Doppler flow velocimetry and the risk of stillbirth.

Cited 10 times

This paper addressed the clinical prediction of stillbirth risk. This is the focus of a number of papers in this thesis. An important contribution of these papers has been to raise the profile of stillbirth as a condition which is potentially predictable on the basis of ultrasonic and biochemical measurements. The clinical problem of stillbirth, its biological determinants, the clinical prediction and the scope for future research is summarised in a review that I was asked to write for Lancet.[3] A key aspect of this work that ties in with other studies in the thesis is the use of time to event analysis to examine the relationship between abnormal uterine artery Doppler and the risk of stillbirth in relation to gestational age using the Cox proportional hazards model. I found highly significant, non-proportionality of the hazards ratio associated with abnormal artery Doppler. This rather technical point led to the clinically very important

observation that uterine artery Doppler was a very good predictor of stillbirth prior to 33 weeks gestation, but it was a poor predictor of stillbirth at term. This is a clinically pertinent point to make as a obstetrician may be falsely reassured about a woman's stillbirth risk at term if she had normal uterine artery Doppler test performed at 23 weeks. This test is seen as a good indicator of impaired trophoblast invasion (thought to be a key determinant of abnormal placentation[47]). The finding that stillbirth was strikingly associated with the measurement made in the middle of pregnancy was consistent with a subsequent study[48] which demonstrated that impaired fetal growth between the first and second trimester was also associated with a very significant risk of perinatal death.

5. Biochemical predictors of pregnancy outcome

The studies in this section all relate biochemical measurements made in pregnancy to the outcome. Measurements are confined to the first and second trimesters. The biochemical measurements were generally made for the purpose of assessing Down's syndrome risk, either from a research study or from routine screening. The exception is the fourth study where proteins were assayed which had been implicated in the pathophysiology of pre-eclampsia. All biochemical measurements are normalised for gestational age and, if appropriate, for maternal age and smoking and expressed as multiples of the median. This reduces the possibility of biases related to the gestational age when the woman attended. Many research studies ignore gestational age variation. This represents poor practice, as no clinical Down's syndrome screening programme would employ non-gestational age corrected values.

5.1 J Clin Endocrinol Metab 2002;87:1762-1767

Early pregnancy levels of pregnancy-associated plasma protein A and the risk of intra-uterine growth restriction, premature birth, pre-eclampsia, and stillbirth.

Cited 114 times

This work was stimulated by the study described in the previous section about early fetal growth and the risk of growth restriction in later pregnancy. The data for this study were collected as part of a Down's syndrome screening study. One of the proteins measured as part of Down's syndrome screening, pregnancy-associated plasma protein A (PAPP-A), is a placentally-derived

regulator of the insulin-like growth factor system. Studies of mice lacking PAPP-A have demonstrated that this is associated with early onset intra-uterine growth restriction.[49] When used in Down's syndrome screening, PAPP-A is measured between 10 and 14 weeks gestation. Therefore, this study allowed an ideal opportunity to test the hypothesis that conditions in very early pregnancy may determine complications in late pregnancy. As this paper elaborates, associations were demonstrated with delivery of a small for gestational age infant, pre-term birth and stillbirth. The analysis has been replicated in many subsequent studies and these findings confirmed. Perhaps the key studies are two other large scale prospective Down's syndrome screening cohorts which were conducted in the United States. Dugoff et al reported data from over 30,000 women recruited as part of the FASTER study.[50] Krantz et al reported the results of another Down's syndrome study recruiting over 8,000 women.[51] Both studies confirmed the association with growth restriction, pre-term delivery and stillbirth. Many centres now incorporate PAPP-A as part of their screening programme to identify women at increased risk of growth restriction and stillbirth.

5.2 Nature 2002;417:916

Early-pregnancy origins of low birth weight.

Cited 47 times

This paper investigated PAPP-A as a marker of variation in fetal growth in uncomplicated pregnancies and in those where the sampling was performed in first trimester of pregnancy. As such, its focus was more on using this clinical measurement as a way of understanding biological variation in fetal growth. A

number of studies have developed this concept. Bukowski et al used maternal serum levels of PAPP-A in uncomplicated pregnancies as a way of characterising its association with normal variation in fetal growth. They then examined customised birth weight percentiles, i.e. adjusting the birth weight percentile for maternal serum levels of PAPP-A and a series of other physiologic determinants of fetal growth and found that customised percentiles better classified women into abnormal and normal outcome of pregnancy.[52] Canini et al confirmed that PAPP-A was associated with physiologic variation in fetal growth in a smaller sample.[53] Bukowski et al, in the same paper referred to above in relation to crown-rump length,[43] confirmed that physiological variation in fetal growth was also determined to some extent in the first trimester of pregnancy. Hence collectively these observations are in support of the concept of both normal and abnormal variation in human fetal growth is determined, at least in part, in the first trimester of pregnancy.

5.3 JAMA 2004;292:2249-2254

First-trimester placentation and the risk of antepartum stillbirth.

Cited 33 times

While understanding the physiological determinants of variation in growth is of interest, perhaps the key practical significance is that poor fetal growth is a major determinant of the risk of antepartum stillbirth. The previous paper in JCEM had assessed overall risks of stillbirth, as had the large American cohort studies. However, stillbirth is simply death of the baby in utero and can be the end point of diverse processes. Some of these could be related to the function of the placenta and some of these could be unrelated to placental function.

Therefore, by relating PAPP-A to all causes of stillbirth, one might underestimate the strength of association with the types of stillbirth which are specifically related to placental function in early pregnancy. Moreover, as discussed above, a particular interest was in the extent to which these associations were true in the very early stages of pregnancy. This analysis developed previous work by (1) strictly confining analysis to measurements made prior to 13 weeks of gestation and, (2) through record linkage to the Scottish Stillbirth and Infant Death Survey (SSBIDS), relating concentrations of PAPP-A to specific causes of stillbirth. This analysis revealed striking associations between levels of PAPP-A and risk of stillbirth attributed to a placental cause. This division of stillbirths into placental and non-placental causes is used in other sections of the thesis. For example, this distinction was also made for the analysis of uterine artery Doppler and risk of stillbirth. As was the case with abnormal uterine artery Doppler, the strongest associations were for stillbirth due to growth restriction, pre-eclampsia and abruption (the three categories of loss which we regarded as placentally related). The term 'placentally related stillbirth' is potentially open to criticism. There is evidence that normally formed babies with an unexplained stillbirth where the birth weight was normal are also related to function of placenta, discussed in my Lancet review of stillbirth published in 2007.[3] However, the pathophysiology of abnormal placental function in this group is less well understood than it is for losses due to growth restriction, pre-eclampsia and abruption.

5.4 Obstet Gynecol 2007;109:1316-1324

Circulating angiogenic factors in early pregnancy and the risk of pre-eclampsia, intrauterine growth restriction, spontaneous preterm birth, and stillbirth.

Cited 23 times

Subsequent to the publications on PAPP-A, maternal circulating levels of another system of proteins was described as being predictive of pre-eclampsia. In a series of papers by Levine it was demonstrated that women who went on to develop pre-eclampsia had elevated levels of soluble fms-like tyrosine-kinase-1 (sFlt-1) and low levels of placental growth factor (PlGF).[54] The model that was proposed was that the placenta releases sFlt-1 as a response to hypoxia. Soluble Flt-1 then binds and inactivates circulating PlGF and VEGF. The reduced levels of PlGF and VEGF then have an anti-endothelial effect which leads to the clinical manifestations of pre-eclampsia. However, the work of Levine et al focused on measurements of sFlt-1 and PlGF in the later stages of pregnancy, from about 16 weeks onwards. I found that low PAPP-A was strikingly associated with outcome even when measured in the first 10 weeks, suggesting that this may precede the observed changes in sFlt-1 and PlGF. Therefore, the stored samples from the Down's syndrome screening study which I had used for the PAPP-A analysis were subsequently analysed for sFlt-1 and PlGF. This paper reports these results. The key observation was that PlGF was low and predictive of pre-eclampsia at a gestational age when the sFlt-1 levels were normal amongst women who subsequently went on to experience pre-eclampsia. That is, among women who go on to develop pre-

eclampsia, low PlGF precedes elevation of sFlt-1. This indicates that low PlGF is not occurring purely as a consequence of elevated levels of sFlt-1. Another key feature of this paper is that low levels of PlGF were also associated with other adverse outcomes, in particular delivery of a small for gestational age baby. Subsequent work has confirmed these findings. Cowans et al confirmed that low PlGF in the first trimester was associated with increased risks of delivery a small for gestational age baby[55] and a similar observation was made by Poon et al.[56] The key finding that low PlGF preceded elevated sFlt-1 was confirmed by Akolekar et al.[57] These observations do not undermine the potential importance of the findings regarding sFlt-1 and PlGF. However, they do indicate that the model of sequestration of PlGF by elevated sFlt-1 is, perhaps, too simplistic. It also suggests that the elevation of sFlt-1 is an event which is downstream of other factors. Therefore, it cannot be regarded as the initiating event that ultimately leads to pre-eclampsia. Nevertheless, sFlt-1 may be an important therapeutic target for the treatment of pre-eclampsia if it is causally related to endothelial dysfunction.

5.5 BJOG 2007;114:705-714

Maternal and biochemical predictors of antepartum stillbirth among nulliparous women in relation to gestational age of fetal death.

Cited 8 times

Unlike the novel observations made about PAPP-A, this paper added to an already extensive existing literature on how maternal levels of AFP and hCG were associated with the subsequent risk of perinatal death. The analysis extended previous studies in two major ways. First, information was obtained

on a large number of women through record linkage of routinely collected prenatal screening data to the SSBIDS. Secondly, as in other analyses in this thesis, I applied time to event analytic methods to determine whether the relative risk of particular adverse outcomes was associated with the gestational age. This analysis very clearly demonstrated that elevated second trimester AFP and hCG were particularly strongly associated with stillbirth at extreme preterm gestations. There is a clear parallel between this finding and the finding made about uterine artery Doppler and the risk of stillbirth. Namely, these were all strikingly associated with the risk of death at extreme preterm gestations but not associated with the risk of death at term. Again, this statistically innovative approach has yielded clinically important information regarding when a woman should be regarded at an increased risk in relation to measurements made in early pregnancy.

5.6 Int J Epidemiol 2006;35:1169-1177

Maternal and biochemical predictors of spontaneous preterm birth among nulliparous women: a systematic analysis in relation to the degree of prematurity.

Cited 15 times

Again, this paper utilised time to event analytic methods. The same parallels can be drawn with the analyses on stillbirth. The analytic approach was that delivery following onset of spontaneous labour was taken as the event, delivery without the onset of spontaneous labour was taken as censoring and gestational age was used as the timescale. This was the same analytic approach that I employed for the estimation of duration of human pregnancy,

described above. However, the approach in this analysis was to try and determine whether these biochemical markers were differentially related to preterm delivery at extreme preterm gestations. The use of the Cox proportional hazards model and the test of the proportional hazards assumption allowed formal assessment of whether the variation in relative risk was significantly different in relation to extreme, moderate or mild prematurity. This paper clearly demonstrated that both AFP and hCG were particularly strongly associated with spontaneous preterm birth at extreme preterm gestational ages. Hence, this is a further example of the innovative use of time to event analysis to understand biological determinants of adverse pregnancy outcome and also to draw inferences about the clinical utility of measurements in relation to degree of prematurity. One aspect of many of these analyses relating maternal characteristics, biochemical measurements or ultrasonic measurements is the performance of the given measurements as a screening test. Again, this is a theme which has run through many analyses, such as predicting caesarean risk, stillbirth and, in this case, spontaneous preterm birth. In this paper, I make the point that, although the biochemical measurements were strongly associated with extreme preterm delivery, predictive models based on these measurements in combination with maternal characteristics performed relatively poorly as a screening test. This partly reflected the fact that preterm delivery at 24-28 weeks (the clinically most important preterm birth) is very uncommon. Therefore, although women in the top 5% of predicted risk had a very significantly elevated relative risk, because the prior risk was so small, the majority of women in the “high risk” did not experience this outcome. The distinctions between relative risk, absolute risk, and the screening

properties of a given factor are important when presenting analyses of this type of association.

5.7 Obstet Gynecol 2006;107:161-166

Pregnancy-associated plasma protein A and alpha-fetoprotein and prediction of adverse perinatal outcome.

Cited 28 times

This analysis combined two of the measurements I had made namely, first trimester PAPP-A and second trimester AFP. The findings of this study are particularly relevant in the context previously described. Women who have a combination of both a low PAPP-A and a high AFP had a very substantial absolute risk of having a complicated pregnancy with approximately one third of them delivering a baby weighing <2.5Kg. This outcome is a composite of both preterm birth and intrauterine growth restriction. This is one of the highest absolute risks described for the prediction of adverse outcome in a low risk population and this level of positive predictive value places this combination in the category of offering clinically useful prediction. Subsequent follow-up studies also examined the same question. Proctor et al evaluated a number of methods of assessing outcome in women who had a low PAPP-A and found that elevated AFP was one of only two measures which offered significant additional prediction.[58] Fox et al also identified a subset of women who had low PAPP-A where the baby was poorly grown in the second trimester.[59] Again, the combination of low PAPP-A and poor growth in the second trimester was associated with a high absolute risk of complications. These studies suggest that multiple measurements may hold the key to generating clinically

useful prediction of risk. Again, this is a theme which I have taken up with our on-going prospective cohort study where I am attempting combined ultrasonic and biochemical assessment of placentation with the aim of generating meaningful separation of high and low risk women with the minority of misclassification.[38]

6. Obstetric predictors of long term infant outcome

The papers in this section all report outcomes in the infant which include events occurring after the neonatal period. All of these analyses have involved record linkage of pregnancy and infant health records. In the first linkage a neonatal database was employed as the source of identifiers to link the two data sources. In the remainder, after the success of the first approach, the birth certificate was employed. Linkage of these data sources represents a highly cost-effective approach to studying long term outcome of the infant in relation to maternal characteristics or pregnancy complications.

6.1 Pediatrics 2003;111:1367-1371

Risk of sudden infant death syndrome and week of gestation of term birth

Cited 3 times

6.2 New Eng J Med 2004;351:978-986

Second-trimester maternal serum levels of alpha-fetoprotein and the subsequent risk of sudden infant death syndrome.

Cited 13 times

6.3 Lancet 2005;366:2107-2111

Sudden infant death syndrome and complications in other pregnancies.

Cited 3 times

6.4 Pediatrics 2006;117:60-66

Predicting the risk for Sudden Infant Death syndrome from obstetric characteristics: a retrospective cohort study of 505,011 live births.

Cited 5 times

These four papers will be discussed together. Very few studies have attempted replication of these analyses, reflecting in part the fact that there are few other countries in the world where these analyses could be performed. Hence, the discussion will focus on the inter-relationships between the four studies and parallels with other work in this thesis.

A major focus of the other work in this thesis is around the factors determining the risk of stillbirth. There are a number of important parallels between stillbirth and SIDS. 60-70% of stillbirths affect a baby which had no congenital abnormality and where there is no specific cause that clearly and wholly explains why the baby died. However, as with SIDS, there is an association with poor growth in utero. Given the body of work developed on stillbirth, it was a logical progression to use the same data sources to study obstetric associations with SIDS. The first of these papers (Pediatrics 2003), addressed the relationship between gestational age and SIDS. This analysis followed on from the paper in Section 1, published in the American Journal of Obstetrics and Gynecology in 2001, where I related the risk of stillbirth to gestational age at term. That paper demonstrated that with advancing week of gestation at term, there was an increased risk of stillbirth. Interestingly, exactly the opposite pattern was observed in relation to SIDS. The risk of SIDS was highest amongst babies delivered at 37 weeks gestation and steadily declined through to 42 weeks gestation. However, this was observed for spontaneous births but not babies delivered electively. This pattern suggests that the association between gestational age and SIDS was not directly related to the week of

gestation of delivery but rather to the factors which led to an earlier onset of labour. In the paper, I then developed a hypothesis to explain the commonalities and differences between SIDS and stillbirth. I postulated that stillbirth and SIDS shared a common characteristic of being related to an adverse intra-uterine environment. I hypothesised that when an adverse intra-uterine environment led to spontaneous labour at an earlier week of gestation, the baby was live-born and at increased risk of SIDS. However, if the process did not lead to the onset of labour, the baby succumbed in utero, hence the association with stillbirth. This interpretation led to a prediction, namely, that any indicator of an adverse intra-uterine environment which was associated with the risk of stillbirth would also be associated with the risk of SIDS. As discussed in the preceding section, many previous studies had observed that second trimester levels of AFP were strongly associated with the risk of stillbirth. By record linking a population-based screening system for Down's syndrome (where AFP was measured in the middle of pregnancy) to the Scottish national registries, I was able to determine whether this prediction held true in a large population. An important issue for the analysis is that SIDS is rare and very large numbers of children would need to be studied in order to draw reliable inferences. The study, published in New England Journal of Medicine in 2004, demonstrated that there was a striking association between mid-trimester maternal serum levels of AFP and the risk of SIDS. This was in part related to the fact that elevated maternal serum AFP was also associated with pre-term birth which is in turn a risk factor for SIDS. However, even after adjustment for birth weight and gestational age, a significant association persisted. Therefore, the hypothesis that SIDS may be the ultimate

manifestation of a hostile uterine environment was supported by this study. Subsequent analyses have analysed the brain stem of SIDS infants and have demonstrated abnormalities in the neurotransmitter, serotonin. Taken together, these data suggest that a hostile uterine environment may adversely affect the baby's autonomic nervous system development which could in turn predispose to SIDS.

The interrelationship between SIDS and obstetric complications are explored further in the Lancet paper of 2005. This analysis addressed an area which was highly topical at the time, namely, whether the risk of SIDS was increased in other children born to the same mother who had lost a baby due to SIDS. The context for interpreting the study is that there had been a number of highly publicised cases where women had had multiple babies affected by SIDS. An expert opinion had been volunteered that the probability of this was extremely small and, hence, the deaths may have been murder. However, this opinion rested on an assumption that the probability of SIDS was independent in different pregnancies. Given that I had shown that SIDS was related to hostile intrauterine environment and given that pregnancy complications tend to recur, it was plausible that the woman who had a sudden infant death event may have been more likely to have had obstetric complications in their prior or following pregnancies. These in turn could predispose the woman's other children to SIDS and could lead to an increased chance of recurrence. Hence, in the Lancet paper, I tested the prediction that the woman who had experienced a baby die of SIDS would have increased rates of obstetric

complications in preceding and subsequent pregnancies, and I found this to be the case.

The final paper in this series of contributions regarding SIDS related to our ability to predict the risk of SIDS on the basis of obstetric characteristics. There are clear parallels between this study and the work I have done creating predictive models for stillbirth and caesarean section. Again, I used the method whereby complex logistic regression models were converted into adjusted likelihood ratios. The issue referred to above in relation to caesarean section prediction, namely, that the odds and the probability significantly differ when the outcome is common was not a problem in this analysis, as SIDS is rare. Therefore, a likelihood ratio model could be developed which would allow parents to make a fairly simple estimation of the risk of their baby being affected by SIDS without needing to have a sophisticated understanding of statistics. An editorial accompanying this paper in Pediatrics described the method as “putting power back into the hands of parents”.[60]

6.5 Arch Dis Child 2004;89:956-960

Neonatal respiratory morbidity at term and the risk of childhood asthma.

Cited 13 times

This paper has parallels with the penultimate paper in Section 1 (Lancet 2003) in that it examined potential long-term effects of caesarean delivery. However, this paper was focused on the long-term outcome of the infant. A number of studies had suggested that there was an association between caesarean delivery and asthma. Other studies had indicated that babies who experienced

respiratory complications following premature birth were more likely to develop asthma in later life. It was already recognised that a planned caesarean section increased the chance of short-term respiratory problems in the early neonatal period. Therefore, it was plausible that respiratory complications secondary to caesarean delivery at term might also be associated with later asthma and that was the primary observation of this paper. Subsequent to that study, two meta-analysis were published which demonstrated striking associations between caesarean section and later asthma.[61;62] Furthermore, two studies specifically followed up our novel observation of the association between transient tachypnoea of the newborn and asthma and both confirmed an association.[63;64]

7. Obstetric outcome and the risk of subsequent maternal disease

As with the previous section, these studies utilise record linkage to allow pregnancy characteristics to be related to other outcomes. These include events that may have occurred in the past, such as IHD in a mother's parents, or events occurring many years after the index birth. Again, record linkage represents a highly cost effective way to address associations with remote outcomes. A theme arising in a number of the papers in this section is the description of associations which are of biological interest, but are not causal. For example, a woman who experiences recurrent miscarriages is more likely to have IHD in later life, and she is also more likely to have parents who have experienced IHD. However, it is not proposed that the miscarriage led directly to either her experience of disease or her parents' experience of disease. Rather, associations are interpreted as indicating some common predisposing factor. Although the relationship is not causal, it may be clinically important as understanding such common underlying determinants may allow identification of women who would benefit from assessment for specific risk factors for IHD.

7.1 Fertil Steril 2006;85:90-95

First caesarean birth and subsequent fertility.

Cited 7 times

This paper presents a further analysis which addresses the potential long-term adverse effects of caesarean delivery. A number of lines of evidence had suggested that there was an association between caesarean delivery and subsequent infertility. However, the studies were small scale and the evidence

was not of particularly high quality. As this will clearly be a critical issue for women who are considering a first delivery by caesarean section, a larger scale adequately powered study was required. This study indicated that there was no strong evidence that caesarean section affected future fertility.

A series of papers in the thesis have addressed the potential beneficial and harmful effects of caesarean section. Some of these papers demonstrated an improved outcome with caesarean section. For example, risks of perinatal death are lower with planned repeat caesarean section among women with a previous section and in women with a twin pregnancy. However, caesarean section was associated with an increased risk of stillbirth in the future and with an increased risk of asthma in the child. Finally, in this paper, caesarean section was neither beneficial or harmful. As an anecdotal aside, I have been asked whether I believe caesarean section is a “good” or “bad” thing, as the individual was confused by the fact that I had published research which suggested both risks and benefits of the procedure. The question betrays a view of medical research that individual researchers may be biased to produce results which support their prior beliefs. However, in my own work I have demonstrated both risks and benefits of caesarean delivery. I feel that this represents a realistic situation. Virtually every medical intervention will be associated with some advantages and some drawbacks and the decision around having a given procedure depends on the balance of all the risks and benefits for the individual making the decision. The goal of all of these studies around caesarean section has not been either to promote or to inhibit caesarean section but merely to provide information to women considering

caesarean section so they can make an informed choice. Moreover, by providing detailed analyses in relation to the mother's characteristics, the work acknowledges that the balance of risks and benefits will vary according to a woman's individual characteristics. For example, a woman of 20 years old and a woman of 40 years old will have a number of differing priorities and concerns in relation to the choice. The woman who is 20 may be exercised by thoughts of future fertility and the possibility that she may have large numbers of future deliveries each of which could be affected by the prior caesarean section. A further argument in favour of attempting normal birth is that, being young, she would have a very good chance of a normal delivery if she laboured. In contrast, an older woman faces an increased risk of emergency caesarean section should she attempt normal birth and may have fewer concerns about future fertility and the effects of large numbers of future pregnancies. Therefore, overall the work on caesarean section in this thesis acknowledges the complexity of both medical interventions and balancing the risks and benefits of interventions in relation to the characteristics of an individual woman.

7.2 Lancet 2001;357:2002-2006

Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,920 births.

Cited 224 times

As indicated by the number of citations, this paper made an important and novel contribution and was followed by a series of studies which replicated the finding and attempted to explore the basis for the observations. As explained in

the paper, there were prior studies which suggested relationships between birth weight and pre-eclampsia and the mother's subsequent risk of cardiovascular disease. However, this paper extended these findings to look at both the delivery of a small for gestational age infant and preterm delivery. Moreover, I was able to incorporate all of these major outcomes and relate them to the mother's subsequent risk of ischaemic heart disease. The key findings of the paper were approximate doubling in the risk of subsequent IHD in association with having experienced delivery of a small baby, preterm birth or pre-eclampsia. The combination of all three was associated with a seven-fold risk of IHD. The association was particularly striking when looked at by birth weight, with a greater than ten-fold risk of death due to IHD amongst women giving birth to low birth weight (<2.5kg) babies.

Subsequent to the paper, multiple studies throughout the world have replicated the findings, confirming associations with pre-eclampsia, preterm birth, delivery of a small for gestational age infant and low birth weight. A number of meta-analyses have been performed. McDonald et al performed a meta-analysis of 5 case control with 10 cohort studies and found a two- to three-fold risk of cardiovascular disease among women who had a history of pre-eclampsia in both types of study design.[65] Smith et al performed a meta-analysis in relation to birth weight and found increased risks of cardiovascular disease in both the mother and the father. Many studies have also performed more detailed investigation for cardiovascular risk factors and found multiple abnormalities in women who had pre-eclampsia including hypertension, dyslipidaemia and endothelial dysfunction.[66-69] The interpretation of these observations is that

there are common risk factors for maternal cardiovascular disease and for pregnancy complications. My hypothesis is that an individual may have occult cardiovascular dysfunction which is manifested in pregnancy complications during her reproductive years and, in later life, is manifested as cardiovascular disease. Further exploration of these associations is described below.

7.3 BMJ 2003;326:423-424

Spontaneous loss of early pregnancy and risk of ischaemic heart disease in later life: retrospective cohort study.

Cited 11 times

In the preceding paper relating pregnancy complications to cardiovascular disease, one of our proposed mechanisms was a common dependence on a pro-thrombotic tendency (thrombophilia). The basis for this was that thrombophilias have been associated both with an increased risk of cardiovascular disease and increased risk of pregnancy complications. However, thrombophilia is particularly associated with the risk of recurrent miscarriage. The use of aspirin and heparin is widely employed to try and improve outcomes in women with recurrent miscarriage. If a pro-thrombotic tendency was part of the explanation for the link between pregnancy complications and cardiovascular disease, one would also anticipate associations between recurrent miscarriage and cardiovascular disease.[70] Therefore, the next study was undertaken to test this hypothesis. The number of miscarriages experienced prior to the first birth was related to the women's subsequent risk of cardiovascular diseases using the same dataset as the Lancet paper of 2001. This study confirmed a positive association between the

number of miscarriages prior to the first birth and the risk of cardiovascular disease. Associations had previously been shown between miscarriage and later cardiovascular disease in a number of papers published in the 1950's and the 1960's. These studies suggested that low oestrogen levels were the potential linking mechanism. The weakness of these studies was that they had not taken into account the total number of pregnancies experienced by a woman. In the BMJ paper I used the number of miscarriages prior to the first birth as obtaining an indication of a woman's propensity to miscarriage which was independent of her total number of pregnancies.

7.4 Am J Epidemiol 2010;171:736-744

Birth weight and the risk of cardiovascular disease in the maternal grandparents.

No citations

My interpretation of the Lancet paper of 2001 was that pregnancy complications and cardiovascular disease were both manifestations of some underlying common determinant. Other authors who subsequently made similar observations in other populations interpreted this slightly differently. It was suggested that pre-eclampsia, growth restriction etc. during a pregnancy may damage the mother's cardiovascular system and that this long-standing damage to the cardiovascular system may provide the link with later cardiovascular disease. One context to the observation relating birth weight to the maternal risk of cardiovascular disease was the extensive literature on the relationship between an individual's birth weight and their personal risk of cardiovascular disease in later life. As it was now apparent that there were

associations between the birth weight of a baby and the risk of the mother having IHD, it was tempting to speculate that there may be some inheritable predisposition involved. If this was the case, it would favour the model that the associations were explained by common predisposing factors rather than the damaging effect of a complicated pregnancy. This hypothesis made a specific prediction, namely, that complicated pregnancies would be associated with a family history of IHD. This paper tested the hypothesis using a complicated record linkage performed using the Scottish data. The pregnancy records were linked to the mother's own birth certificate and the birth certificate was used to link the pregnancy record to the hospital admission and death data for the women's parents (i.e. the grandparents of the baby). By assessing the risk of cardiovascular disease in the grandparents, I was able to quantify the association between pregnancy complications and family history in first degree relatives. The risk of both IHD and cerebro-vascular disease in the grandparents declined with increasing birth weight of the baby. This strongly supported the model that the relationship between pregnancy complications leading to low birth weight and cardiovascular disease was some inheritable predisposition as the association was evident both for the individual, for the parent and for the grandparents. Perhaps the most tempting interpretation would be that there may be some common genetic link. However, I was able to adjust these associations for the characteristics of the mother at the time of the birth. Specifically, I adjusted for her age, height, smoking status, marital status and the area of socio-economic deprivation that she lived in (another striking feature of this paper was that the socio-economic area where the woman lived at the time of her pregnancy was itself strongly associated with her parents'

risk of heart disease). Adjusting for this series of characteristics attenuated the association between pregnancy complications and the grandparents risk of cardiovascular disease. Therefore, rather than placing a genetic interpretation on these data, I interpreted them as indicating familial aggregation of environmental factors. For example, a woman who smokes during her pregnancy is more likely to have a small baby. The woman who smokes during her pregnancy is more likely to have parents who smoke. Therefore, the same risk factor tends to stay within the family, a property known as familial aggregation. This paper has been published in 2010 and I understand following a discussion at a scientific meeting that a very similar observation has been made in one of the Scandinavian databases and that this should be published soon.

7.5 BJOG 2010 In press

Recurrent miscarriage is associated with a family history of ischaemic heart disease: a retrospective cohort study.

This paper has clear parallels with the paper immediately preceding. I had demonstrated that women who experience miscarriage were more likely to experience IHD in later life and had hypothesised that this may be due to common genetic predisposing factors. This made the prediction that recurrent miscarriage would be associated with a family history of IHD. I addressed this by examining the relationship between the number of miscarriages prior to a woman's first birth and her parents' risk of IHD. I found that there was an association. Interestingly, and in contrast to the previous paper, this was not affected by adjusting for available maternal characteristics. This led me to

interpret the finding as being supportive of other common determinants of miscarriage and IHD. The hypothesis predicts that genetic predisposing factors for IHD will also be associated with an increased risk of recurrent miscarriage and this hypothesis is readily testable.

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Section 1. Maternal and fetal characteristics and the outcome of pregnancy

Papers

Teenage pregnancy and risk of adverse perinatal outcomes associated with first and second births: population based retrospective cohort study

Gordon C S Smith, Jill P Pell

Abstract

Objective To determine whether first and second births among teenagers are associated with increased risk of adverse perinatal outcomes after confounding variables have been taken into account.

Design Population based retrospective cohort study using routine discharge data for 1992-8.

Setting Scotland.

Main outcome measures Stillbirth, preterm delivery, emergency caesarean section, and small for gestational age baby among non-smoking mothers aged 15-19 and 20-29.

Results The 110 233 eligible deliveries were stratified into first and second births. Among first births, the only significant difference in adverse outcomes by age group was for emergency caesarean section, which was less likely among younger mothers (odds ratio 0.5, 95% confidence interval 0.5 to 0.6). Second births in women aged 15-19 were associated with an increased risk of moderate (1.6, 1.2 to 2.1) and extreme prematurity (2.5, 1.5 to 4.3) and stillbirth (2.6, 1.3 to 5.3) but a reduced risk of emergency caesarean section (0.7, 0.5 to 1.0).

Conclusions First teenage births are not independently associated with an increased risk of adverse pregnancy outcome and are at decreased risk of delivery by emergency caesarean section. However, second teenage births are associated with an almost threefold risk of preterm delivery and stillbirth.

Introduction

Teenage pregnancy is an important public health problem as it often occurs in the context of poor social support and maternal wellbeing. Some studies have suggested that first teenage pregnancies have a higher frequency of adverse perinatal outcomes.[1 2] However, there is argument about whether this is an independent association[1 2] or explained by confounding factors.[3–5] In general, the risk of adverse outcomes is lower in second pregnancies. However, longitudinal studies comparing outcomes in first and second pregnancies in teenagers have produced inconsistent results.[6–9] Cross sectional studies comparing the outcome of second births in teenagers and older women have observed increased rates of preterm birth, low birth weight, and perinatal death[10 11] but have failed to adjust for potential confounding factors such as smoking and socioeconomic deprivation.

Scotland is well placed to study the outcomes of teenage pregnancy. Teenage pregnancy rates in the United Kingdom are the highest in western Europe. Routine obstetric data have been collected on more than 99% of births in Scotland for over 20 years.[12] Scotland has a population that is relatively homogeneous in terms of race, and health care is free at the point of access, including all medical, surgical, drug, and dental treatment during pregnancy. The aims of this study were to determine whether teenage pregnancy was associated with increased rates of adverse perinatal outcome, whether the association differed by parity, and whether any associations were independent of confounding factors.

Methods

Data collection and selection criteria

Throughout Scotland discharge data are routinely collected on all patients admitted to NHS maternity hospitals using the Scottish morbidity record 2 (SMR2).[12] The SMR2 database has regular quality assurance studies. An analysis of 1414 records in 1996-7 showed that the database was free of major errors in more than 98% of records in all the fields used in the present analysis, with the exception of postcode (94.0%), height (96.2%), and estimated gestation (94.4%) (Jim Chalmers, Information and Statistics Division, NHS, Scotland, personal communication).

We used the SMR2 database to identify all singleton births resulting in a live or stillborn baby during 1992-8. Inclusion in the main study group was restricted to first or second births, gestation at birth of between 24 and 43 weeks, birth weight >500 g, maternal age between 15 and 29 years, and non-smoking mothers. We also selected a second cohort who fulfilled all the above criteria except that they were classified as smokers at the time of first attendance for antenatal care.

Definitions and denominators

First births were defined as births to women who had had no previous pregnancies or whose previous pregnancies had all ended in abortion. Second births were defined as having been preceded by only one

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pregnancy that did not result in abortion. Gestational age at birth was defined as the number of completed weeks of gestation based on the estimated delivery date in the clinical record. A small for gestational age baby was defined as a live baby who was less than the 5th percentile of birth weight for the given week of gestation, using percentiles derived from all Scottish singleton live births recorded in the SMR2 database with values for both birth weight and gestational age in 1992-8 (n = 409 541). The denominator was all live births.

Very preterm delivery was defined as birth of a live baby at 24 to 32 weeks' gestation, and the denominator was all live births at or after 24 weeks' gestation. Moderately preterm delivery was defined as live births at 33 to 36 weeks' gestation, and the denominator was all live births at or after 33 weeks' gestation. Stillbirth was defined as delivery of a dead baby at or after 24 weeks' gestation, and the denominator was all births at or after 24 weeks' gestation. Neonatal death was defined as death of a liveborn baby in the first 28 days of life, and the denominator was all live births. Emergency caesarean section was defined as any unplanned caesarean delivery, and the denominator was all live births.

Maternal age was defined as the age of the mother in completed years at the time of birth because many of the outcomes were delivery related. Maternal height was measured in centimetres. Postcode of residence was used to derive Carstairs socioeconomic deprivation scores.[13] These are based on 1991 census data on car ownership, unemployment, overcrowding, and social class within postcode sectors. The deprivation scores were then used to categorise women into quintiles based on the study population. Non-smoking was defined as never having smoked at the time of first attendance for antenatal care, and smokers were defined as women who were current smokers at the time of first attendance for antenatal care.

Table 1 Study group characteristics and crude outcomes. Values are numbers (percentages) of women unless stated otherwise

	Women aged 15-19		Women aged 20-29		
	First births (n=9699)	Second births (n=1225)	First births (n=59 315)	Second births (n=39 994)	P value*
Demographic characteristics					
Mean (SD) height (cm)	161.8 (6.3)	160.9 (5.9)	162.9 (6.5)	162.3 (6.4)	<0.001
Socioeconomic deprivation quintile:					
1	698 (7.2)	65 (5.3)	11 411 (19.2)	6 856 (17.1)	
2	1299 (13.4)	150 (12.2)	11 890 (20.0)	8 014 (20.0)	
3	1889 (19.5)	265 (21.6)	11 737 (19.8)	8 141 (20.4)	<0.001
4	2340 (24.1)	309 (25.2)	11 719 (19.8)	8 113 (20.3)	
5	3257 (33.6)	411 (33.6)	11 163 (18.8)	7 969 (19.9)	
Unclassified	216 (2.2)	25 (2.0)	1 395 (2.4)	901 (2.3)	
Previous spontaneous abortions:					
0	9206 (94.9)	1099 (89.7)	52 647 (88.8)	32 781 (82.0)	
1	452 (4.7)	119 (9.7)	5 726 (9.7)	5 954 (14.9)	<0.001
>1	41 (0.4)	7 (0.6)	942 (1.6)	1 259 (3.1)	
Previous therapeutic abortions:					
0	9192 (94.8)	1158 (94.5)	54 581 (92.0)	36 598 (91.5)	
1	488 (5.0)	66 (5.4)	4 345 (7.3)	3 053 (7.6)	<0.001
>1	19 (0.2)	1 (0.1)	389 (0.7)	343 (0.9)	
Outcomes					
Birth weight <5th percentile	410 (4.2)	24 (2.0)	2 281 (3.8)	832 (2.1)	<0.001
Delivery 24-32 weeks	121 (1.2)	17 (1.4)	602 (1.0)	220 (0.6)	<0.001
Delivery 33-36 weeks	481 (5.0)	56 (4.7)	2 588 (4.4)	1 173 (2.9)	<0.001
Stillbirth	46 (0.5)	9 (0.7)	247 (0.4)	121 (0.3)	0.002
Neonatal death	22 (0.2)	3 (0.2)	146 (0.2)	67 (0.2)	0.07
Emergency caesarean section	831 (8.6)	51 (4.2)	8 346 (14.1)	2 240 (5.6)	<0.001

*χ^2 and analysis of variance tests applied to categorical and continuous data respectively.

Statistical analyses

We did separate analyses for six dichotomous outcomes: delivery of a small for gestational age baby, moderately and extremely preterm delivery, stillbirth, neonatal death, and emergency caesarean section. For each outcome, we compared the risk between different groups using odds ratios and 95% confidence intervals. We tested the null hypothesis that the risk of adverse outcomes associated with maternal age 15 to 19 was the same for first and second births using the Mantel-Haenszel test of homogeneity.[14]

We calculated adjusted odds ratios by logistic regression analysis.[15] Height category, maternal age category, socioeconomic deprivation quintile, and previous spontaneous and therapeutic abortion were entered into the model as dummy variables. We excluded cases with missing values for height from multivariate analysis.

We estimated the significance of main effects using the Wald test and the significance of interaction terms using the likelihood ratio test. We assessed goodness of fit of models using the Hosmer and Lemeshow test based on deciles of probability.[15] Continuous variables were summarised by the mean and standard deviation, and we compared groups using analysis of variance. We used the Stata software package (Stata Corporation, Texas, USA), version 6.0, for all analyses.

Results

There were 411 553 singleton births in Scotland during 1992 to 1998. Data were missing on gestational age at birth for 691 (0.2%), on parity for 1012 (0.2%), on birth weight for 304 (0.1%), on maternal age for 12 (<0.1%) and on smoking status for 38 334 (9.3%). Data on all these variables were complete in 371 531 (90.3%) cases, and the main study group comprised the 110 233 non-smoking women aged between 15 and 29 years having a first or second birth between 24 and 43 weeks gestation of a baby weighing over 500 g.

Table 1 shows the demographic characteristics and the frequency of adverse outcomes in the study group. Within the study group there were missing values for mode of delivery in 24 (<0.1%) and for maternal height in 8201 (7.4%). Several women who had live births experienced multiple adverse outcomes (preterm birth, emergency caesarean section, being small for gestational age, or neonatal death): 1942 had two adverse outcomes, 159 had three, and four women had all four outcomes.

We then compared the risk of adverse outcomes associated with maternal age 15-19 between first and second births using the Mantel-Haenszel test. This indicated that the risk of delivering a small for gestational age baby and of having an emergency caesarean section did not differ significantly by parity. However, when the risk of adverse obstetric outcomes associated with maternal age 15-19 was compared for first and second births, there were significant differences in the odds ratios of moderately premature birth (P = 0.01), extremely premature birth (P = 0.004), and stillbirth (P = 0.03) (table 2). Therefore, the multivariate analyses were stratified by parity.

Table 2 Univariate and multivariate logistic regression analysis of the risk of adverse perinatal outcomes among women aged 15 to 19 years of age compared with women aged 20-29 years (non-smokers)

	First births (n=63 565)		Second births (n=38 467)	
Outcomes	**Unadjusted odds ratio (95% CI)**	**Adjusted odds ratio† (95% CI)**	**Unadjusted odds ratio (95% CI)**	**Adjusted odds ratio† (95% CI)**
Birth weight <5th percentile	1.1 (1.0 to 1.2)	1.0 (0.9 to 1.1)	1.0 (0.7 to 1.5)	0.9 (0.6 to 1.4)
Delivery 24-32 weeks	1.2 (0.9 to 1.4)	1.1 (0.9 to 1.4)	2.7 (1.6 to 4.6)**	2.5 (1.5 to 4.3)***
Delivery 33-36 weeks	1.1 (1.0 to 1.2)*	1.1 (1.0 to 1.2)	1.7 (1.2 to 2.2)***	1.6 (1.2 to 2.1)**
Stillbirth	1.2 (0.8 to 1.7)	1.1 (0.8 to 1.6)	2.7 (1.4 to 5.4)**	2.6 (1.3 to 5.3)**
Neonatal death	0.8 (0.4 to 1.3)	0.8 (0.5 to 1.4)	1.2 (0.3 to 5.0)	1.0 (0.2 to 4.3)
Emergency caesarean section	0.6 (0.5 to 0.6)***	0.5 (0.5 to 0.6)***	0.8 (0.6 to 1.0)	0.7 (0.5 to 1.0)*

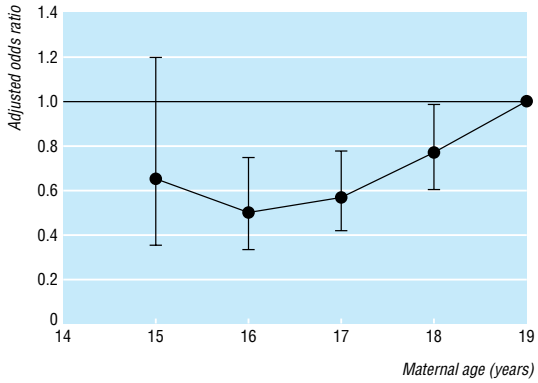
* P<0.05, **P<0.01, ***P<0.001.
†Adjusted for maternal height category, socioeconomic deprivation quintile, previous spontaneous and therapeutic abortions, and year (risks associated with second births also adjusted for previous perinatal death).

Among first births, women aged 15-19 years were not at increased risk of any of the six adverse outcomes studied compared with women aged 20-29 (table 2). However, among second births, mothers aged 15-19 were at significantly increased risk of moderately and extremely premature birth and stillbirth (table 2). The sizes of these associations were minimally attenuated by adjustment for socioeconomic deprivation quintile, height, year of delivery, previous abortions, and previous pregnancy resulting in a perinatal death. On multivariate analysis, emergency caesarean section was less likely among younger mothers at both first and second births. There were no significant interactions between maternal age at the time of delivery and socioeconomic deprivation quintile, height, year of delivery, or previous abortions for any of the outcomes for either first or second births.

When the risk of adverse outcome was compared within the age range 15-19, there was no significant variation in the risk of moderately or extremely premature birth, stillbirth, neonatal death, or delivery by emergency caesarean section. However, compared with 19 year old women, the risk of delivering a baby weighing less than the fifth percentile for gestational age was significantly lower among women aged 16 to 18 (figure).

The proportion of women who were current smokers but fulfilled the other inclusion criteria at the time of first attendance for antenatal care varied by age and parity. Among women aged 15-19, 12 862 (47.5%) of first births and 2148 (54.8%) of second births were to smokers, whereas among women aged 20-29, 28 875 (27.4%) of first births and 26 120 (34.1%) of second births were to smokers ($P < 0.001$).

When outcomes among 70 005 smokers were analysed, the risks associated with maternal age 15-19 again varied by parity. Among first births to smokers, there was a weak positive association between being aged 15-19 and moderately premature birth (table 3). Among second births to smokers, women aged 15-19 were at increased risk of moderately and extremely premature delivery and neonatal death. For both first and second births among smokers, being aged 15-19 was associated with a decreased risk of delivering a small for gestational age baby and being delivered by emergency caesarean section (table 3).



Adjusted odds ratios and 95% confidence intervals for delivering a small for gestational age baby (less than the 5th percentile for gestational age) associated with maternal age among first teenage births to non-smokers. Odds ratios were adjusted for maternal height category, socioeconomic deprivation quintile, previous spontaneous and therapeutic abortions, and year. The reference category was women giving birth aged 19

Discussion

Compared with older women, women who had a first birth during their teenage years were not at increased risk of any of the adverse outcomes studied and, indeed, were at significantly decreased risk of requiring emergency caesarean section. A previous study from the United States found that first teenage birth was independently associated with an increased risk of intrauterine growth restriction and of premature delivery,[1] and a Swedish study observed that first teenage births were at increased risk of perinatal death.[2] The main weakness of both studies was the failure to adjust for maternal smoking. Smoking is one of the strongest risk factors for adverse perinatal outcomes,[16] and previous studies have shown that pregnant teenagers are more likely to smoke than pregnant older women.[17 18] Our findings in non-smoking mothers suggest that the positive associations previously reported among first births might simply reflect inadequate adjustment for

Table 3 Adjusted odds ratios† (95% confidence intervals) for adverse outcomes in first and second births to women aged 15 to 19 compared with women aged 20-29 (smokers)

Outcomes	**First births (n=38 087)**	**Second births (n=25 992)**
Birth weight <5th percentile	0.8 (0.7 to 0.9)***	0.8 (0.6 to 1.0)*
Delivery 24-32 weeks	1.1 (0.9 to 1.4)	2.1 (1.5 to 2.9)***
Delivery 33-36 weeks	1.1 (1.0 to 1.3)**	1.5 (1.2 to 1.8)***
Stillbirth	0.9 (0.7 to 1.2)	0.5 (0.2 to 1.2)
Neonatal death	1.4 (0.9 to 2.1)	2.5 (1.3 to 4.8)**
Emergency caesarean section	0.5 (0.5 to 0.6)***	0.7 (0.6 to 0.9)**

*P<0.05, **P<0.01, ***P<0.001. †Odds ratios adjusted for maternal height category, socioeconomic deprivation quintile, previous spontaneous and therapeutic abortions, and year (risks associated with second births also adjusted for previous perinatal death).

confounding variables. Indeed, when outcomes were compared within the age range 15-19, women aged 16-18 had a decreased risk of intrauterine growth retardation, which is consistent with a previous population based study from the United States.[19]

By contrast, we found that second births among women aged between 15 and 19 years were associated with an almost threefold risk of extremely premature birth and stillbirth compared with women aged between 20 and 29 years (table 2). A similar pattern was observed among women who smoked. However, the Scottish mortality record database does not include information on the number of cigarettes smoked a day or the duration of smoking. Both of these might be expected to vary systematically with age. Since there is a dose-effect relation between smoking and adverse outcomes,[20] the findings among smokers should be interpreted with caution.

Study design and confounding factors

Previous longitudinal studies of first and second births among teenagers have produced conflicting results. Some have described consistently worse outcomes in the second birth,[6] others have reported better outcomes,[8] and others have described reduced risk of intrauterine growth retardation but increased risk of preterm birth.[9] The weakness of longitudinal studies is that, overall, first births are at a greater risk of intrauterine growth retardation, preterm birth, and stillbirth than subsequent births.[21 22] The cross sectional design of our study allows the normal protective effect of second birth to be taken into account.

The strength of the association between second teenage birth and adverse outcomes was virtually unaltered by adjusting for confounding variables. This suggests that there may be a causal relation between second teenage birth and these outcomes. Alternatively, the persistence of the association in the multivariate analysis might reflect incomplete adjustment for social deprivation. Although not perfect, deprivation scores based on postcode sector have been shown to be strongly associated with deprivation related diseases.[13] Furthermore, other methods of adjusting for deprivation used in previous studies have greater weaknesses. Some studies have used marital status as a measure of deprivation.[1 19] However, the relation between preterm delivery and marriage varies with maternal age.[10] Some studies used the woman's highest eventual educational attainment as an index of social deprivation.[17 23] It is difficult to distinguish between cause and effect with this indicator because childbearing in teenage years and complications of pregnancy may both adversely affect a woman's chance of completing higher education.

Conclusions

Our findings suggest a causal relation between second teenage birth and adverse pregnancy outcome. It is unlikely that the association can be explained by differences in the interval between pregnancies among teenage and older mothers since the associations observed were much greater than those previously reported for short intervals between pregnancies.[24] Furthermore, teenage mothers were not at increased risk of a small for gestational age baby, which is known to be more common after a short interval between pregnancies.[24] A biological cause could be confirmed or refuted only by access to more detailed socioeconomic information at the individual level. This would require prospective collection of data.

What is already known on this topic

Teenage mothers are more likely to deliver prematurely and to have a perinatal death than older women

Teenage mothers are also more likely to smoke, be having a first baby, and live in adverse social circumstances

What this study adds

Non-smoking women aged 15-19 having a first birth were not at increased risk of adverse obstetric outcomes compared with women aged 20-29 after potential confounding variables were adjusted for

Non-smoking women aged 15-19 having a second birth were at significantly increased risk of both premature delivery and stillbirth compared with women aged 20-29

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Maternal Obesity in Early Pregnancy and Risk of Spontaneous and Elective Preterm Deliveries: A Retrospective Cohort Study

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Objectives. We sought to determine the association between maternal body mass index and risk of preterm delivery.

Methods. We assessed 187 290 women in Scotland and estimated adjusted odds ratios for spontaneous and elective preterm deliveries among overweight, obese, and morbidly obese women relative to normal-weight women.

Results. Among nulliparous women, the risk of requiring an elective preterm delivery increased with increasing BMI, whereas the risk of spontaneous preterm labor decreased. Morbidly obese nulliparous women were at increased risk of all-cause preterm deliveries, neonatal death, and delivery of an infant weighing less than 1000 g who survived to 1 year of age (a proxy for severe long-term disability). By contrast, obesity and elective preterm delivery were only weakly associated among multiparous women.

Conclusions. Obese nulliparous women are at increased risk of elective preterm deliveries. This in turn leads to an increased risk of perinatal mortality and is likely to lead to increased risks of long-term disability among surviving offspring. (*Am J Public Health.* 2007;97:157–162. doi:10.2105/AJPH.2005.074294)

The association between maternal obesity and pregnancy outcomes is complex. Maternal obesity is known to be associated with increased rates of complications in late pregnancy such as stillbirth, cesarean delivery, gestational diabetes, and shoulder dystocia.[1–3] However, a low body mass index (BMI) is associated with an increased risk of preterm delivery, and some studies have shown that BMIs above the "normal" range are protective against spontaneous preterm births.[4–6] A large-scale retrospective cohort study demonstrated an interaction between BMI and parity: obese nulliparous women were at increased risk of extreme preterm deliveries and neonatal death, whereas obese multiparous women were not at increased risk of these outcomes.[7] The reasons for these complex patterns of association are unclear.

Preterm deliveries can occur as a result of preterm labor or can be elective procedures. Preeclampsia is the reason for elective preterm deliveries in more than 40% of cases.[4] It is well recognized that obese women are at increased risk of preeclampsia[8] and that nulliparous women are at higher risk of preeclampsia than multiparous women. We hypothesized that the higher background risk of preeclampsia among nulliparous women might lead to a stronger association between obesity and elective preterm deliveries and might therefore explain the association between obesity and extreme preterm deliveries among these women.

Our aim was to determine the association between maternal obesity in early pregnancy and risk of preterm delivery, with attention given to type of delivery (spontaneous vs elective), parity (nulliparous vs multiparous), and the most important negative consequences of prematurity. In assessing consequences of prematurity, we examined both neonatal death and long-term survival of extremely low-birthweight (ELBW) infants. Because ELBW infants have a 40% to 45% risk of severe neurodevelopmental delays in childhood,[9] we used ELBW as a proxy measure of severe long-term morbidity.

METHODS

Data Sources and Patient Selection

The Scottish Morbidity Record (SMR2) collects information on clinical and demographic characteristics and outcomes for all women discharged from Scottish maternity hospitals. The registry is subjected to regular quality assurance checks, and its data have been more than 99% complete since the late 1970s.[10] In addition, the Scottish Stillbirth and Infant Death Enquiry (SSBIDE), a national register, routinely classifies all perinatal deaths in Scotland.[11]

All women presenting for prenatal care in the west of Scotland are offered biochemical screening, using maternal serum α-fetoprotein and human chorionic gonadotrophin, to assess their risk of having a fetus affected by Down syndrome or a structural fetal abnormality.[12] Maternal weight is recorded at the time of sampling for biochemical screening to allow for weight correction of analytes. This process corrects levels of these proteins for the effect of maternal size and improves prediction of Down syndrome risk. The laboratory information management system of the West of Scotland Regional Genetics Service (Institute of Medical Genetics) contains a database including this maternal information along with biochemical screening results. The General Registrar's Office maintains computerized birth and death registration records.

We used a probability-based matching approach[13] with maternal identifiers to link information from the SMR2, the SSBIDE, the Institute of Medical Genetics prenatal screening database, and the General Registrar's Office database of birth certificates. We used offspring identifiers contained in the birth certificates used to link biochemical, pregnancy, and perinatal mortality data to the death certificate registry, allowing us to identify deaths among offspring. We excluded multiple births, stillbirths, and births occurring outside 22 to 43 weeks of gestation.

Births in the cohort assessed here occurred between November 1991 and December

2001. The cohort was defined as women who (1) had a record in the prenatal screening database (in which maternal weight was recorded), (2) could be linked to an SMR2 record, (3) had given birth to a singleton infant weighing more than 400 g, and (4) had given birth between 22 and 43 weeks of gestation. In addition to excluding stillbirths and perinatal deaths because of fetal abnormalities, we excluded women with missing data.

Definitions

Several outcomes were examined: preterm delivery, spontaneous preterm delivery, elective preterm delivery, neonatal death, delivery of an ELBW infant, delivery of an ELBW infant surviving to 1 year of age, and preeclampsia. A preterm delivery was defined as a birth occurring before 37 weeks of gestation, and a term delivery was defined as a birth occurring at or after 37 weeks of gestation. A spontaneous delivery was defined as a vaginal birth or a birth in which the woman was documented as having been in labor at the time of delivery but the labor was not documented as having been induced and was therefore presumed to be spontaneous. An elective delivery was defined as a birth in which the woman did not experience spontaneous labor (i.e., an induced vaginal birth or cesarean birth without a documented duration of labor).

Infants weighing between 400 g and 1000 g were classified as ELBW infants. Infants recorded as having been live born but not as having died (according to either the SSBIDE database or the General Registrar's Office death certificate database) in the first year of life were defined as surviving to 1 year of age. Preeclampsia was defined according to *International Classification of Diseases, Ninth Revision,* diagnostic codes in relation to postdelivery hospital discharge.[14]

Maternal age, parity, postcode of residence, and all outcome data were obtained solely from the SMR2. Data on maternal weight were obtained solely from the biochemical database. When possible, maternal height and smoking data were obtained from the SMR2; in instances in which this information was missing, the biochemical database was used. Smoking status (defined as the smoking status of the woman at the time of her first prenatal care visit) was determined as recorded in the patient's case record. Maternal age was classified as the age of the mother at the time of delivery. Maternal weight was defined as that recorded at the time of Down syndrome screening. BMI (defined as weight in kilograms divided by height in meters squared) was categorized as lean (less than 20 kg/m^2), normal (20–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (30–34.9 kg/m^2), and morbidly obese (35 kg/m^2 or above).

Postcode of residence was used to calculate Carstairs socioeconomic deprivation values (higher values indicated greater deprivation). Deprivation classifications were based on 1991 census data on car ownership, unemployment, overcrowding, and social class within postcode sectors containing, on average, approximately 1600 residents.[15] Since the early 1990s, gestational age has been confirmed (in the first half of pregnancy) using ultrasound in more than 95% of pregnancies in the United Kingdom.[16] Gestational age at birth was defined as completed weeks of gestation on the basis of the estimated date of delivery from each woman's clinical record, and standard national criteria exist for using menstrual and ultrasound data to estimate date of delivery. However, the specific means employed in a given record are not specified. Birthweight was categorized into gender-specific and gestational age–specific percentiles derived from the study cohort.

Statistical Analysis

We summarized continuous variables (age, height, and BMI) using medians and interquartile ranges, and we compared groups using the Kruskal–Wallis test. We made univariate comparisons of dichotomous data categories using the χ^2 test or the Fisher exact test. All continuous variables were categorized. The level of statistical significance was set at $P<.05$ (2-sided). Logistic regression analyses were used to calculate adjusted odds ratios (ORs).[17] Independent variables were BMI, age, height, deprivation category, smoking and marital status, and numbers of previous spontaneous early pregnancy losses and therapeutic abortions.

In analyses of birth outcomes for which the same women may have been included 2 or more times as a result of successive pregnancies, we estimated odds ratios using logistic regressions involving robust standard errors and clustering with maternal identifiers. We assessed interaction terms using the Wald test, as is appropriate for clustered data.[17] We used Stata Version 8.2 (Stata Corp, College Station, Tex) to conduct all statistical analyses.

RESULTS

The linked database contained 227 490 records of singleton births. Data for height were missing in 6270 cases (2.8%) and data for weight in 24 835 cases (10.9%); in 26 171 (11.5%) records, either or both of these values were missing. Among the remaining 201 319 records, we excluded 206 (0.1%) deaths because of fetal abnormalities and 893 (0.4%) stillbirths because of other causes, leaving 200 220 records. Of this total, birthweight data were missing or birthweights were less than 400 g in 57 cases (0.03%), and data on gestational age were missing or gestational age was outside 22 to 43 weeks in 62 cases (0.03%). Among the remaining 200 104 records, maternal age was missing in 3 cases (less than 0.01%), parity was missing in 23 cases (0.01%), deprivation category was missing in 347 cases (0.2%), and smoking status was missing in 12 487 cases (6.2%). Overall, 1 or more of these values were missing in 12 814 records (6.4%), leaving a study sample of 187 290 singleton births.

Table 1 presents maternal characteristics and basic outcome data broken down by term delivery, spontaneous preterm delivery, and elective preterm delivery. All of the factors assessed varied among these 3 categories, although the highly statistically significant differences in maternal height actually reflected very small differences in mean height and the 3 groups had identical median values. Among women with preterm deliveries, elective delivery was associated with a reduced risk of neonatal death (relative risk [RR]=0.72; 95% confidence interval [CI]=0.55, 0.94; $P=.02$) and no overall increased risk of delivering an ELBW infant (RR=1.06; 95% CI=0.88, 1.28; $P=.51$). However, it was associated with an increased risk of delivering an ELBW infant who survived to 1 year of age (RR=1.92; 95% CI=1.49, 2.47; $P<.001$).

In the case of all adverse outcomes, nulliparous women were at greater risk than

TABLE 1—Maternal Characteristics and Pregnancy Outcome Data, by Type of Delivery: Cohort of Scottish Women, 1991–2001

	Term Delivery (n = 177 098)	Preterm Spontaneous Delivery (n = 5835)	Preterm Elective Delivery (n = 4357)
Median age, y (IQR)	28 (24–32)	28 (23–31)	29 (25–32)
Median height, cm (IQR)	162 (158–167)	162 (157–166)	162 (157–166)
Median body mass index, kg/m^2 (IQR)	23.9 (21.7–27.0)	23.1 (20.8–26.2)	24.2 (21.7–27.7)
Deprivation category, no. (%)			
1 (least deprivation)	26 055 (14.7)	673 (11.5)	558 (12.8)
2	30 841 (17.4)	924 (15.8)	691 (15.9)
3	33 577 (19.0)	1023 (17.5)	787 (18.1)
4	36 703 (20.7)	1219 (20.9)	939 (21.6)
5 (most deprivation)	49 922 (28.2)	1996 (34.2)	1382 (31.7)
Smoking status, no. (%)			
Never	110 657 (62.4)	3044 (52.2)	2497 (57.3)
Former	13 428 (7.6)	374 (6.4)	302 (6.9)
Current	53 113 (30.0)	2417 (41.4)	1558 (35.8)
Marital status, no. (%)			
Married	106 841 (60.3)	3002 (51.5)	2423 (55.6)
Not married	70 257 (39.7)	2833 (48.6)	1934 (44.4)
Previous spontaneous losses, no. (%)			
0	142 618 (80.5)	4531 (77.7)	3293 (75.6)
≥1	34 480 (19.5)	1304 (22.4)	1064 (24.4)
Previous therapeutic abortions, no. (%)			
0	159 033 (89.8)	5081 (87.1)	3882 (89.1)
≥1	18 065 (10.2)	754 (12.9)	475 (10.9)
Parity status, no. (%)			
Nulliparous	79 421 (44.9)	3101 (53.1)	2179 (50.0)
Multiparous	97 677 (55.2)	2734 (46.9)	2178 (50.0)
Outcome of pregnancy, no. (%)			
Neonatal death	91 (0.1)	160 (2.8)	87 (2.0)
ELBW infant	0 (0.0)	265 (4.5)	210 (4.8)
ELBW infant surviving to 1 year	0 (0.0)	105 (1.8)	148 (3.4)
Preeclampsia	3 910 (2.2)	73 (1.3)	934 (21.4)

Note. IQR = interquartile range; ELBW = extremely low birthweight. All between-group differences were significant at $P \leq .001$ level (P values derived from the Kruskal–Wallis test, the χ^2 test, or the Fisher exact test as appropriate).

TABLE 2—Associations Between Parity and Pregnancy Outcomes: Cohort of Scottish Women, 1991–2001

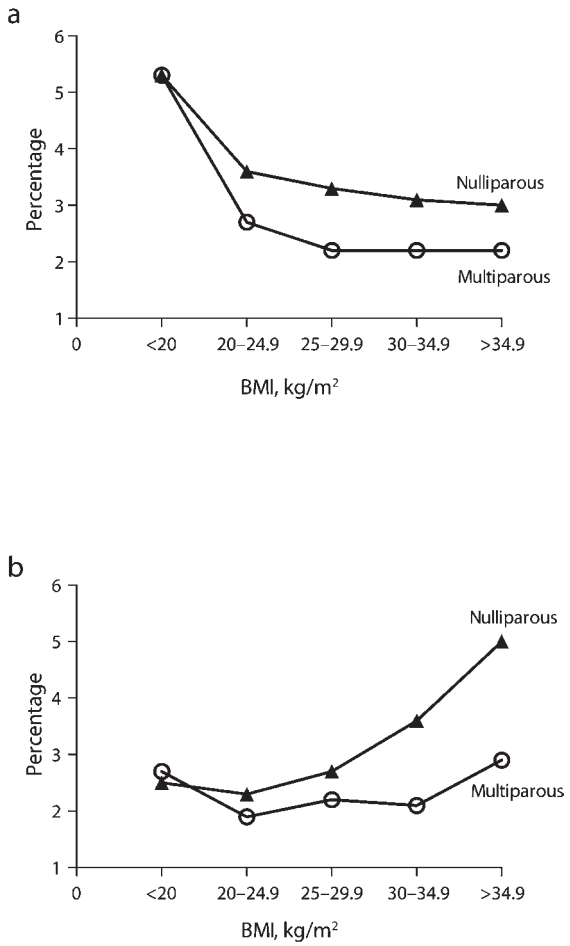
Outcome	Nulliparous (n = 84 701), No. (%)	Multiparous (n = 102 589), No. (%)	Odds Ratio[a] (95% Confidence Interval)
Overall preterm delivery	5280 (6.2)	4912 (4.8)	1.32 (1.27, 1.38)
Spontaneous preterm delivery	3101 (3.7)	2734 (2.7)	1.39 (1.32, 1.46)
Elective preterm delivery	2179 (2.6)	2178 (2.1)	1.22 (1.15, 1.29)
Neonatal death	203 (0.24)	135 (0.13)	1.82 (1.47, 2.27)
ELBW infant	298 (0.35)	177 (0.17)	2.04 (1.69, 2.46)
ELBW infant surviving to 1 year	162 (0.19)	91 (0.09)	2.16 (1.67, 2.80)
Preeclampsia	3272 (3.9)	1645 (1.6)	2.47 (2.32, 2.62)

Note. ELBW = extremely low birthweight. All outcomes were significant at $P < .001$.
[a]Estimated via logistic regressions clustered on maternal identifiers.

multiparous women (Table 2). There were statistically significant interactions between nulliparity and BMI for overall preterm deliveries, spontaneous preterm deliveries, and elective preterm deliveries (all Ps$<.001$). There was a nonsignificant trend toward interactions between BMI and nulliparity for preeclampsia ($P=.12$), delivery of an ELBW infant ($P=.06$), and neonatal death ($P=.23$). All further analyses of outcomes related to BMI involved stratification according to parity.

Risk of spontaneous preterm deliveries decreased with increasing BMI, and this protective effect of increasing BMI was stronger among multiparous women (Figure 1a; Tables 3 and 4). By contrast, risk of elective preterm deliveries increased with increasing BMI, and the association was stronger among nulliparous women (Figure 1b; Tables 3 and 4). Therefore, the net effect of BMI on key outcomes associated with prematurity differed according to parity status. Among nulliparous women, a BMI of 35 or above was associated with increased risks of overall preterm birth, neonatal death, and delivery of an ELBW infant still alive at 1 year of age (Table 3). By contrast, multiparous women with a BMI of 35 or above were not at increased risk of any of these outcomes (Table 4).

Among nulliparous women with a BMI of 35 or above who had had an elective preterm delivery, 40.2% (49 of 122) had been diagnosed with preeclampsia; the corresponding percentage for multiparous women was 18.0% (25 of 139; $P<.001$). Preeclampsia had been diagnosed in 4917 (2.6%) women in the cohort overall. Among nulliparous women, neither neonatal death (adjusted OR=1.23; 95% CI=0.57, 2.66; $P=.59$) nor delivery of an ELBW infant who survived until 1 year of age (adjusted OR=1.75; 95% CI=0.81, 3.77; $P=.15$) was associated with obesity (BMI of 35 or above) after adjustment for gestational age at delivery. In the same group, adjustment for preeclampsia resulted in attenuation of the associations between obesity and elective preterm delivery (adjusted OR=1.43; 95% CI=1.16, 1.75; $P=.001$), neonatal death (adjusted OR=2.43; 95% CI=1.35, 4.41; $P=.003$), and delivery of an ELBW infant who survived until 1 year of age (adjusted OR=2.52; 95% CI=1.40, 4.52; $P=.002$).



Note. The χ^2 test for trend was significant at $P < .001$ for all associations except elective preterm birth among multiparous women ($P = .12$).

FIGURE 1—Relationship between maternal body mass index (BMI) in early pregnancy in nulliparous and multiparous women and the proportion of spontaneous preterm births (a) and elective preterm births (b).

Of the original 227 490 records, 38 795 (17.1%) were excluded as a result of missing data for BMI, maternal age, parity, deprivation category, or smoking status. The rates of prematurity (5.84%) and low birthweight (5.65%) in this group were slightly higher than (but similar to) those of the study population. Among the group with missing data, 12 814 (33.0%) had a BMI recorded. We compared the relation between BMI (expressed as a continuous variable) and risk of prematurity in the group with missing data and the study population. The odds ratio for spontaneous preterm delivery associated with a 1-unit increase in BMI was 0.96 in both the group with missing data (95% CI=0.94, 0.98; $P<.001$) and the study population (95% CI=0.95, 0.96; $P<.001$). Odds ratios for elective preterm delivery were 1.03 (95% CI=1.01, 1.05; $P=.008$) in the group with missing data and 1.02 (95% CI=1.01, 1.04; $P<.001$) in the study population.

DISCUSSION

The main finding of this study is that obesity in early pregnancy is associated with an increased risk of elective preterm delivery. By contrast, obesity was associated with a decreased risk of spontaneous preterm delivery. The net effect of obesity depends, therefore, on the balance between these 2 outcomes. We found that morbidly obese nulliparous women had a more than 2-times greater risk of elective preterm delivery but only a 20% lower risk of spontaneous preterm delivery. The net effect was that these women were at increased risk of all-cause prematurity, neonatal death, and delivery of an ELBW infant who survived to 1 year of age. These data indicate that morbidly obese women who are planning to conceive should be encouraged to lose weight before their first birth and that rising rates of morbid obesity in the prepregnant population are likely to lead to increased rates of severe morbidity and neonatal death related to prematurity.

This is the first study, to our knowledge, to demonstrate an increased risk of elective preterm delivery among obese women. It has previously been shown that obese women are at lower risk of spontaneous preterm birth.[4–6] Two recent studies analyzing the relation between BMI and elective preterm delivery did not demonstrate an overall association.[4,18] The probable explanation for this apparent discrepancy is that data on nulliparous and multiparous women were pooled. In addition, both cohorts included fewer than 3000 women. The cohort used in our study was more than 50-times larger than the cohorts from these previous studies, and the highly statistically significant results indicate that the associations described are very unlikely to be chance findings.

Moreover, it is biologically plausible that such associations would be observed. Forty percent of morbidly obese nulliparous women who had had an elective preterm delivery had been diagnosed with preeclampsia, compared with only 2.6% of the remainder of the study population. Many previous studies have shown that preeclampsia risk increases with increasing BMI, and this effect is thought to be mediated by the cardiovascular influences of insulin resistance and dyslipidemia.[19] We found that increasing BMI was associated with comparably increased relative risks of preeclampsia in nulliparous and multiparous women (Tables 3 and 4). However, overall rates of preeclampsia were 3.9% and 1.6%, respectively, in these 2 groups (Table 2). The stronger association

TABLE 3—Body Mass Index (BMI) in Early Pregnancy and Outcome of First Pregnancy: Cohort of Scottish Women (n = 84 701), 1991–2001

	BMI < 20		BMI 20–24.9[b]	BMI 25–29.9		BMI 30–34.9		BMI ≥ 35	
	No. (%)	OR[a] (95% CI)	No. (%)	No. (%)	OR[a] (95% CI)	No. (%)	OR[a] (95% CI)	No. (%)	OR[a] (95% CI)
Overall preterm delivery	750 (7.8)	1.36 (1.25, 1.48)	2697 (5.9)	1234 (5.9)	0.99 (0.93, 1.07)	404 (6.7)	1.12 (1.00, 1.25)	195 (8.0)	1.34 (1.15, 1.56)
Spontaneous preterm delivery	507 (5.3)	1.46 (1.32, 1.62)	1654 (3.6)	678 (3.3)	0.89 (0.82, 0.98)	189 (3.1)	0.85 (0.73, 0.99)	73 (3.0)	0.81 (0.64, 1.03)
Elective preterm delivery	243 (2.5)	1.16 (1.00, 1.34)	1043 (2.3)	556 (2.7)	1.15 (1.03, 1.27)	215 (3.6)	1.52 (1.31, 1.77)	122 (5.0)	2.13 (1.75, 2.58)
Neonatal death	31 (0.3)	1.67 (1.10, 2.54)	88 (0.2)	54 (0.3)	1.35 (0.96, 1.90)	17 (0.3)	1.46 (0.86, 2.46)	13 (0.5)	2.77 (1.54, 4.99)
ELBW infant	40 (0.4)	1.35 (0.94, 1.93)	135 (0.3)	73 (0.4)	1.20 (0.90, 1.60)	26 (0.4)	1.47 (0.96, 2.24)	24 (1.0)	3.31 (2.13, 5.14)
ELBW infant surviving to 1 year	18 (0.2)	1.02 (0.61, 1.72)	79 (0.2)	36 (0.2)	1.02 (0.69, 1.52)	15 (0.3)	1.47 (0.84, 2.56)	14 (0.6)	3.36 (1.89, 5.98)
Preeclampsia	208 (2.2)	0.79 (0.68, 0.91)	1350 (3.0)	1025 (4.9)	1.68 (1.54, 1.82)	446 (7.4)	2.57 (2.30, 2.88)	243 (10.0)	3.60 (3.12, 4.17)

Note. OR = odds ratio; CI = confidence interval; ELBW = extremely low birthweight. The total numbers of births across the 5 BMI categories were 9573 (11.3%), 45 812 (54.1%), 20 819 (24.6%), 6060 (7.2%), and 2437 (2.9%), respectively.
[a]Adjusted for maternal age, height, deprivation category, smoking and marital status, and number of previous spontaneous early pregnancy losses and therapeutic abortions and referent to women with a BMI of 20–24.9.
[b]Reference group.

TABLE 4—Body Mass Index (BMI) in Early Pregnancy and Outcomes of Multiparous Women: Cohort of Scottish Women (n = 102 589), 1991–2001

	BMI < 20		BMI 20–24.9[b]	BMI 25–29.9		BMI 30–34.9		BMI ≥ 35	
	No. (%)	OR[a] (95% CI)	No. (%)	No. (%)	OR[a] (95% CI)	No. (%)	OR[a] (95% CI)	No. (%)	OR[a] (95% CI)
Overall preterm delivery	675 (8.0)	1.70 (1.55, 1.86)	2280 (4.6)	1273 (4.3)	0.93 (0.87, 1.00)	438 (4.3)	0.91 (0.81, 1.01)	246 (5.1)	1.09 (0.95, 1.26)
Spontaneous preterm delivery	447 (5.3)	1.87 (1.67, 2.10)	1320 (2.7)	639 (2.2)	0.82 (0.74, 0.90)	221 (2.2)	0.80 (0.69, 0.92)	107 (2.2)	0.83 (0.67, 1.01)
Elective preterm delivery	228 (2.7)	1.37 (1.18, 1.60)	960 (1.9)	634 (2.2)	1.10 (0.99, 1.22)	217 (2.1)	1.06 (0.91, 1.24)	139 (2.9)	1.45 (1.21, 1.75)
Neonatal death	17 (0.2)	1.49 (0.86, 2.58)	58 (0.1)	39 (0.1)	1.18 (0.78, 1.77)	17 (0.2)	1.44 (0.84, 2.47)	4 (0.1)	0.73 (0.27, 2.01)
ELBW infant	22 (0.3)	1.61 (0.99, 2.62)	70 (0.1)	54 (0.2)	1.33 (0.93, 1.90)	24 (0.2)	1.65 (1.03, 2.64)	7 (0.1)	1.04 (0.48, 2.26)
ELBW infant surviving to 1 year	7 (0.1)	0.96 (0.43, 2.14)	41 (0.1)	24 (0.1)	0.96 (0.58, 1.59)	13 (0.1)	1.46 (0.78, 2.76)	6 (0.1)	1.45 (0.61, 3.44)
Preeclampsia	62 (0.7)	0.77 (0.59, 1.01)	515 (1.0)	531 (1.8)	1.72 (1.52, 1.94)	307 (3.0)	2.89 (2.50, 3.34)	230 (4.7)	4.57 (3.88, 5.38)

Note. OR = odds ratio; CI = confidence interval; ELBW = extremely low birthweight. The total numbers of births in the 5 BMI categories were 8395 (8.2%), 49 704 (48.5%), 29 395 (28.7%), 10 245 (10.0%), and 4850 (4.7%), respectively.
[a]Adjusted for maternal age, height, deprivation category, smoking and marital status, and number of previous spontaneous early pregnancy losses and therapeutic abortions and referent to women with a BMI of 20–24.9; estimated via logistic regressions clustered on maternal identifiers.
[b]Reference group.

between obesity and elective preterm delivery among nulliparous women was probably because of these women's higher background risk of preeclampsia.

Areas of Future Study

Among nulliparous women, obesity was not associated with risk of either neonatal death or delivery of an ELBW infant who survived to 1 year of age after adjustment for gestational age at delivery. This finding suggests that the association between obesity and these clinically important outcomes is mediated by obesity's association with prematurity. Adjustment for preeclampsia resulted in marked, but not complete, attenuation of the associations observed between morbid obesity and elective preterm delivery, neonatal death, and delivery of an ELBW infant who survived to 1 year of age. The persistence of positive associations between morbid obesity and these outcomes after adjustment for preeclampsia may reflect errors in preeclampsia diagnoses, or, alternatively, other complications of pregnancy may be associated with obesity and may lead to an increased risk of these outcomes. This issue requires further study.

Many studies addressing factors associated with preterm labor lack either the data or the statistical power necessary to address the important consequences of prematurity. In addition to neonatal deaths, the record linkages used in the present study allowed us to identify long-term survivors whose birthweights were below 1000 g. Follow-up studies of these survivors in childhood demonstrated that 40% to 45% had severe neurodevelopmental impairments,[9] as mentioned earlier,

and this finding led to our designation of ELBW as a proxy for severe long-term morbidity. We demonstrated that morbidly obese nulliparous women were at increased risk of both perinatal mortality and perinatal outcomes likely to lead to severe morbidity. This underlines the clinical significance of the association with preterm delivery described here. Ideally, future studies will analyze risks of long-term severe morbidity directly rather than use a proxy measure.

The overall rate of prematurity in our study was relatively low, at 5.4%. This result is consistent with the findings of other European studies.[7] By contrast, previous US studies have reported overall prematurity rates of 10% to 15%.[4,18] However, these cohorts included 40% to 60% African American women and involved similarly high percentages of women who were unmarried or living in households with incomes below the poverty level. The present data are applicable to a relatively low-risk population. However, as observed in our comparisons of nulliparous and multiparous women, associations of birth outcomes with BMI depend on the relative balance of background risks of spontaneous and elective preterm deliveries. Among nulliparous women at high risk of spontaneous preterm delivery, an increased BMI may be associated with a reduced overall risk of prematurity. Again, this is an issue for further study.

Limitations

As is the case with any large-scale study in which routinely collected data are used, our study involved a number of weaknesses. The SMR2 database does not routinely collect data on maternal weight, and we were able to obtain this information only by linking records to a prenatal screening database. As a result, the population studied was selected on the basis of women having accepted screening for congenital abnormalities. However, 81% of women in the west of Scotland undergo serum screening,[12] and thus, the study included most women seeking prenatal care.

Because maternal weight was used to adjust prenatal screening results, the value recorded was that from early pregnancy. As a result, we lacked data on prepregnancy weight and weight gain during pregnancy. However, our primary aim was to determine the probable effects of rising obesity rates in the general population on negative consequences of prematurity. BMI in early pregnancy is a good proxy for prepregnancy BMI, given that relatively little weight gain will have occurred between these intervals. Finally, approximately 17% of eligible women were excluded because of missing data, raising the possibility that our study population was biased. However, associations between BMI and spontaneous and elective preterm deliveries were similar when women with missing data on other maternal variables were compared with the study population.

Our results show that maternal obesity is associated with an increased risk of elective preterm delivery. The association is stronger among nulliparous women, probably as a result of their increased risk of preeclampsia, and here it led to an overall association between obesity and preterm birth in this group. Obese nulliparous women are at increased risk of the serious negative consequences associated with preterm births. ■

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Contributors

G.C.S. Smith originated the study and drafted the article. G.C.S. Smith and I. Shah analyzed and interpreted the data. All of the authors contributed to critical revisions of the article.

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Human Participant Protection

The record linkage for this study was approved by the Privacy Advisory Committee, National Health Service for Scotland.

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The Effect of Delaying Childbirth on Primary Cesarean Section Rates

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Abbreviations: CI, confidence interval

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ABSTRACT

Background

The relationship between population trends in delaying childbirth and rising rates of primary cesarean delivery is unclear. The aims of the present study were (1) to characterize the association between maternal age and the outcome of labor, (2) to determine the proportion of the increase in primary cesarean rates that could be attributed to changes in maternal age distribution, and (3) to determine whether the contractility of uterine smooth muscle (myometrium) varied with maternal age.

Methods and Findings

We utilized nationally collected data from Scotland, from 1980 to 2005, and modeled the risk of emergency cesarean section among women delivering a liveborn infant in a cephalic presentation at term. We also studied isolated myometrial strips obtained from 62 women attending for planned cesarean delivery in Cambridge, England, from 2005 to 2007. Among 583,843 eligible nulliparous women, there was a linear increase in the log odds of cesarean delivery with advancing maternal age from 16 y upwards, and this increase was unaffected by adjustment for a range of maternal characteristics (adjusted odds ratio for a 5-y increase 1.49, 95% confidence interval [CI] 1.48–1.51). Increasing maternal age was also associated with a longer duration of labor (0.49 h longer for a 5-y increase in age, 95% CI 0.46–0.51) and an increased risk of operative vaginal birth (adjusted odds ratio for a 5-y increase 1.49, 95% CI 1.48–1.50). Over the period from 1980 to 2005, the cesarean delivery rate among nulliparous women more than doubled and the proportion of women aged 30–34 y increased 3-fold, the proportion aged 35–39 y increased 7-fold, and the proportion aged $\geq$40 y increased 10-fold. Modeling indicated that if the age distribution had stayed the same over the period of study, 38% of the additional cesarean deliveries would have been avoided. Similar associations were observed in multiparous women. When studied in vitro, increasing maternal age was associated with reduced spontaneous activity and increased likelihood of multiphasic spontaneous myometrial contractions.

Conclusions

Delaying childbirth has significantly contributed to rising rates of intrapartum primary cesarean delivery. The association between increasing maternal age and the risk of intrapartum cesarean delivery is likely to have a biological basis.

The Editors' Summary of this article follows the references.

Introduction

Rising rates of cesarean delivery are a major public health concern. In recent years, the proportion of women attempting vaginal birth after cesarean (VBAC) has declined [1]. Hence, rates of primary cesarean delivery will become an increasingly important determinant of overall cesarean rates. Many studies have demonstrated that rates of primary cesarean delivery have risen throughout the developed world in recent years [2–4], and the reasons for this are unclear. Some of the increase can be explained by changes in obstetric practice, such as the trend toward elective cesarean delivery when the infant presents by the breech [5]. However, the rise in primary cesarean rates has coincided with a trend of increasing average maternal age at the time of first birth. Previous studies have demonstrated that the risk of cesarean delivery increases with advancing maternal age. However, it is currently unclear whether the association reflects a biological effect of advanced age [6,7] or is a consequence of physician and maternal preference [8,9]. The contribution of delaying childbirth to recent rises in cesarean delivery rates is also unclear [3,10–12]. The aims of the present study were (1) to characterize the association between maternal age and the outcome of labor, (2) to determine the proportion of the increase in primary cesarean rates that could be attributed to changes in maternal age distribution, and (3) to determine whether the contractility of uterine smooth muscle (myometrium) varied with maternal age.

Methods

Population

The Scottish Morbidity Record (SMR2) collects information on clinical and demographic characteristics and outcomes for all patients discharged from Scottish maternity hospitals. The register has been greater than 99% complete since the late 1970s [13]. A quality assurance analysis in 1996–1997 compared 1,414 records with the clinical notes. This analysis demonstrated that the register was free from significant errors in greater than 98% of records in all the specific fields used in the present analysis, with the exception of postcode (94.0%), height (96.2%), estimated gestation (94.4%), and method of induction of labor (93.6%). The mode of delivery field was 99.2% accurate. The main focus of the present study was nulliparous women having a singleton birth in Scotland between 1980 and 2005, inclusive. The exclusion criteria were preterm birth, stillbirth, delivery by prelabor cesarean, noncephalic presentation of the infant, and records with missing data on key variables. We repeated the analyses in women who had one or two previous vaginal births.

Definitions

Emergency intrapartum cesarean delivery was defined as any nonplanned cesarean delivery with a documented duration of labor. Operative vaginal delivery was defined as birth using the assistance of obstetric forceps or vacuum (ventouse). Maternal age was defined as the age of the mother at the time of birth. Maternal height was measured in centimeters, and the value used was that documented in each

Table 1. Demographic and Outcome Characteristics of Eligible Nulliparous in Relation to Mode of Delivery

Characteristic	Category/Units	Vaginal Birth[a] ($n = 518,787$)	Cesarean Section[a] ($n = 65,056$)	p-Value[b]
Age (y)	Median (IQR)	24 (21–28)	27 (23–31)	<0.001
Height (cm)	Median (IQR)	162 (158–167)	160 (156–165)	<0.001
	Missing	58,239 (11.2)	8,737 (13.4)	<0.001
Deprivation category	1 (least deprived)	26,311 (5.1)	3,696 (5.7)	<0.001
	2	66,416 (12.8)	8,711 (13.4)	—
	3	102,152 (19.7)	12,988 (20.0)	—
	4	125,015 (24.1)	15,994 (24.6)	—
	5	80,840 (15.6)	10,142 (15.6)	—
	6	61,787 (11.9)	7,809 (12.0)	—
	7 (most deprived)	42,293 (8.2)	4,944 (7.6)	—
	Missing	13,973 (2.7)	772 (1.2)	<0.001
Gestational age (wk)	37	23,111 (4.5)	2,369 (3.6)	<0.001
	38	54,602 (10.5)	5,164 (7.9)	—
	39	103,701 (20.0)	9.495 (14.6)	—
	40	189,502 (36.5)	19,952 (30.7)	—
	41	121,778 (23.5)	21,561 (33.1)	—
	42	25,324 (4.9)	6,278 (9.7)	—
	43	769 (0.2)	237 (0.4)	—
Onset of labor	Spontaneous	378,390 (72.9)	31,313 (48.1)	<0.001
	Induced	140,397 (27.1)	33,743 (51.9)	—
Sex	Male	262,114 (50.5)	37,408 (57.5)	<0.001
	Female	256,655 (49.5)	27,645 (42.5)	—
	Missing	18 (<0.1)	3 (<0.1)	0.5
Birth weight percentile	Median (IQR)	43 (21–67)	56 (26–81)	<0.001
	Missing	221 (<0.1)	29 (<0.1)	0.76

[a]Data summarized as n (%) unless stated otherwise.
[b]Mann-Whitney U test, the χ^2 test or χ^2 test for trend, as appropriate.
IQR, interquartile range.
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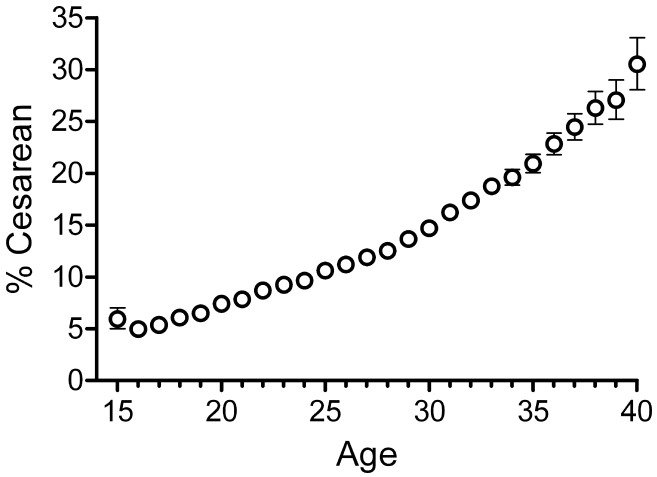

Figure 1. Maternal Age and the Risk of Cesarean Delivery

Proportion of women being delivered by emergency intrapartum cesarean section in relation to age of mother (n = 583,847). Bars are binomial 95% CIs.

doi:10.1371/journal.pmed.0050144.g001

woman's clinical record. Gestational age at birth was defined as completed weeks of gestation on the basis of the estimated date of delivery in each woman's clinical record. Gestational age has been confirmed by ultrasound in the first half of pregnancy in more than 95% of women in the United Kingdom since the early 1990s. Preterm birth was defined as delivery before 37 completed wk of gestation. Birth weight was converted into percentiles for week of gestation and these were calculated separately for males and females.

Myometrial Contractility Studies

Biopsies of the uterus were obtained from nonlaboring patients, undergoing routine elective cesarean delivery at the Rosie Hospital, Cambridge, UK at 38–40 wk pregnancy. Most of the cesarean deliveries were performed for breech presentation or previous cesarean delivery. The procedure was approved by the Cambridge Local Research Ethics Committee 2, and all patients gave written informed consent to participate. Following delivery of the infant, placenta, and membranes, specimens were taken from the upper edge of the lower segment uterine incision and placed into ice-cold Krebs solution. Samples were stored in Krebs solution at 4 °C (with EDTA-free protease inhibitors) overnight and then cleared of serosa, fibrous or damaged tissue, and any visible blood vessels. The muscle tissue was dissected into longitudinal strips (following the plane of the muscle fibers) of approximately 1–3 mm × 8–12 mm. Tissue strips were mounted in an organ bath (Radnoti) filled with Krebs solution at 37 °C and gassed with 95% O_2 and 5% CO_2. The Krebs solution was changed at 15-min intervals. Myometrial strips were secured by thread to an isometric tension transducer (MLT0201/RAD, ADInstruments), and the signal amplified and stored in a commercial data acquisition system (Octal ML228 Bridge Amplifier; Chart, version 5.2.2, both ADInstruments). Strips were stretched to 2 g tension, which was re-set 30 min later. After a total period of 90 min of equilibration following initial set up, a standardized contraction in response to 50 mM KCl was obtained.

Statistics

Continuous variables were summarized by the median and interquartile range, and groups were compared using the Mann-Whitney U test. Dichotomous data were compared between groups using the χ^2 test or χ^2 test for trend, as appropriate. All p-values were two sided, and statistical significance was assumed at $p < 0.05$. In the analysis of cesarean section risk, the numerator was all intrapartum cesarean deliveries and the denominator was all births. In the analysis of the risk of operative vaginal delivery, the numerator was all forceps or vacuum deliveries and the denominator was all vaginal births. Adjusted odds ratios were obtained using logistic regression using age as a continuous variable and with all other variables categorized [14]. Women with missing data on covariates were excluded from the multivariate analysis. The association between maternal age and cesarean section risk was compared between the whole population and those with complete data on covariates. Linearity of age in logistic models was tested using fractional polynomials, and interactions were tested using the likelihood ratio test.

In order to estimate the effect of changes in the age distribution on cesarean rates, we performed an analysis where we estimated what the annual cesarean section rate would have been had the age distribution of mothers remained unchanged over the period from 1980 to 2005. We did this by calculating a new age variable to represent the age of each mother had the age distribution remained constant over the period from 1980

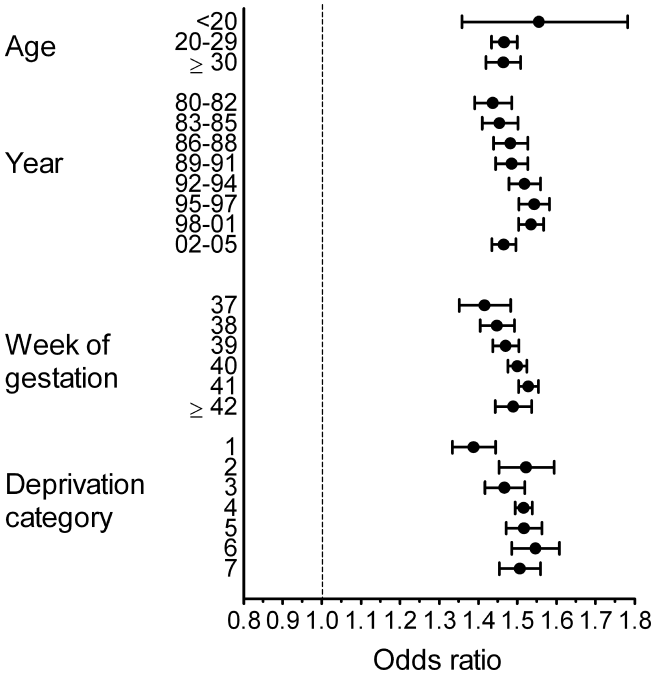

Figure 2. Stratified Analysis of Maternal Age and Risk of Cesarean Section

Adjusted odds ratio for a 5-y increase in maternal age (bars are 95% CIs) stratified by maternal age, year of delivery, week of gestation, and deprivation category. Interactions were statistically significant for year of delivery ($p < 0.001$), week of gestation ($p = 0.002$), and deprivation category ($p = 0.002$) using the likelihood ratio test. Odds ratios are adjusted for maternal age, height, deprivation category, onset of labor, week of gestation, sex, birth weight percentile of infant, and year. The vertical dashed line indicates unity.

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Table 2. Unadjusted and Adjusted Odds Ratios for Intrapartum Cesarean Section among Nulliparous Women, Scotland 1980–2005

Characteristic	Category/Units	Unadjusted Odds Ratio	95% CI	*p*-Value	Adjusted Odds Ratio[a]	95% CI	*p*-Value
Age	Per 5 y	1.49	1.48–1.51	<0.001	1.49	1.48–1.51	<0.001
Onset of labor[b]	Induced	2.93	2.88–2.98	<0.001	2.48	2.43–2.53	<0.001
Week of gestation	37	0.96	0.92–1.01	0.14	0.82	0.78–0.86	<0.001
	38	0.90	0.87–0.93	<0.001	0.81	0.78–0.84	<0.001
	39	0.87	0.84–0.89	<0.001	0.85	0.82–0.87	<0.001
	40	(1.00)[c]	—	—	(1.00)[c]	—	—
	41	1.64	1.61–1.68	<0.001	1.35	1.32–1.38	<0.001
	≥42	2.35	2.28–2.43	<0.001	1.79	1.73–1.86	<0.001
Deprivation category	1 (least deprived)	1.08	1.04–1.13	<0.001	0.91	0.87–0.96	<0.001
	2	1.03	1.00–1.06	0.04	0.91	0.88–0.94	<0.001
	3	1.00	0.97–1.03	0.98	0.94	0.91–0.97	<0.001
	4	(1.00)[c]	—	—	(1.00)[c]	—	—
	5	0.99	0.96–1.01	0.33	1.04	1.01–1.07	0.01
	6	1.02	0.99–1.05	0.18	1.06	1.02–1.09	0.001
	7 (most deprived)	0.94	0.91–0.98	0.002	1.08	1.04–1.12	<0.001
Height (cm)	<155	2.47	2.40–2.55	<0.001	3.98	3.85–4.11	<0.001
	155–159	1.59	1.54–1.63	<0.001	2.19	2.13–2.26	<0.001
	160–164	1.22	1.19–1.25	<0.001	1.44	1.41–1.49	<0.001
	165–169	(1.00)[c]	—	—	(1.00)[c]	—	—
	170–174	0.86	0.83–0.90	<0.001	0.73	0.70–0.76	<0.001
	≥175	0.75	0.71–0.80	<0.001	0.53	0.49–0.57	<0.001
Sex[b]	Male	1.33	1.31–1.36	<0.001	1.39	1.37–1.42	<0.001
Birth weight percentile	1–5	1.27	1.22–1.31	<0.001	1.03	0.99–1.07	0.17
	6–10	0.86	0.82–0.90	<0.001	0.74	0.70–0.77	<0.001
	11–20	0.78	0.76–0.81	<0.001	0.71	0.69–0.74	<0.001
	21–80	(1.00)[c]	—	—	(1.00)[c]	—	—
	81–90	1.69	1.64–1.74	<0.001	1.88	1.82–1.93	<0.001
	91–95	2.26	2.18–2.35	<0.001	2.59	2.49–2.70	<0.001
	96–100	3.60	3.47–3.74	<0.001	4.28	4.11–4.46	<0.001

Analysis confined to women with complete data.

[a]Adjusted for maternal age, height, deprivation category, onset of labor, week of gestation, sex, birth weight percentile of infant, and year (unadjusted and adjusted odds ratios for year are presented in Table 3).

[b]Referent category for onset of labor was spontaneous and for sex was female.

[c]Referent category.

OR, odds ratio.

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to 2005. For example, a woman having a first birth in 2003 who was on the 76th percentile of age for 2003 would have a new age variable equivalent to the 76th percentile of age in 1980. The logistic regression equations fitted for the observed values of age were then used to derive an estimated probability of cesarean delivery using the new age variable. The mean probability for all women in a given year was then taken as the estimated rate of cesarean delivery had the maternal age distribution stayed the same as in 1980.

All recording of spontaneous contractile activity was performed blind to the mother's age. Contractile activity was quantified by integrating the area under the tension curve. Spontaneous activity was quantified as the ratio of the area under the curve for the 15 min prior to addition of potassium to the area under the curve for the 7 min in the presence of 50 mM potassium. The ratio was log transformed to normalize its distribution and the $\log_{10}$ of the ratio was called the "contraction unit." A multiphasic contraction was defined as having two or more distinct peaks prior to the return to baseline. In order to maximize the statistical power of the analysis, we studied multiple strips from the same women. However, most regression methods assume that observations are independent and our approach necessitated that we use regression methods that could account for the nonindependence of different strips from the same woman. Hence, analysis of the association between maternal age and spontaneous contractile activity was performed using a linear mixed model with a random effect at the maternal level, to account for the nonindependence of different strips obtained from the same woman. The probability of multiphasic contractions was assessed using logistic regression, and the frequency of spontaneous contractions prior to potassium was assessed using Poisson regression. Both regression methods employed generalized estimating equations and were clustered on the maternal identifier to account for nonindependence. All analyses were performed using Stata, version 10 (Stata Corporation).

Results

Study Cohort

There were 1,531,261 available records from the Scottish Morbidity Record over the period from 1980 to 2005. Among these, there were 8,111 stillbirths (0.5%), 72,119 noncephalic births (4.7%), 851,486 multiparous women (55.6%), 89,964 preterm births (5.9%), 91,904 elective cesarean deliveries (6.0%), 40,224 prelabor emergency cesarean deliveries (2.6%), 510 with missing data on mode of delivery (<0.1%), and 478 with missing data on method of induction of labor (<0.1%). A total of 947,414 women had one or more of these exclusions

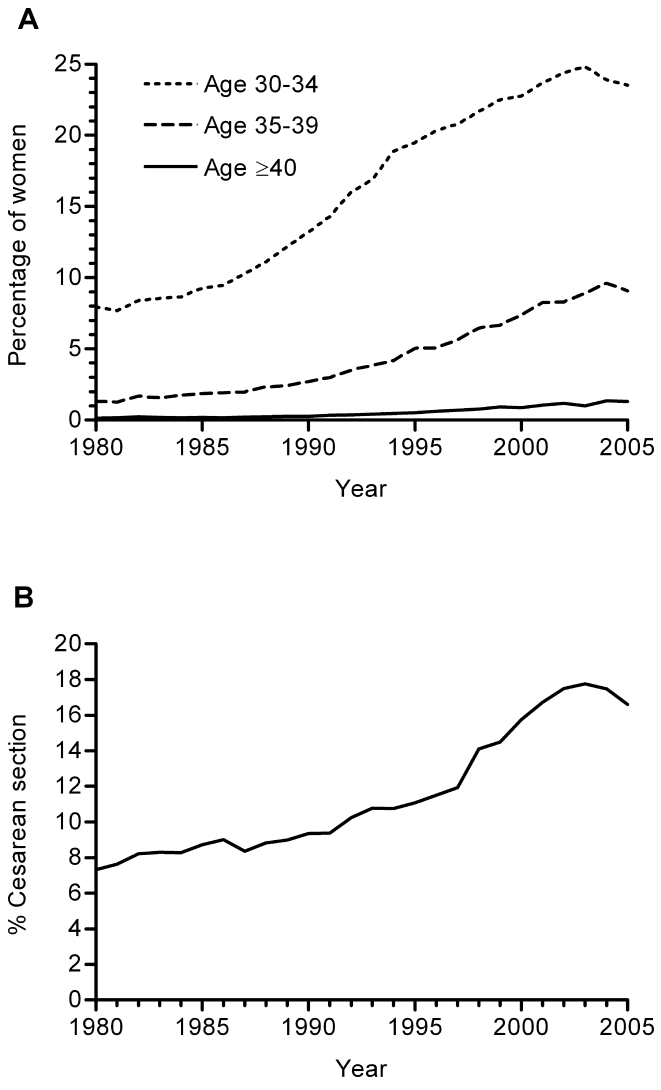

Figure 3. Time Trends in Maternal Age Distribution and Cesarean Section Rates in Scotland between 1980 and 2005

(A) Proportion of women per year delivering within the age ranges 30–34, 35–39, and ≥40 y.

(B) Proportion of women per year delivered by emergency cesarean section.

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leaving a main study group of 583,847 nulliparous women delivering a liveborn infant at term in a cephalic presentation, which was 86% of all nulliparous women in the database. The characteristics of the study group are described in relation to whether the women were delivered by emergency cesarean section (Table 1). This latter group was older, shorter, and likely to live in an area of low socioeconomic deprivation. They delivered at later weeks of gestation, were more likely to have an induced labor, more likely to deliver a male infant, and the birth weight percentile of their infants was higher. A total of 81,407 (13.9%) records had missing data for one or more of height, birth weight percentile, or deprivation category.

Age and Cesarean Risk

The risk of cesarean delivery increased progressively from 16 y of age (Figure 1). The proportional increase in risk for a 5-y increase in age was similar comparing women <20 y, those aged 20–29 y, and those aged ≥30 y (Figure 2). The linearity of the relationship between age and risk of cesarean was further assessed using fractional polynomials. None of eight polynomial expressions tested provided a better fit than a simple linear model. The odds ratio for a 5-y increase in age was 1.51 (95% confidence interval [CI], 1.50–1.53) and was 1.49 (95% CI, 1.48–1.51) when confined to records with no missing data. Adjusting for a series of maternal and obstetric characteristics (Table 2) was without effect. When the covariate data were expressed continuously and nonlinear terms selected using multiple fractional polynomials, the odds ratio for a 5-y increase in age was 1.52 (95% CI, 1.51–1.54), which was very similar to the odds ratio obtained when the continuous variables were categorized. There were statistically significant interactions between age and week of gestation, socioeconomic deprivation, and year (all $p < 0.01$), and these are illustrated in a stratified analysis (Figure 2). This analysis demonstrates that the degree of variation between strata of these variables was relatively minor, and the statistical significance of the interaction terms reflects the large sample size.

Information on body mass index was available for a previously described subset of the cohort [15]. Among the 72,137 of these women who fulfilled the inclusion criteria for the main cohort and who had complete data, the odds ratio for a 5-y increase in age was 1.52 (95% CI, 1.49–1.55) adjusted for the same characteristics as the present analysis and was 1.48 (95% CI, 1.44–1.51) when also adjusted for body mass index. The database employed lacked details on the indication for cesarean delivery. However, we performed a subgroup analysis where we compared the strength of association between maternal age and the risk of emergency intrapartum cesarean section in relation to whether the baby had a 5-min Apgar score of <7. The adjusted odds ratio for a 5-y increase in maternal age was 1.52 (95% CI, 1.50–1.54) for cesarean delivery with a normal Apgar score and 1.30 (95% CI, 1.22–1.38) for cesarean delivery with a low Apgar score.

Population Trends, 1980–2005

Over the period from 1980 to 2005, the proportion of women having their first birth aged 30–34 y increased approximately 3-fold, the proportion aged 35–39 y increased approximately 7-fold, and the proportion aged ≥40 y increased approximately 10-fold (Figure 3A). Over the same period of time, the rate of cesarean delivery more than doubled (Figure 3B). Adjustment for age significantly reduced the strength of the association between year of delivery and the risk of cesarean delivery, both when analyzing year alone and when included with all other covariates (Table 3). Over the period 1981–2005, there were 16,548 more cesarean deliveries than would have occurred had the rate stayed the same as it was in 1980. Of these additional procedures, it was estimated that 37.6% would not have been performed had the maternal age distribution remained constant. The figure was very similar when adjusted for all other maternal characteristics (37.8%) and all other maternal characteristics plus statistically significant interactions (38.7%).

Duration of Labor and Operative Vaginal Birth

The average duration of spontaneous labor progressively increased from aged 16 y upwards (Figure 4A). The

Table 3. Effect of Adjusting for Age on the Association between Year of Delivery and the Risk of Emergency Intrapartum Cesarean Section among Nulliparous Women, Scotland 1980–2005

Year	Unadjusted			Adjusted for Age Alone			Adjusted for All Factors Except Age[a]			Fully Adjusted[b]		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
1980–1982	(1.00)[c]	—	—	(1.00)[c]	—	—	(1.00)[c]	—	—	(1.00)[c]	—	—
1983–1985	1.09	1.05–1.14	<0.001	1.07	1.03–1.12	0.001	1.19	1.14–1.24	<0.001	1.16	1.11–1.21	<0.001
1986–1988	1.12	1.07–1.16	<0.001	1.07	1.03–1.11	0.001	1.27	1.22–1.32	<0.001	1.21	1.16–1.26	<0.001
1989–1991	1.16	1.12–1.20	<0.001	1.06	1.02–1.10	0.004	1.35	1.30–1.41	<0.001	1.23	1.18–1.28	<0.001
1992–1994	1.35	1.30–1.40	<0.001	1.17	1.12–1.21	<0.001	1.60	1.54–1.66	<0.001	1.37	1.32–1.43	<0.001
1995–1997	1.47	1.42–1.53	<0.001	1.23	1.18–1.27	<0.001	1.76	1.69–1.83	<0.001	1.46	1.40–1.52	<0.001
1998–2001	2.00	1.93–2.07	<0.001	1.63	1.57–1.69	<0.001	2.37	2.28–2.46	<0.001	1.93	1.86–2.01	<0.001
2002–2005	2.33	2.24–2.41	<0.001	1.87	1.80–1.94	<0.001	2.93	2.82–3.05	<0.001	2.34	2.25–2.44	<0.001

[a]Adjusted for height, deprivation category, onset of labor, week of gestation, sex, and birth weight percentile of infant.
[b]As above plus maternal age.
[c]Referent category.
OR, odds ratio.
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association appeared to plateau around 35 y of age and above. Between the ages of 16 and 30 y, a 5-y increase in age was associated with a 0.49 h longer duration of labor (95% CI, 0.46–0.51). The risk of operative vaginal birth also increased linearly with age (Figure 4B). The odds ratio for a 5-y increase in age, adjusted for the same factors as employed in the multivariate analysis described in Table 2, was 1.49 (95% CI, 1.48–1.50).

Multiparous Women

We then examined the relationship between maternal age and the risk of emergency cesarean section in multiparous women, analyzing women who had either one or two previous vaginal births but who otherwise fulfilled the inclusion criteria for the main study group (Table 4). All women who had a previous cesarean delivery were excluded. The odds ratio for intrapartum cesarean delivery associated with a 5-y increase in maternal age and adjusted for the same series of maternal characteristics as above was 1.38 (95% CI, 1.34–1.41) among women with one previous vaginal birth and 1.49 (95% CI, 1.43–1.55) among women with two previous vaginal births. The adjusted odds ratios for operative vaginal birth associated with a 5-y increase in maternal age were 1.48 (95% CI, 1.45–1.50) and 1.52 (95% CI, 1.47–1.58), respectively. Approximately 30% of the increase in cesarean section rate among multiparous women was related to increasing maternal age.

Age and Myometrial Contractility

Myometrial biopsies were obtained from 62 women of varying parity, and a total of 181 strips were studied in vitro. The average number of strips studied per woman was 2.9 and the range 2–4. The characteristics of this group are summarized in Table 5. Figure 5A illustrates estimation of contraction units and shows an example of a multiphasic contraction in a biopsy from a 40-y-old woman. The mean peak response to potassium was 3.5 g tension, and there was no association between the age of the mother and the peak response to potassium (coefficient for a 5-y increase in age = 0.15 g tension, 95% CI, –0.12 to 0.43, $p = 0.27$).

Of the 181 strips, 67 (37.0%) exhibited one or more spontaneous contractions prior to potassium stimulation. There was a nonsignificant trend towards a decreased frequency of spontaneous contraction with advancing age (change in contraction frequency for a 5-y increase in age = –26.4%, 95% CI, –50.9% to 10.2%, $p = 0.14$). When expressed as contraction units, the mean spontaneous activity was –0.49 contraction units and the standard deviation 0.44. The mean contraction unit value for each patient is plotted against maternal age (Figure 5B). Regression modeling demonstrated a significant negative association between spontaneous contractile activity and maternal age, with a coefficient of –0.086 contraction units for a 5-y increase in age (95% CI, –0.161 to –0.012, $p = 0.02$). Spontaneous activity increased with advancing gestational age (coefficient for one week increase = 0.10; 95% CI, 0.01–0.18, $p = 0.04$) and number of previous vaginal births (coefficient for each additional vaginal birth = 0.17; 95% CI, –0.01 to 0.34, $p = 0.07$). However, adjustment for these factors and other maternal characteristics (number of previous cesarean deliveries, height, and body mass index) had virtually no effect on the association between age and spontaneous activity (adjusted coefficient for 5-y increase in age = –0.084, 95% CI, –0.155 to –0.012, $p = 0.02$). When the analysis was confined to the 67 strips that exhibited at least one spontaneous contraction, there was still a statistically significant decrease in contractility with advancing age (coefficient of –0.080 contraction units for a 5-y increase in age, 95% CI, –0.149 to –0.009, $p = 0.03$). The risk of these spontaneous contractions being multiphasic also increased with advancing maternal age (Figure 5C). A 5-y increase in age was associated with an odds ratio for multiphasic contractions of 1.93 (95% CI, 1.41–2.63, $p < 0.001$). This odds ratio was also virtually unaltered by adjusting for maternal characteristics (adjusted odds ratio 1.95, 95% CI, 1.43–2.64, $p < 0.001$), and age was the only maternal characteristic associated with multiphasic contractions.

Discussion

We show that the risk of intrapartum cesarean delivery among women having their first birth at term increased with advancing maternal age from 16 y old upwards. The

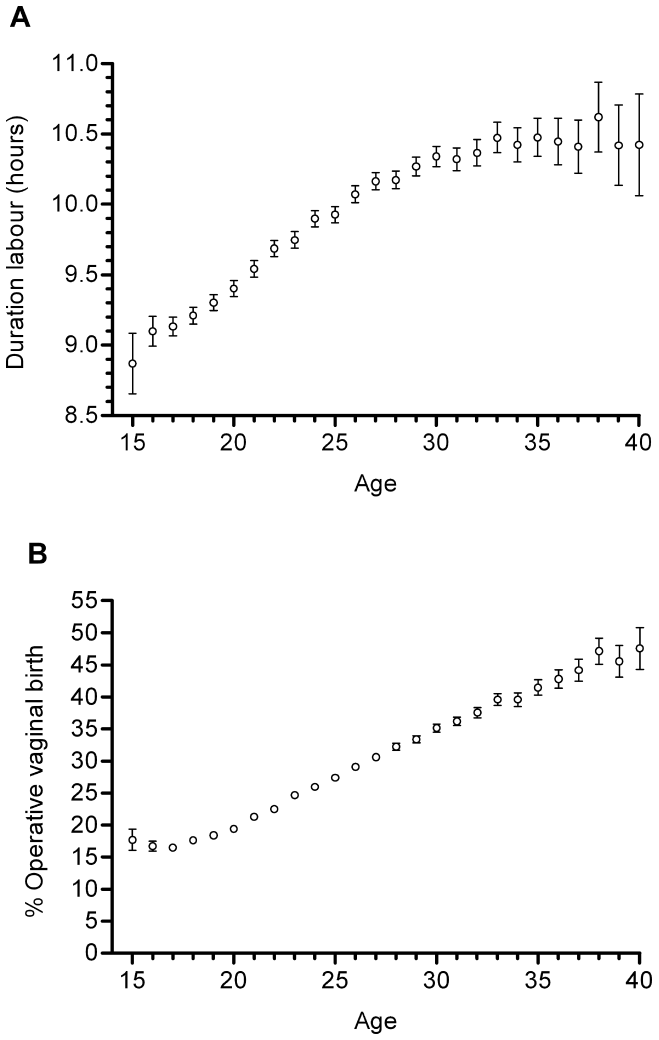

Figure 4. Maternal Age and the Duration of Labor and Risk of Operative Vaginal Birth

(A) Mean duration of spontaneous labor in relation to maternal age ($n = 409,703$). Bars are 95% CIs of the mean.

(B) Proportion of nulliparous women who required operative vaginal delivery in relation to maternal age among the 518,787 women delivered by a means other than emergency cesarean section. Bars are binomial 95% CIs.

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association was linear and was not explained by a range of other maternal characteristics. Over the period 1980 to 2005, the proportion of women in Scotland having their first birth aged 30–34 y increased approximately 3-fold, the proportion aged 35–39 y increased approximately 7-fold, and the proportion aged ≥40 y increased approximately 10-fold (Figure 3B). The cesarean rate more than doubled over the same period. This increase represented approximately 16,500 more procedures than would have occurred had the cesarean rate stayed at the level observed in 1980. Using these nationally collected data, we estimated that approximately 38% of these additional procedures would have been avoided had the maternal age distribution stayed the same as in 1980. Hence, we show that a substantial proportion of the increase in rate of emergency primary cesarean delivery in recent years may be attributed to the trend of delaying of first childbirth. The current observations cannot be explained by the offer of planned cesarean delivery to older women.

Previous studies addressing the effects of population trends in delaying childbirth on cesarean delivery rates had produced inconsistent findings. An analysis of US birth certificate data from 1991 to 2002 concluded that increasing rates of cesarean delivery were unrelated to maternal risk profiles [12]. A recent study of 432,327 singleton cephalic births at term in Western Australia reached the same conclusion [10]. However, an earlier study of 225,466 births in Washington State estimated that 18% of the increase in cesarean rates between 1970 and 1987–1990 might be explained by the combined effects of changes in maternal age, parity, and birth weight [11], and an analysis of 127,564 births between 1988 and 2000 in Nova Scotia suggested that virtually all of the increase in cesarean rates over that period could be attributed to changes in age, parity, and maternal weight [3]. The strengths of the present analysis are that we studied a large number of women, that we had quality assured data collected in a standardized fashion, that data were nationally collected covering a population with free access to health care, and that we could exclude prelabor cesarean deliveries. Moreover, the analytic method employed directly addressed the question of what would have been predicted had the age distribution remained constant. The analysis also indicates that part of the increase in cesarean rates was independent of changes in maternal age. Other possible determinants of increased rates of cesarean delivery may include changes in other maternal characteristics, such as

Table 4. Outcome of Labor among Multiparous Women, Scotland 1980–2005

Numbers, Odds Ratios, and Population Trends	Mode of Delivery	One Previous Birth ($n = 412,253$)	Two Previous Births ($n = 186,141$)
Operative births, *n* (%)	Cesarean section	8,254 (2.0)	2,960 (1.8)
	Operative vaginal birth	18,282 (4.4)	4,014 (2.4)
Adjusted[a] odds ratio (95% CI) for 5-y increase in age	Emergency cesarean section	1.38 (1.34–1.41)	1.49 (1.43–1.55)
	Operative vaginal birth	1.48 (1.45–1.50)	1.52 (1.47–1.58)
Additional cesarean deliveries compared with static rate	—	2,361[b]	776[b]
Proportion additional procedures attributed to age	—	29.8%[c]	28.8%[c]

[a]Adjusted for maternal age, height, deprivation category, onset of labor, week of gestation, sex, birth weight percentile of infant, and year.

[b]Number of cesarean deliveries that would have been avoided had the rate stayed the same as it was in 1980.

[c]Estimated proportion of the additional cesarean deliveries that would have been avoided had the maternal age distribution stayed the same as it was in 1980.

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Table 5. Characteristics of Women Who Provided Myometrial Biopsies

Characteristic	Unit/Category	Values
Age (y)	Median (IQR)	33 (29–36)
Height (cm)	Median (IQR)	165 (159–170)
Body mass index	Median (IQR)	23.4 (21.4–27.9)
Week of gestation	≤37	4 (6.4)
	38	12 (19.4)
	39	42 (67.7)
	≥40	4 (6.5)
Previous vaginal births	1	12 (19.4)
	2	1 (1.6)
	≥3	0
Previous cesarean deliveries	1	29 (49.8)
	2	8 (12.9)
	≥3	0

Data expressed as *n* (%) unless stated otherwise. IQR, interquartile range.
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body mass index, or changes in obstetric practice, such as generally more liberal use of cesarean section.

Some authors had interpreted higher rates of cesarean delivery among older women as reflecting physician and maternal preference. We interpret the current data as supporting a biological effect of aging on performance during labor. First, we adjusted for a range of maternal characteristics. The lack of effect of statistical adjustment for both body mass index and birth weight percentile suggest the findings are not explained by comorbidities, such as obesity or gestational diabetes. Secondly, previous analysis by indication for cesarean delivery demonstrated that 80% of procedures performed during term labor in nulliparous women include failure to progress in the indication [16]. This finding suggests that any factor that is strongly associated with primary intrapartum cesarean delivery among nulliparous women at term is likely to be associated with poor progress during labor. Thirdly, we found that other indicators of poor progress in labor were also associated with increasing age. The duration of labor increased linearly with advancing age, as did the risk of requiring operative vaginal delivery. The latter observation also indicates that the association between age and cesarean delivery is not merely a reflection of a tendency toward performing a cesarean delivery rather than an operative vaginal birth in older women. Finally, the associations were all strikingly linear across the maternal age range 20–29 y. This pattern cannot plausibly be explained either by bias on the part of the obstetrician or a tendency to vascular complications affecting older women. We also found that the association was stronger for procedures performed where the infant had a normal Apgar score than procedures where the infant was delivered with a depressed Apgar, indicating that the association is unlikely to be explained by effects of aging on the risk of fetal distress, other than as a consequence of prolonged labor.

Given these findings, we hypothesized that aging is associated with impairment of myometrial contractility. We

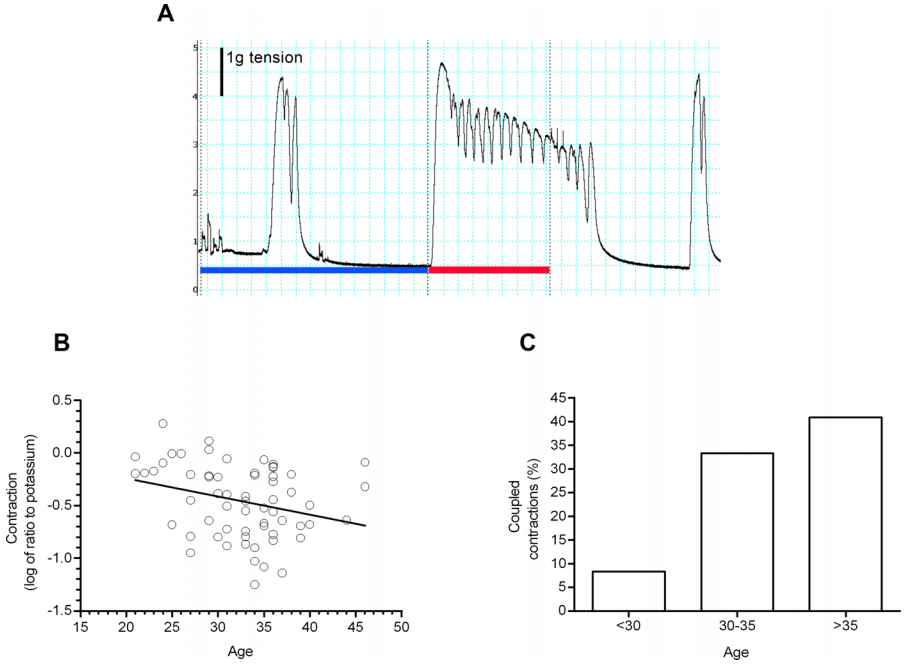

Figure 5. Myometrial Contractility in Relation to Maternal Age

(A) Trace of isometric tension from myometrial strip obtained from a 40-y-old woman being delivered by planned cesarean section. The blue line represents the 15 min before addition of potassium, and the red line 7 min in the presence of 50 mM of potassium. The area under the curve is the space between the tension trace and the baseline, indicated by the blue and red lines. The $\log_{10}$ of the ratio of these two areas is the contraction unit. The spontaneous contraction before the addition of potassium and the contraction following potassium being washed out are both multiphasic.
(B) Mean spontaneous contractile activity (quantified as contraction units) of isolated strips of myometrium obtained from women ($n = 62$) at the time of planned cesarean section in relation to the age of the donor. Regression line: $y = 0.1078 + (-0.0174 \times \text{age})$; 95% CI for slope, −0.0326 to −0.0022.
(C) Proportion of spontaneous contractions that were multiphasic in relation to maternal age ($n = 62$, 181 samples). See text for regression analysis of (B) and (C).
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tested this hypothesis by obtaining uterine biopsies at the time of planned cesarean section and assessing their contractility in vitro. We quantified spontaneous contractile activity blind to the age of the donor. We found that advancing age was associated with a reduced degree of spontaneous contraction compared with a standardized response to potassium. Moreover, the spontaneous contractions observed were more likely to be multiphasic. Our contractility studies included women of mixed parity. However, we demonstrated that the association between maternal age and the risk of both cesarean section and operative vaginal birth was similar in multiparous women as we observed in nulliparous women. Moreover, multivariate statistical methods demonstrated that the association between age and the contractility of isolated myometrial strips was independent of other maternal characteristics. The association between age and both spontaneous activity and the coordination of contractions may indicate adverse effects of aging on control of electrical activity in the myometrium, for example, membrane depolarization or conduction between cells, which could be mediated by effects of aging on the composition of the uterine wall, such as increasing connective tissue between muscle bundles. Alternatively, it could be mediated at the cellular level, such as effects of aging on gap junction or ion channel expression. Further studies will be required to define further the extent of this functional impairment and its molecular basis. Whatever the case, these observations suggest that the increased risk of operative delivery associated with advancing maternal age may be a manifestation of impaired uterine function, which is consistent with the overall importance of poor progress in labor as an indication for cesarean delivery [17]. There are also specific findings that are consistent with an association, for example the observation that the presence of multiphasic (also called "coupled") contractions during labor among nulliparous women monitored with intra-uterine pressure catheters was associated with prolonged labor and an increased risk of emergency cesarean delivery [18].

We propose that an association between advancing age and impaired uterine function is biologically plausible. Women who delay childbirth using the combined oral contraceptive pill, barrier methods, nonhormonal intra-uterine devices, or sexual abstinence (which collectively constitute the majority of women), will have repetitive cyclical stimulation by estrogens and progestogens. Myometrium expresses both estrogen and progesterone receptors and these hormones have profound effects on myometrial growth, metabolism, and contractility (see review [19]). We hypothesize that the adverse effect of advancing maternal age on myometrial contractility may be a consequence of this prolonged cyclical stimulation of the myometrium by estrogen and progesterone. This hypothesis is falsifiable, as it predicts that early menarche would be independently predictive of the risk of dysfunctional labor. If this hypothesis is true, it may be that the effect of delaying childbirth on the outcome of labor varies according to the method of contraception used, which could be of clinical and public health relevance. Whatever the case, understanding the determinants and management of dysfunctional labor in older women is central to designing strategies for reducing population cesarean delivery rates without adversely affecting maternal and infant outcomes.

Acknowledgments

Author contributions. GCSS had full access to all of the data in the study, takes responsibility for the integrity of the data, the accuracy of the data analysis, and is the guarantor. GCSS formed the hypothesis. MF performed the linkage and extracted the population data. GCSS and IRW performed the statistical analysis. GCSS and YC designed the contractility studies. YC, DP, and HML recruited patients, conducted the contractility studies, and extracted data. GCSS drafted the paper. GCSS, YC, IRW, DP, HML, JPP, DSCJ, and MF critically reviewed the draft for content and approved the final version of the paper.

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Editors' Summary

Background. The rising rates of cesarean sections have been a concern for over two decades. An acceptable rate of cesarean sections is between 10% and 15% for countries in the developed world, according to the World Health Organization (WHO). However, the estimated rate in the United Kingdom was 20% in 2004. In Canada, it was estimated at 22.5% in 2001–2002. And in the United States, the rate was 30.2% in 2005 (rising 46% since 1996).

This increase may have implications for the mother, baby, healthcare providers, and policy makers. Though it is difficult to directly compare risks between vaginal and cesarean deliveries, higher mortality and morbidity rates are associated with the latter. Risks encountered during the operation may include anesthetic complications and difficulty in stopping bleeding. Later risks include infections, wound healing problems, and increased risk of problems in subsequent pregnancies including malpresentation, placenta previa, and uterine rupture.

Why Was This Study Done? The trend of increased rates of cesarean sections with maternal age appears to be consistent in different countries and has previously been reported by several epidemiological studies. However, it remains unclear why the risk of having cesarean section is associated with advancing maternal age. Could the association reflect a biological effect of advanced age, or is it a consequence of physician and maternal preference?

The researchers aimed to (1) characterize the association between maternal age and the outcome of labor, (2) determine the proportion of the increase in primary cesarean rates that could be attributed to changes in maternal age distribution, and (3) determine whether the contractility of uterine smooth muscle (myometrium) varied with maternal age.

What Did the Researchers Do and Find? To address aims (1) and (2), the researchers analyzed data collected over the period 1980 to 2005 by the Scottish Morbidity Record (SMR2), which has been demonstrated to be 99% complete since the late 1970s and free from substantial errors in more than 98% of the records in most of the specific fields used for their analysis.

Their analysis showed a linear association between the risk of having a cesarean section and advancing maternal age in first pregnancies. The cesarean rate also more than doubled over the study period. They estimated that 38% of the additional procedures would have been avoided if maternal age distribution had remained the same as in 1980. Therefore they conclude that a substantial part of the increase may be associated with the trend of delaying of first childbirth.

They then hypothesized that this trend is a result of a biological effect of aging on the contractility of the uterus. This hypothesis was further evaluated with aim (3) of the study, where they biopsied the uteri of 62 women (of mixed parity) undergoing routine elective cesarean delivery to test their contractility. They found that advancing age was associated with impaired uterine function as evidenced by a reduced degree of spontaneous contraction and the type of spontaneous contraction.

What Do These Findings Mean? This study adds to the evidence that advancing maternal age is associated with higher rates of cesarean sections. It also suggests a possible mechanism for this association, i.e., impaired uterine function. Though it was not studied here, the researchers hypothesize that impaired uterine contractility may be a consequence of prolonged stimulation of the uterus by estrogen and progesterone, resulting from a prolonged interval between menarche and first birth. Further research is needed to understand the determinants and management of dysfunctional labor in older women to help design strategies for reducing population cesarean delivery rates without adversely affecting maternal and infant outcomes.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0050144.

- NHS Choices is a patient information Web site developed to help patients take control of their health care
- Wikipedia has a section on cesarean section (Note that Wikipedia is an internet encyclopedia that anyone can edit)
- MedlinePlus also has information on cesarean section

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Age at menarche and the risk of operative first delivery

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Objective The risk of operative delivery at term increases linearly with age at first birth. It has been hypothesised that this is because of a deleterious effect of a prolonged interval between menarche and first birth on uterine function. The aim of this study was to test a prediction from the hypothesis, namely, that the risk of operative first delivery would decline with later age at menarche.

Design Retrospective analysis of a prospective cohort study.

Setting The ALSPAC prospective cohort study enrolled pregnant women resident in Avon, UK with expected dates of delivery from 1 April 1991 to 31 December 1992.

Population A total of 3739 primipara recruited to the ALSPAC cohort who experienced labour at term with a singleton infant in a cephalic presentation.

Main outcome measure Operative delivery, defined as caesarean section or operative vaginal birth.

Result The rate of operative delivery was highest among women with age at menarche in the bottom quartile (32.4%, menarche aged ≤12) and was lower in the second (30.3%, menarche aged 13), third (29.2%, menarche aged 14) and top (26.9%, menarche aged ≥15) quartiles (test for trend, $P = 0.01$). When adjusted for height, body mass index, marital status, smoking status, induction of labour, week of gestation of delivery and birthweight percentile; the odds ratio for operative delivery associated with a 5-year increase in age at menarche (0.78, 95% CI 0.61–0.99) was very similar to the odds ratio for a 5-year decrease in age at delivery (0.73, 95% CI 0.67–0.79). There was no association between age at menarche and the risk of operative delivery following adjustment for the interval between menarche and the first birth (adjusted odds ratio 0.98, 95% CI 0.77–1.25).

Conclusion Later menarche is associated with a decreased risk of operative delivery by decreasing the interval between menarche and first birth. The observation is consistent with the hypothesis that prolonged hormonal stimulation of the uterus prior to the first birth has a deleterious effect on uterine function.

Keywords Age, ALSPAC, menarche, operative delivery, pregnancy.

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Introduction

Many studies have demonstrated that the risk of caesarean delivery was increased among older parturients. Some have suggested that this observation may reflect physician or maternal preference[1,2] and others that it may reflect a true biological effect of aging.[3,4] The risk of emergency caesarean delivery, the risk of operative vaginal delivery and the duration of labour all increase linearly with age, from 16 years upwards.[3–5] It has been suggested that the presence of a linear relationship across the whole range of age at first birth cannot be explained by physician or maternal preference and is most likely to represent a true biological effect of aging.[3] Consistent with this, it has been shown that the spontaneous contractility of isolated human myometrial strips *in vitro* declines with advancing maternal age.[5] Collectively, these observations are consistent with a biological effect of aging on uterine function. However, it is currently unclear why advancing age across the range of the reproductive years might impair uterine function.

Women who delay childbirth will experience prolonged exposure to the female sex hormones prior to their first birth. Depending on the contraceptive method employed, these could be endogenous (for example, women using barrier methods, non-hormonal intrauterine devices and sexual abstinence) or exogenous synthetic derivatives of progesterone and estrogen (for example, women using the combined pill). Uterine smooth muscle (myometrium) and

the cervix express estrogen and progesterone receptors[6,7] and many aspects of uterine function are controlled by the levels of these hormones (see review[8]). It had previously been hypothesised that the association between increasing age at first birth and dysfunctional labour may be related to an adverse effect of prolonged pre-pregnancy stimulation of the uterus by estrogen and progesterone.[5] The aim of the present study was to test a prediction arising from the hypothesis, namely, that later age at menarche would be independently predictive of a lower risk of operative first delivery.

Methods

The ALSPAC prospective cohort study enrolled pregnant women resident in Avon, UK with expected dates of delivery from 1 April 1991 to 31 December 1992. The study design is described in detail elsewhere.[9] Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. Women recruited to the study completed questionnaires in the prenatal period. Pregnancy outcome data were obtained for cohort members delivering at Southmead or St Michael's Hospitals by linking the ALSPAC data to the hospitals' computerised birth records (both hospitals employed the same maternity database, 'STORK'). These data were not available for women who delivered in the other local hospital (Weston General) or who delivered at home.

Ethnicity, pre-pregnancy weight, height, marital status, parity and smoking status were all obtained from prenatal questionnaires. Gestational age was defined using the last menstrual period with adjustment for ultrasound estimation of gestation where this was available. The birthweight was taken from the infant's birth record and was converted into a percentile for gestational age using previously described data.[10] Cephalic presentation was defined as any case where the presentation was by the occiput, brow or face and where both the mode of delivery and indication for operative delivery were consistent with cephalic presentation. Labour was defined by a non-missing value for duration of labour and where the mode of delivery was not elective caesarean delivery. Operative vaginal delivery was defined as delivery using forceps or vacuum (ventouse) and all operative delivery was defined as operative vaginal or caesarean delivery. The computerised birth record was compared with the clinical notes in a random sample of 50 women from each hospital in both 1991 and 1992. This demonstrated overall rates of error in coding of method of labour onset in 6%, presentation in 2% and mode of delivery in 3%. Checks of internal consistency of the hospital database also indicated low rates of error. Among 11 089 records documenting cephalic vaginal delivery, only 23 (0.2%) had a missing value for duration of labour. Among 542 records documenting delivery by elective caesarean, there was only a single record (0.2%) with a documented duration of labour. Among 11 883 records documenting cephalic presentation, only 27 (0.2%) documented a mode of delivery that was indicative of non-cephalic presentation.

The inclusion criteria for the current study were nulliparous women, delivering a singleton, liveborn infant in a cephalic presentation, in labour at term, who had a documented age at menarche. Records with any of the above internal inconsistencies were excluded.

Statistics

Continuous variables were summarised by the median and inter-quartile range and groups were compared using the Kruskal–Wallis test. Univariate comparisons of categorical data were performed using the χ^2 test for trend. All P values were two-sided, and a P value <0.05 was considered significant. Adjusted odds ratios were estimated using multivariate logistic regression.[11] Analysis of the association between age at menarche and the risk of operative birth was performed by categorizing age at menarche into quartiles. In further analyses, to compare the relationship between age at menarche and age at delivery, both variables were treated as continuous. When treated continuously, age-related variables were divided by 5 to result in a more precise estimate of the association when odds ratios were expressed to 2 decimal places. Age at delivery was expressed as the odds ratio for a 5-year decrease in age to allow direct comparison with age at menarche. Approximately 0.5% of values for age at menarche were outside the range 9–17: values below and above this range were truncated as 9 or 17 respectively. Approximately 0.7% of values for age at delivery were outside the range 16–40: values below and above this range were truncated as 16 or 40 respectively. Linearity in the log odds scale was assessed using fractional polynomials.[12] Interactions were tested using the likelihood ratio test. The principal method for treatment of missing data was multiple imputation using chained equations.[13] To assess whether the method of treatment of missing variables influenced the analysis, the results of multivariate analysis using this method was also compared with using dummy variables to indicate missing data and replacing missing values with the median (continuous) or most common (categorical) value for the population. The interrelationships between age at menarche, duration of labour, the interval between menarche and first birth, body mass index and height were analyzed using multiple linear regression. All of the above statistical analyses were performed using the Stata software package (Stata Corporation, College Station, TX, USA), version 10.1. The power of the study to assess the relationship between age at menarche and mode of delivery was assessed using the SD of

the age at menarche within the study cohort. Power was calculated using the assumption that a given magnitude of increase in age at menarche would have the same proportional effect on the odds of operative delivery as the same decrease in age at the time of the first birth. Power calculations were performed using nQuery Advisor version 7.0 (Statistical Solutions, Saugus, MA, USA).

Results

The ALSPAC study recruited 14 541 pregnant women who either returned at least one questionnaire or attended a 'Children in Focus' clinic by 19/7/99. There were 9997 (68.2%) records of a liveborn, singleton pregnancy, with a mode of delivery recorded on the STORK database and with a documented age at menarche. Among this group, 4382 (43.8%) were documented as nulliparous. Among these women, 284 (6.5%) delivered outside the range 37–43 weeks, 369 (8.4%) did not document the infant as being in a cephalic presentation and 216 (4.9%) had no documented duration of labour. A total of 643 (14.7%) records had one or more of these exclusions leaving 3739 eligible women who were the study group for the present analysis.

The distribution of age at menarche and age at first birth are illustrated (Figure 1). The mean age at menarche was 12.9 and the SD was 1.55. Age at menarche was positively associated with height and negatively associated with body mass index (Table 1). There was a linear decline in the risk of operative delivery with increasing quartile of age at menarche (Figure 2). The rate of operative delivery was highest among women with age at menarche in the bottom quartile (32.4%, menarche aged ≤12) and was lower in the second (30.3%, menarche aged 13), third (29.2%, menarche aged 14) and top (26.9%, menarche aged ≥15) quartiles (odds ratio for 1 quartile increase 0.92, 95% CI 0.86 to 0.98, test for trend, $P = 0.01$). Adjustment for other maternal characteristics, with missing data handled using multiple imputation, had a minimal effect on the association between age at menarche and the risk of operative delivery (adjusted odds ratio for 1 quartile increase 0.93, 95% CI 0.87 to 1.00, test for trend, $P = 0.04$, Table 2). When the composite outcome was divided into its two components, a one quartile increase in age at menarche was associated with an odds ratio for caesarean section of 0.94 (95% CI 0.82–1.08, $P = 0.39$) and an odds ratio for assisted vaginal delivery of 0.92 (95% CI 0.86–0.99, $P = 0.02$).

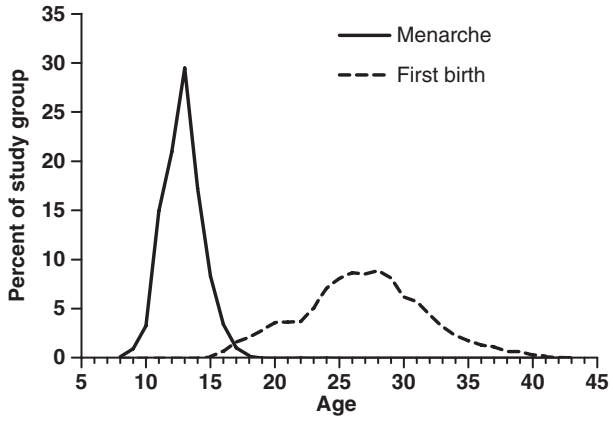

Figure 1. Distributions of age at menarche and age at the time of first birth.

A series of analyses was then conducted where age at menarche and age at delivery were treated as continuous variables. Logistic regression analysis using multiple fractional polynomials demonstrated that the association between operative delivery and both age at menarche and age at delivery were linear in the log odds scale. The protective effect of a 5 year increase in age at menarche was very similar to the protective effect of a 5 year decrease in age at the time of the first delivery (Table 3). Adjustment for other maternal characteristics has a minimal effect on the nature and statistical significance of the associations. Three methods for handing missing data yielded virtually identical results. The association between operative delivery and a 5-year increase in age at menarche was unchanged if cases with extreme values of menarche were excluded rather than truncated (unadjusted odds ratio 0.72, 95% CI 0.60–0.96, $P = 0.02$). There was no significant interaction between age at menarche and whether the onset of labour was spontaneous or induced (odds ratio for interaction term 0.86, 95% CI 0.51–1.48, $P = 0.59$).

The median interval from menarche to first delivery was 14 years (inter-quartile range 11 to 17). This interval was inversely correlated with age at menarche ($r^2 = 0.06$, $P < 0.001$). Adjustment for the duration of this interval resulted in complete loss of the association between age at menarche and the risk of operative delivery, but had no effect on the associations between age at menarche and the pre-pregnancy body mass index or height (Table 4).

The duration of labour did not differ across the quartiles of age at menarche. The relationship between age at menarche, age at delivery and duration of labour was explored using linear regression. A 5-year increase in age at menarche was associated with −0.09 hour difference in the duration of labour (95% CI −0.61 to 0.43, $P = 0.7$). A 5-year decrease in age at delivery was associated with a −0.33 difference in duration of labour (95% CI −0.49 to −0.16, $P < 0.001$).

Power calculations were performed with the assumption that a 1 SD increase in age at menarche would be associated with an odds ratio of 0.879, based on a previous analysis.[5] Setting alpha at 0.05 (two-sided), the size of the study group yielded 38% power for an outcome with 5% frequency, 89% power for an outcome with 25% frequency

Table 1. Characteristics of the cohort by quartile of age at menarche

Maternal characteristics and outcome	Quartile of age at the time of menarche*				**P
	1 (*n* = 1503)	2 (*n* = 1102)	3 (*n* = 644)	4 (*n* = 490)	
Age at menarche (range)	8–12	13	14	15–24	
Age at delivery					
Median (IQR)	27 (24–30)	27 (24–30)	28 (24–30)	27 (24–30)	0.053
Height					
Median (IQR)	163 (160–168)	165 (160–170)	165 (160–170)	165 (160–170)	<0.001
Body mass index					
Median (IQR)	22.4 (20.6–24.5)	21.7 (20.3–23.6)	21.6 (20.3–23.5)	21.5 (19.9–23.5)	<0.001
Smoking status					
Current	261 (17.4)	168 (15.2)	112 (17.4)	83 (16.9)	0.89
Ethnicity					
White	1409 (97.2)	1054 (98.2)	607 (98.1)	447 (97.4)	0.46
Marital status					
Married	1033 (70.0)	785 (72.6)	442 (70.5)	314 (66.8)	0.33
Week of gestation					
Median (IQR)	40 (39–41)	40 (39–41)	40 (39–41)	40 (39–41)	0.59
Onset of labour					
Spontaneous	1171 (77.9)	890 (80.8)	514 (79.8)	398 (81.2)	0.10
Duration of labour					
Median (IQR)	8.8 (5.8–12.3)	8.9 (6.0–12.4)	8.5 (5.7–11.9)	8.6 (5.6–12.1)	0.37
Mode of delivery					
Operative vaginal	401 (26.7)	278 (25.2)	152 (23.6)	110 (22.4)	0.03
Caesarean	86 (5.7)	56 (5.1)	36 (5.6)	22 (4.5)	0.39
Birthweight percentile					
1–5	75 (5.0)	66 (6.1)	34 (5.4)	25 (5.2)	0.85
6–10	76 (5.1)	48 (4.4)	22 (3.5)	21 (4.4)	0.19
11–25	206 (13.9)	134 (12.3)	83 (13.0)	65 (13.5)	0.70
26–75	819 (55.2)	620 (56.9)	353 (55.5)	269 (55.8)	0.80
76–90	218 (14.7)	153 (14.0)	103 (16.2)	73 (15.2)	0.54
91–95	56 (3.8)	45 (4.1)	27 (4.2)	18 (3.7)	0.84
96–100	35 (2.4)	23 (2.1)	14 (2.2)	11 (2.3)	0.87

IQR, inter-quartile range.
Data were missing from (*n*) records in relation to height (61), body mass index (254), marital status (86), ethnicity (138) and birthweight percentile (47).
*Numbers in quartiles are unequal due to ties.
**Chi-square test for trend or Kruskal–Wallis test, as appropriate. Data expressed as *n* (percent) unless stated otherwise.

and 92% power for an outcome with 30% frequency. The frequency of caesarean delivery in the study group was 5.4%, the frequency of operative vaginal delivery was 25.2% and the frequency of the composite outcome of all operative delivery was 30.5%.

Discussion

The main finding of the present study is that the risk of operative delivery at term among nulliparous women decreased with later age at menarche. The association was linear and persisted after adjusting for potential confounders, such as maternal height and body mass index. The relationship between age at menarche and the risk of operative delivery was because of the fact that age at menarche in part determined the duration of the interval from menarche to the first birth (also known as the gynaecologic age[14]). Adjustment for this interval resulted in complete loss of the association between age at menarche and the risk of operative delivery. Hence, it is concluded that later menarche is associated with a decreased risk of operative delivery by decreasing the interval between menarche and first birth.

It had previously been hypothesised that increasing age at the time of first birth increased the risk of operative delivery by increasing the interval between menarche and first birth.[5] This hypothesis predicts that a woman's age at menarche would be negatively associated with her risk of

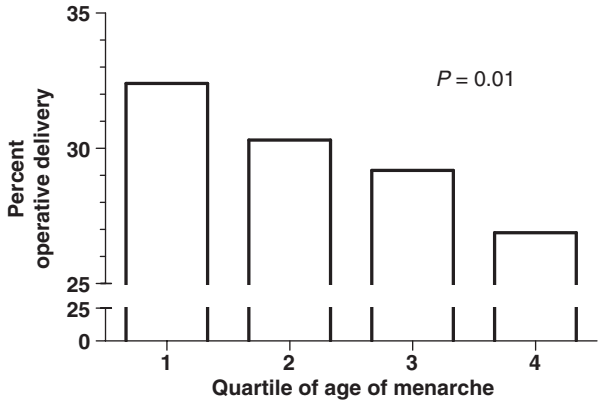

Figure 2. Proportion of operative deliveries by age at menarche. *P* value is estimated using chi-square test for trend.

operative delivery. Three features of the present analysis support this hypothesis. First, the relationship between age at menarche and the risk of operative delivery was independent of other maternal characteristics. Second, the proportional effect of a given increase in the age at menarche was similar to a given decrease in age at first birth. Third, the association between age at menarche and the risk of operative delivery was no longer apparent when adjusted for the interval between menarche and first birth. The current analysis provides strong evidence in support of the hypothesis. Hence, this analysis is significant in that it is the first description of the association between age at menarche and the risk of operative birth. However, the key significance of the current analysis is that it suggests a mechanism linking delayed childbirth to the risk of operative delivery, that is that the true mediator of the associations between the risk of operative delivery and both age at menarche and age at first birth is the duration of the interval between menarche and first birth. The public health importance of this is that delaying childbirth is a major determinant of recent rises in the caesarean section rate.[5]

A prolonged interval between menarche and first birth will result in prolonged pre-pregnancy stimulation of the uterus by estrogen and progesterone, with the exact pattern being determined by the contraceptive method employed. The most common cause for operative delivery among women having their first birth during labour at term is poor progress during labour.[15,16] The current analysis is consistent with the hypothesis that prolonged pre-pregnancy stimulation of the uterus by estrogen and progesterone adversely affects the uterus in a way that impairs its function during labour. The hypothesis has parallels in relation to other disorders of the female reproductive organs, in particular the risk of breast cancer. The risk of this condition is also decreased with later age at menarche. This association is thought to be because of an adverse effect of prolonged stimulation by mammotrophic hormones, principally estrogens and progestogens.[17] Given that the uterus is also profoundly under the control of these hormones,[8] it is biologically plausible that prolonged pre-pregnancy stimulation of the uterus by estrogen and progesterone could also adversely affect uterine function.

The prospective design of this study means that women were asked about their age at menarche prior to delivery, precluding the possibility of recall bias in relation to ultimate mode of delivery. A further strength of this study was the availability of detailed information on relevant potential confounders. Early menarche was associated with short stature and obesity and both are recognised to be risk factors for operative delivery.[18] Although the association was largely unchanged by multivariate analysis, the persisting association may be explained by residual confounding. In particular, body mass index is a proxy measure of adiposity and it is possible that residual confounding by obesity may explain the results observed. This question was addressed by examining the effect of adjusting associations between age at menarche for the interval between menarche and first birth. It was observed that adjustment for this interval abolished the association between age at menarche and the risk of operative delivery (Table 4). By contrast, adjustment for the interval between menarche and first birth had no material effect on the association between age at menarche and either maternal height or BMI. This analysis demonstrates that age at menarche is associated with the risk of operative delivery by its contribution to the interval between menarche and first birth. Moreover, it indicates that the association between age at menarche and maternal anthropometric characteristics is mediated by a different mechanism.

A relative weakness of this study is that these data were collected in 1991–1992. Consequently, the rates of operative delivery were relatively low, with a caesarean delivery rate of 5.4%. Power calculations demonstrated that the study had approximately 90% power to detect an effect of age at menarche on the risk of all operative delivery, but only approximately 40% power to detect an association with caesarean delivery. Hence, the study was underpowered to detect an effect of age at menarche on caesarean section risk alone but was adequately powered to detect an effect on the composite outcome of operative delivery. It may be argued that the composite outcome is determined by many factors, such as fetal distress and maternal exhaustion. However, the primary aim of the present study was to shed light on the relationship between maternal age and the risk of operative delivery. In a previous study of nulliparous women in labour at term with an infant in a cephalic presentation, we demonstrated that a 5-year increase in maternal age was associated with an odds ratio for assisted vaginal delivery of 1.49 (95% CI 1.48–1.50) and an odds

Table 2. Unadjusted and adjusted odds ratios for operative delivery in relation to maternal characteristics

Variable	Unadjusted		Adjusted	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Quartile of age at menarche				
1 (referent)	(1.0)		(1.0)	
2	0.91 (0.77–1.07)	0.26	0.94 (0.79–1.12)	0.47
3	0.86 (0.70–1.05)	0.14	0.87 (0.71–1.08)	0.21
4	0.77 (0.61–0.97)	0.02	0.80 (0.63–1.01)	0.06
Trend	0.92 (0.86–0.98)	0.01	0.93 (0.87–1.00)	0.04
Age at delivery				
<20	0.33 (0.23–0.47)	<0.001	0.34 (0.23–0.50)	<0.001
20–24.9	0.54 (0.44–0.67)	<0.001	0.53 (0.43–0.67)	<0.001
25–29.9	0.76 (0.63–0.91)	0.002	0.74 (0.62–0.89)	0.001
30–34.9 (referent)	(1.0)		(1.0)	
35–39.9	0.99 (0.72–1.36)	0.96	0.98 (0.70–1.36)	0.90
≥40	0.88 (0.37–2.10)	0.78	1.00 (0.41–2.43)	>0.99
Height				
<155	1.53 (1.18–1.99)	0.001	1.75 (1.33–2.31)	<0.001
155–159	1.31 (1.03–1.68)	0.03	1.48 (1.14–1.92)	0.003
160–164	1.20 (0.99–1.46)	0.06	1.25 (1.02–1.53)	0.03
165–169 (referent)	(1.0)		(1.0)	
170–174	0.88 (0.71–1.10)	0.26	0.84 (0.67–1.05)	0.12
>175	0.94 (0.68–1.31)	0.73	0.84 (0.60–1.18)	0.31
Body mass index				
<20	0.91 (0.75–1.10)	0.33	1.08 (0.89–1.31)	0.44
20–24.9 (referent)	(1.0)		(1.0)	
25–29.9	1.18 (0.96–1.46)	0.12	1.06 (0.85–1.31)	0.61
30–34.9	1.36 (0.88–2.09)	0.17	1.05 (0.67–1.64)	0.83
≥35	2.09 (1.06–4.13)	0.03	1.49 (0.73–3.04)	0.28
Smoking status				
Nonsmoker (referent)	(1.0)		(1.0)	
Smoker	0.80 (0.66–0.96)	0.02	0.98 (0.80–1.21)	0.87
Ethnicity				
White (referent)	(1.0)		(1.0)	
Non-White	0.86 (0.53–1.39)	0.53	0.95 (0.57–1.57)	0.84
Marital status				
Married (referent)	(1.0)		(1.0)	
Un-married	0.68 (0.58–0.80)	<0.001	0.89 (0.74–1.08)	0.24
Onset of labour				
Spontaneous (referent)	(1.0)		(1.0)	
Induced	1.89 (1.61–2.23)	<0.001	1.72 (1.44–2.05)	<0.001
Week of gestation				
37	0.67 (0.46–0.96)	0.03	0.53 (0.36–0.78)	0.001
38	0.74 (0.57–0.96)	0.02	0.64 (0.49–0.84)	0.001
39	0.79 (0.64–0.97)	0.02	0.74 (0.60–0.92)	0.006
40 (referent)	(1.0)		(1.0)	
41	1.40 (1.16–1.69)	<0.001	1.41 (1.17–1.71)	<0.001
42	1.88 (1.46–2.42)	<0.001	1.65 (1.26–2.16)	<0.001
43	1.60 (0.56–4.52)	0.38	1.16 (0.39–3.43)	0.79
Birthweight percentile				
1–5	1.00 (0.73–1.37)	>0.99	0.82 (0.59–1.15)	0.25
6–10	0.94 (0.66–1.33)	0.74	0.85 (0.59–1.22)	0.38
11–25	0.87 (0.69–1.08)	0.20	0.78 (0.62–0.98)	0.04
26–75 (referent)	(1.0)		(1.0)	
76–90	1.12 (0.91–1.37)	0.28	1.23 (0.99–1.53)	0.06
91–95	1.29 (0.91–1.84)	0.15	1.61 (1.11–2.32)	0.01
96–100	2.17 (1.40–3.38)	0.001	2.66 (1.67–4.25)	<0.001

CI, confidence interval.

*Adjusted for quartile of age at menarche (categorical), maternal age, height, body mass index, smoking status, ethnicity, marital status, induced labour, gestational age at birth and birthweight percentile. Missing data handled by multiple imputation using chained equations.

Table 3. Analysis of age at menarche and age at birth as continuous variables

	OR for 5 year increase in age at menarche (95% CI)	*P*	OR for 5 year decrease in age at delivery (95% CI)	*P*
Unadjusted	0.76 (0.60–0.95)	0.02	0.73 (0.71–0.75)	<0.001
Adjusted* 1	0.78 (0.61–0.99)	0.04	0.73 (0.67–0.79)	<0.001
Adjusted* 2	0.78 (0.61–1.00)	0.046	0.72 (0.67–0.79)	<0.001
Adjusted* 3	0.77 (0.60–0.98)	0.04	0.72 (0.66–0.78)	<0.001

CI, confidence interval; OR, odds ratio.
Adjusted odds ratios using three methods for treating missing data: 1 using multiple imputation using chained equations, 2 by assigning median or most common value to missing value, 3 by creating dummy variables for missing value and including in the model.
*Adjusted for height, body mass index, smoking status, ethnicity, marital status, induced labour, gestational age at birth and birthweight percentile.

Table 4. The effect of adjustment for the duration of the interval between menarche and first delivery on the associations with age at menarche

	Associations with a 5-year increase in age at menarche			
	Unadjusted (95% CI)	*P*	Adjusted* (95% CI)	*P*
Operative delivery				
Odds ratio	0.76 (0.60–0.95)	0.02	0.98 (0.77–1.25)	0.87
Body mass index				
Coefficient	−1.69 (−2.07 to −1.31)	<0.001	−1.58 (−1.97 to −1.19)	<0.001
Height				
Coefficient	2.16 (1.46–2.85)	<0.001	2.40 (1.69 to 3.11)	<0.001

Body mass index is expressed in kg/m^2, height is expressed in cm. Odds ratios estimated using logistic regression and coefficients by linear regression.
*Adjusted for the interval between menarche and first birth only.

ratio for emergency caesarean section of 1.49 (95% CI 1.48–1.51).[5] Given the virtually identical relationships between maternal age and the risk of both assisted vaginal delivery and emergency caesarean section, we conclude that the composite outcome is appropriate given our primary interest in the effects of maternal age.

The STORK database lacked validated information on the indication for delivery. However, a prospective analysis of the indication for primary intrapartum caesarean section in nulliparous women at term in 1991 demonstrated that over half of these procedures with the infant in a cephalic presentation were due to failure to progress.[19] Although we did not observe significant variation in the duration of labour in association with age at menarche, linear regression analysis demonstrated wide confidence intervals and these included the point estimate for the association with maternal age. Duration of labour is difficult to define and any retrospective analysis of data collected for other purposes is likely to face problems with the reliability of indicators of progress in labour. We are addressing this by conducting a prospective cohort study of unselected nulliparous women, which addresses some of the weaknesses of the present analysis, in that we are collecting detailed information on contraceptive history, in addition to age at menarche, and outcome data is being collected in a systematic fashion and includes information on duration and dose of oxytocin use.[20]

The public health importance of this finding is that population trends in delaying childbirth appear to be an important determinant of recent increases in caesarean delivery rates.[5] The present analysis suggests a likely mechanism for this association. Moreover, age at menarche has fallen over recent years.[21] The current data suggest that a consequence of this change may be to increase the incidence of poor progress during labour and, hence, population trends of earlier menarche may also have contributed to recent rises in rates of caesarean delivery. Mechanistic understanding of the basis for this effect could possibly identify whether different methods of hormonal contraception might have different effects on the deterioration in

uterine function among women who wish to delay childbirth. For example, it is possible that any adverse effect on the uterus of prolonged pre-pregnancy use of exogenous synthetic estrogen and progesterone for contraception may differ in relation to cyclical or noncyclical administration.

Disclosure of interests

The author has no competing interests of any form in relation to this work.

Contribution to authorship

The sole author is wholly responsible for all aspects of this study.

Details of ethics approval

The analysis is covered by the ALSPAC ethical approval, given by Bristol and Weston Health Authority (reference E1808) on 28 November 1989.

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Papers

Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study

Gordon C S Smith, Jill P Pell, Richard Dobbie

Abstract

Objective To determine whether a short interval between pregnancies is an independent risk factor for adverse obstetric outcome.
Design Retrospective cohort study.
Setting Scotland.
Subjects 89 143 women having second births in 1992-8 who conceived within five years of their first birth.
Main outcome measures Intrauterine growth restriction (birth weight less than the 5th centile for gestational age), extremely preterm birth (24-32 weeks), moderately preterm birth (33-36 weeks), and perinatal death.
Results Women whose subsequent interpregnancy interval was less than six months were more likely than other women to have had a first birth complicated by intrauterine growth restriction (odds ratio 1.3, 95% confidence interval 1.1 to 1.5), extremely preterm birth (4.1, 3.2 to 5.3), moderately preterm birth (1.5, 1.3 to 1.7), or perinatal death (24.4, 18.9 to 31.5). They were also shorter, less likely to be married, and more likely to be aged less than 20 years at the time of the second birth, to smoke, and to live in an area of high socioeconomic deprivation. When the outcome of the second birth was analysed in relation to the preceding interpregnancy interval and the analysis confined to women whose first birth was a term live birth (n = 69 055), no significant association occurred (adjusted for age, marital status, height, socioeconomic deprivation, smoking, previous birth weight vigesimal, and previous caesarean delivery) between interpregnancy interval and intrauterine growth restriction or stillbirth. However, a short interpregnancy interval (< 6 months) was an independent risk factor for extremely preterm birth (adjusted odds ratio 2.2, 1.3 to 3.6), moderately preterm birth (1.6, 1.3 to 2.0), and neonatal death unrelated to congenital abnormality (3.6, 1.2 to 10.7). The adjusted attributable fractions for these associations were 6.1%, 3.9%, and 13.8%. The associations were very similar when the analysis was confined to married non-smokers aged 25 and above.
Conclusions A short interpregnancy interval is an independent risk factor for preterm delivery and neonatal death in the second birth.

Introduction

Several studies have shown that women with a very short interval between pregnancies are at increased risk of complications such as preterm birth, neonatal death, and intrauterine growth restriction.[1–10] However, these studies do not clarify whether the associations are due to confounding effects of adverse obstetric history or to demographic factors. Women with very short interpregnancy intervals are more likely to have had complications such as perinatal death, preterm birth, and intrauterine growth restriction in their first pregnancy.[11] A short interpregnancy interval is also associated with known demographic risk factors for complications of pregnancy.[12 13] Many previous studies of the association between interpregnancy interval and the risk of adverse outcome have lacked information on maternal demographic factors and have had either no information on the outcome of previous pregnancies or minimal information. None of the studies that were powered to detect differences in rare but important outcomes, such as perinatal death and extremely preterm birth, had data on key obstetric and demographic confounders.[6 7 9 10] We report the relation between interpregnancy interval and the outcome of first and second births in a cohort of 89 143 women.

Methods

Data sources

The Scottish Morbidity Record collects information on clinical and demographic characteristics and outcomes for all patients discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been greater than 99% complete since the late 1970s.[14] We linked records from the register to records from the Scottish Stillbirth and Infant Death Enquiry, a national register that routinely classifies all perinatal deaths in Scotland. It is virtually 100% complete and has been described in detail elsewhere.[15 16] We also linked the records from different pregnancies in the same women. All linkages were performed as previously described.[17]

Study cohort

The population studied consisted of all second births in Scotland in 1992-8. The study focused on births in 1992-8 as the Scottish Morbidity Record database included smoking status only from 1992 onwards. When studying the relation between interpregnancy

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interval and the outcome of the first pregnancy, we used exclusion criteria (both pregnancies) of multiple pregnancy, delivery outside the range 24-43 weeks' gestation, and birth weight less than 500 g. We also excluded cases in which the interpregnancy interval was negative or implausibly short, a discrepancy existed between the documented mode of delivery in the first record and the previous caesarean delivery field in the second record, or the number of previous spontaneous or therapeutic abortions differed between the first and second birth record. The last of these processes excluded cases in which the records were discrepant (fewer losses documented for the second birth) and cases in which the woman had experienced losses between the two births (more losses documented for the second birth). These inclusions and exclusions identified the first study group.

We analysed the relation of interpregnancy interval to the outcome of the second birth in a subgroup of the main cohort. We defined this subgroup by excluding cases in which the first birth was outside the range 37-43 weeks, the first birth was a perinatal or infant death, or the birth weight of the first child was less than 1500 g. We also excluded cases in which data were missing on potential confounders in the second pregnancy record: maternal age, marital status, height, deprivation category, or smoking status. We also excluded cases in which the birth weight vigesimal of the first pregnancy was missing. These inclusions and exclusions identified the second study group.

Definitions

Maternal characteristics

In the comparison of risk of adverse obstetric outcome, we considered the following demographic factors as possible confounders: socioeconomic deprivation, smoking, maternal age, and maternal height; their classification has been defined elsewhere.[18] We also included marital status, defined as the status documented at the time of booking for antenatal care and categorised into married and non-married.

Obstetric characteristics

We defined first births as either first pregnancies or births preceded only by pregnancies that resulted in abortion. We defined second births as having been preceded by one pregnancy that did not result in abortion. We defined gestational age at birth as the number of completed weeks of gestation based on the estimated delivery date contained in the clinical record. Over the study period the vast majority of estimates of gestational age in the United Kingdom incorporated ultrasound measurements taken in the first half of pregnancy.[19] We defined interpregnancy interval as the interval from the first birth until the estimated date of the last menstrual period before the second pregnancy, expressed in completed months. We calculated the ultrasound corrected date of the last menstrual period by subtracting the gestational age at birth from the date of delivery. In order to avoid bias in categorisation of interpregnancy interval, we used the categories used by a previous large scale study.[7]

We categorised birth weight into sex specific and gestational age specific vigesimals (20 equal groups) derived from live births among the whole population. We defined a small for gestational age baby as a liveborn baby with a birth weight in the smallest vigesimal (that is, 0 to 5th centile), and the denominator was all live births. We defined very preterm delivery as live births between 24 and 32 weeks' gestation inclusive, and the denominator was all live births at or after 24 weeks' gestation. We defined moderately preterm delivery as live births between 33 and 36 weeks' gestation inclusive, with a denominator of all live births at or after 33 weeks' gestation. We defined spontaneous preterm birth as vaginal birth at the given gestational age, excluding cases in which labour was induced. We defined stillbirth as delivery of a dead baby at or after 24 weeks' gestational age, and the denominator was all births at or after 24 weeks' gestational age. We defined neonatal death as death of a liveborn infant in the first four weeks of life, and the denominator was all live births.

Perinatal deaths

We defined deaths caused by congenital anomaly as any structural or genetic defect incompatible with life or potentially treatable but causing death. We classified stillbirths as antepartum (deaths before the onset of labour) or intrapartum (deaths during labour). We classified the cause of antepartum stillbirth according to a modified version of the Wigglesworth hierarchical system,[20] which is described in detail elsewhere.[16] We classified perinatal deaths into four mutually exclusive categories: *(a)* all deaths related to fetal abnormality or rhesus isoimmunisation; *(b)* unexplained stillbirths; *(c)* all other stillbirths; and *(d)* all other neonatal deaths (excluding category *(a)*).

Statistical analyses

We summarised continuous variables by the median and interquartile range and used the Mann-Whitney U test to make comparisons between groups. We made univariate comparisons of dichotomous data by using the χ^2 test (>5 observations in all cells) or Fisher's exact test (≤ 5 observations in one or more cells). The P values for all hypothesis tests were two sided, and we set statistical significance at $P<0.05$. We used multivariate logistic regression analysis to assess the risk of adverse obstetric outcome. We did both univariate and multivariate analyses on only those records with no missing values for any of the maternal covariates included in the multivariate model. We used the Hosmer and Lemeshow test to assess the goodness of fit of logistic regression models.[21] We assessed the statistical significance of interaction terms by using the likelihood ratio test and assumed significance of interactions at $P<0.01$. We defined the attributable fraction as Pr(exposed/disease)*(1 – 1/relative risk). This can be conceptualised as the proportion of cases that would have been prevented if the exposure did not exist in a population. We calculated adjusted attributable fractions after multivariate logistic regression by using the method of Greenland and Drescher.[22] We used the Stata software package, version 7.0, for all statistical analyses.

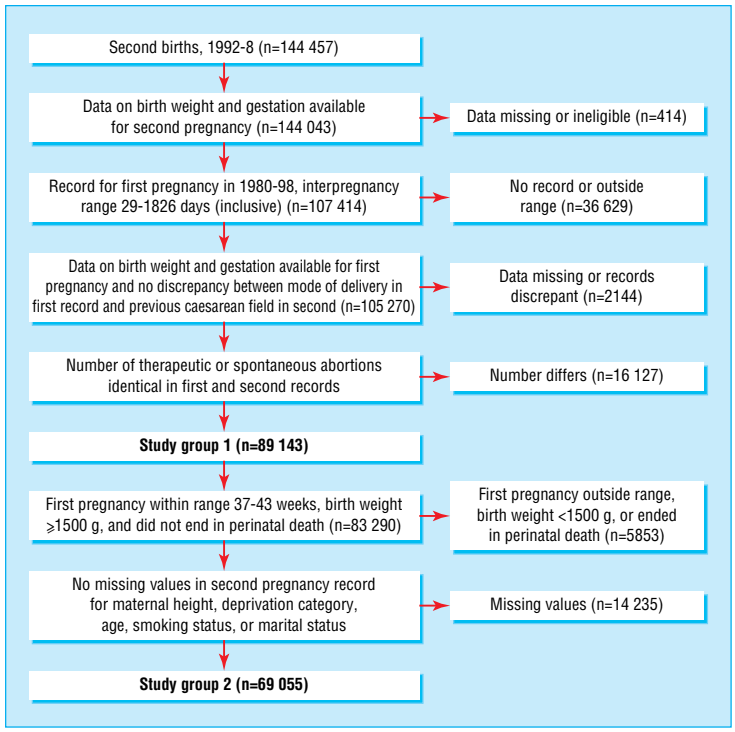
Results

The figure outlines the selection of the two study groups. Approximately 5.4% of the cohort had an interpregnancy interval of less than six months.

Women who subsequently had a short interpregnancy interval were more likely to have experienced complications in their first pregnancy (table 1). Compared with women who had an interpregnancy interval of 18-23 months, those with an interval of less than six months had a 30-50% excess of intrauterine growth restriction and moderately preterm birth in their first pregnancy, a fourfold excess of extremely preterm birth, and a greater than 20-fold excess of perinatal deaths. An excess of extremely preterm first births existed among women whose subsequent interpregnancy interval was 2-5 years.

All analyses of the outcome of the second birth were confined to the subgroup of women whose first birth was a term live birth. Even among this group, at the time of their second delivery, women with a short interval between their first and second pregnancy were more likely to be aged less than 20, to smoke, and to live in an area of high deprivation and were less likely to be married, to be aged greater than 35, and to live in an area of low socioeconomic deprivation (table 2).

On univariate analysis of obstetric outcome in the second birth, women with a short interpregnancy interval were more likely to have an extremely preterm birth, a moderately preterm birth, or a neonatal death (table 3). The strength of these associations was attenuated by adjustment for maternal age, marital status, height, socioeconomic deprivation category, smoking, previous birth weight vigesimal, and previous caesarean section, but significant associations persisted in multivariate analysis. The adjusted attributable fractions for these associations were 6.1% (95% confidence interval 1.9% to 10.2%) for extremely preterm birth, 3.9% (1.3% to 4.2%) for moderately preterm birth, and 13.8% (0.2% to 25.6%) for neonatal death unrelated to fetal abnormality. The excess of preterm second births persisted when the analysis was confined to spontaneous preterm births. An interpregnancy interval of less than six months was associated with an increased risk (compared with an interpregnancy interval of 18-23 months) of spontaneous preterm birth, both 24-32 weeks (adjusted odds ratio 2.2, 95% confidence interval 1.2 to 4.1) and 33-36 weeks (1.6, 1.2 to 2.2). The associations between interpregnancy interval and unexplained stillbirth were virtually identical when estimated using time to event methods (data not shown).



Flow diagram of cohort selection

We explored the relations between interpregnancy interval, maternal age, and other maternal factors and the outcome of the second birth in more detail. The attenuation of the association between interpregnancy interval and adverse outcome in multivariate analysis was principally due to the effect of adjustment for age (table 4). The odds ratio for interpregnancy interval adjusted for age alone was very similar to the odds ratio adjusted for age plus the other maternal covariates. Maternal age less than 20 years at the time of the second birth was strongly associated with preterm birth and neonatal death. The association remained statistically significant in multivariate analysis but was attenuated by adjustment for both interpregnancy interval and other maternal factors. No statistically significant interactions existed between interpregnancy interval and maternal age, marital

Table 1 Outcome of first pregnancy in relation to interval between first and second pregnancies (n=89 143)

	Interpregnancy interval*								
	1-5 months		6-11 months		12-17 months		18-23 months*	24-59 months	
Outcome of first pregnancy	No (%)	Odds ratio (95% CI)	No (%)	Odds ratio (95% CI)	No (%)	Odds ratio (95% CI)	No (%)	No (%)	Odds ratio (95% CI)
No of births	4816	–	11 927	–	15 771	–	15 014	41 615	–
Birth weight <5th centile	298 (6.6)	1.3 (1.1 to 1.5)	613 (5.2)	1.0 (0.9 to 1.1)	804 (5.1)	1.0 (0.9 to 1.1)	768 (5.1)	2347 (5.6)	1.1 (1.0 to 1.2)
Preterm delivery:									
24-32 weeks	146 (3.2)	4.1 (3.2 to 5.3)	181 (1.5)	1.9 (1.5 to 2.4)	155 (1.0)	1.2 (1.0 to 1.6)	120 (0.8)	458 (1.1)	1.4 (1.1 to 1.7)
33-36 weeks	257 (5.9)	1.5 (1.3 to 1.7)	570 (4.9)	1.2 (1.1 to 1.4)	662 (4.3)	1.1 (1.0 to 1.2)	592 (4.0)	1830 (4.4)	1.1 (1.0 to 1.2)
Perinatal death:									
All causes†	481 (10.0)	24.4 (18.9 to 31.5)	247 (2.0)	4.6 (3.5 to 6.1)	103 (0.6)	1.4 (1.1 to 2.0)	68 (0.4)	120 (0.3)	0.6 (0.5 to 0.9)
Fetal abnormality or rhesus	71 (1.5)	15.0 (8.6 to 26.1)	38 (0.3)	3.2 (1.8 to 5.8)	21 (0.1)	1.3 (0.7 to 2.6)	15 (0.1)	26 (0.1)	0.6 (0.3 to 1.2)
Unexplained stillbirth	188 (3.9)	30.5 (19.2 to 48.3)	87 (0.7)	5.5 (3.4 to 9.0)	37 (0.2)	1.8 (1.0 to 3.0)	20 (0.1)	36 (0.1)	0.6 (0.4 to 1.1)
All other stillbirths	109 (2.3)	20.4 (12.2 to 34.1)	55 (0.5)	4.1 (2.4 to 7.0)	21 (0.1)	1.2 (0.6 to 2.2)	17 (0.1)	24 (0.1)	0.5 (0.3 to 0.9)
All other neonatal deaths	110 (2.3)	23.4 (13.6 to 40.1)	65 (0.5)	5.5 (3.1 to 9.6)	23 (0.2)	1.5 (0.8 to 2.8)	15 (0.1)	34 (0.1)	0.8 (0.4 to 1.5)

All percentages calculated relative to appropriate denominators (see methods).
*Reference category for odds ratios was women with interpregnancy interval of 18-23 months.
†Seven perinatal deaths were not classified.

Table 2 Demographic factors at time of second pregnancy in relation to interpregnancy interval in women with previous term live birth (n=69 055). Values are numbers (percentages)

	Interpregnancy interval (months)						
	1-5 (n=3282)	6-11 (n=8999)	12-17 (n=12 220)	18-23 (n=11 793)	24-59 (n=32 761)	Total (n=69 055)	P value
Height (cm):							
<155	349 (10.6)	843 (9.3)	1 068 (8.7)	1 125 (9.5)	3 614 (11.0)	6 990 (10.1)	<0.001
155-170	2654 (80.9)	7160 (79.6)	9 868 (80.8)	9 398 (79.7)	26 299 (80.3)	55 379 (80.2)	
>170	279 (8.5)	1005 (11.2)	1 284 (10.5)	1 270 (10.8)	2 848 (8.7)	6 686 (9.7)	
Age (years):							
<20	547 (16.7)	669 (7.4)	501 (4.1)	278 (2.4)	234 (0.7)	2 229 (3.2)	<0.001
20-35	2624 (80.0)	7899 (87.8)	11 120 (91.0)	10 961 (92.9)	30 655 (93.6)	63 259 (91.6)	
>35	111 (3.4)	431 (4.8)	599 (4.9)	554 (4.7)	1 872 (5.7)	3 567 (5.2)	
Marital status:							
Married	1949 (59.4)	6714 (74.6)	9 681 (79.2)	9 615 (81.5)	25 315 (77.3)	53 274 (77.2)	<0.001
Other	1333 (40.6)	2285 (25.4)	2 539 (20.8)	2 178 (18.5)	7 446 (22.7)	15 781 (22.8)	
Deprivation category:							
1 (least deprived)	484 (14.8)	1919 (21.3)	2 933 (24.0)	2 720 (23.1)	6 045 (18.4)	14 101 (20.4)	<0.001
2-4	1915 (58.4)	5397 (60.0)	7 242 (59.3)	7 104 (60.2)	19 809 (60.5)	41 467 (60.0)	
5 (most deprived)	883 (26.9)	1683 (18.7)	2 045 (16.7)	1 969 (16.7)	6 907 (21.1)	13 487 (19.5)	
Smoking status:							
Non-smoker	1839 (56.0)	6078 (67.5)	8 560 (70.0)	8 309 (70.5)	21 279 (65.0)	46 065 (66.7)	<0.001
Ex-smoker	193 (5.9)	536 (6.0)	797 (6.5)	759 (6.4)	2 533 (7.7)	4 818 (7.0)	
Smoker	1250 (38.1)	2385 (26.5)	2 863 (23.4)	2 725 (23.1)	8 949 (27.3)	18 172 (26.3)	

status, height, socioeconomic deprivation category, smoking, previous birth weight vigesimal, or previous caesarean section in predicting adverse obstetric outcome in the second pregnancy. The strengths of the associations were virtually identical when confined to married non-smokers aged 25 or above: in this group an interpregnancy interval of less than six months was associated with an odds ratios of 2.8 (1.3 to 5.9) for extremely preterm birth and 1.7 (1.2 to 2.4) for moderately preterm birth.

We considered the possibility that misclassification of gestational age may have affected the results by examining the association between interpregnancy interval and absolute values of birth weight in the second pregnancy. An interpregnancy interval of less than six months was associated with an increased risk of delivering a low birth weight neonate (adjusted odds ratio 1.5, 1.2 to 1.8) or a very low birth weight neonate (1.9, 1.0 to 3.4). We considered the possibility that excluding the 14 255 cases with missing values for potential confounders from the second study group may have affected our results. However, univariate analysis of second pregnancy outcomes including these cases showed positive associations between a one to five month interval (18-23 months as reference group) and extreme preterm birth (odds ratio 2.8, 1.9 to 4.2), moderate preterm birth (2.0, 1.6 to 2.4), and neonatal death unrelated to congenital abnormality (3.2, 1.3 to 7.9).

Discussion

The main finding of this study is that in women having a second birth a short preceding interpregnancy inter-

Table 3 Crude and adjusted odds ratios for interpregnancy interval and the outcome of the second pregnancy (n=69 055)

	Interpregnancy interval*												
	1-5 months (n=3282)			6-11 months (n=8999)			12-17 months (n=12 220)			18-23 months* (n=11 793)	24-59 months (n=32 761)		
Outcome of second pregnancy		Odds ratio (95% CI)			Odds ratio (95% CI)			Odds ratio (95% CI)				Odds ratio (95% CI)	
	No (%)	Crude	Adjusted†	No (%)	Crude	Adjusted†	No (%)	Crude	Adjusted†	No (%)	No (%)	Crude	Adjusted†
Birth weight <5th centile	99 (3.0)	1.1 (0.9 to 1.4)	0.8 (0.7 to 1.1)	234 (2.6)	1.0 (0.8 to 1.1)	0.9 (0.8 to 1.1)	325 (2.7)	1.0 (0.8 to 1.1)	1.0 (0.8 to 1.2)	321 (2.7)	987 (3.0)	1.1 (1.0 to 1.3)	1.0 (0.9 to 1.1)
Preterm delivery:													
24-32 weeks	32 (1.0)	3.1 (1.9 to 4.9)	2.2 (1.4 to 3.6)	46 (0.5)	1.6 (1.0 to 2.4)	1.4 (0.9 to 2.2)	48 (0.4)	1.2 (0.8 to 1.9)	1.2 (0.8 to 1.8)	38 (0.3)	122 (0.4)	1.2 (0.8 to 1.7)	1.1 (0.8 to 1.6)
33-36 weeks	130 (4.0)	2.0 (1.6 to 2.4)	1.6 (1.3 to 2.0)	218 (2.4)	1.2 (1.0 to 1.4)	1.1 (0.9 to 1.3)	280 (2.3)	1.1 (0.9 to 1.3)	1.1 (0.9 to 1.3)	244 (2.1)	800 (2.5)	1.2 (1.0 to 1.4)	1.2 (1.0 to 1.3)
Perinatal death:													
Fetal abnormality or rhesus	6 (0.2)	1.4 (0.6 to 3.7)	1.2 (0.5 to 3.3)	12 (0.1)	1.0 (0.5 to 2.2)	1.0 (0.5 to 2.1)	17 (0.1)	1.1 (0.5 to 2.2)	1.2 (0.5 to 2.2)	15 (0.1)	45 (0.1)	1.1 (0.6 to 1.9)	1.1 (0.6 to 2.0)
Unexplained stillbirth	7 (0.2)	1.6 (0.6 to 3.8)	1.2 (0.5 to 3.0)	10 (0.1)	0.8 (0.4 to 1.8)	0.7 (0.3 to 1.7)	20 (0.2)	1.2 (0.6 to 2.3)	1.2 (0.6 to 2.3)	16 (0.1)	55 (0.2)	1.2 (0.7 to 2.2)	1.2 (0.7 to 2.1)
All other stillbirths	5 (0.2)	2.6 (0.8 to 8.1)	2.3 (0.7 to 7.2)	9 (0.1)	1.7 (0.6 to 4.5)	1.7 (0.6 to 4.5)	12 (0.1)	1.7 (0.7 to 4.2)	1.7 (0.7 to 4.3)	7 (0.1)	27 (0.1)	1.4 (0.6 to 3.2)	1.2 (0.5 to 2.8)
All other neonatal deaths	9 (0.3)	5.4 (1.9 to 15.2)	3.6 (1.2 to 10.7)	10 (0.1)	2.2 (0.8 to 6.0)	1.9 (0.7 to 5.2)	2 (0.0)	0.3 (0.1 to 1.6)	0.3 (0.1 to 1.5)	6 (0.1)	20 (0.1)	1.2 (0.5 to 3.0)	1.2 (0.5 to 3.0)

All percentages calculated relative to appropriate denominators (see methods).
*Reference category for odds ratios was women with interpregnancy interval of 18-23 months.
†Adjusted for maternal age, marital status, height, socioeconomic deprivation category, smoking, previous birth weight vigesimal, and previous caesarean section.

Table 4 Interpregnancy interval, maternal age, other demographic factors, and risk of adverse obstetric outcome

	Odds ratios (95% CI) for interpregnancy interval <6 months				Odds ratios (95% CI) for age <20 years			
Outcome	Crude	Adjusted 1	Adjusted 2	Adjusted 3	Crude	Adjusted 1	Adjusted 2	Adjusted 3
Delivery 24-32 weeks	3.1 (1.9 to 4.9)	2.3 (1.4 to 3.8)	2.5 (1.5 to 4.0)	2.2 (1.4 to 3.6)	4.0 (2.6 to 6.2)	3.2 (2.0 to 5.1)	2.6 (1.6 to 4.2)	2.0 (1.2 to 3.4)
Delivery 33-36 weeks	2.0 (1.6 to 2.4)	1.7 (1.3 to 2.1)	1.7 (1.4 to 2.1)	1.6 (1.3 to 2.0)	2.3 (1.9 to 2.9)	2.2 (1.7 to 2.7)	1.6 (1.3 to 2.1)	1.5 (1.2 to 2.0)
Neonatal death unrelated to congenital abnormality or rhesus	5.4 (1.9 to 15.2)	3.8 (1.3 to 11.0)	4.3 (1.5 to 12.3)	3.6 (1.2 to 10.7)	8.4 (3.2 to 22.2)	5.6 (2.0 to 15.9)	5.0 (1.6 to 15.7)	3.5 (1.0 to 11.6)

Adjusted 1=adjusted only for maternal age or interpregnancy interval; adjusted 2=adjusted only for maternal smoking, socioeconomic deprivation, height, previous birth weight vigesimal, and previous caesarean section; adjusted 3=adjusted for maternal smoking, socioeconomic deprivation, height, previous caesarean section, birth weight vigesimal, and maternal age or interpregnancy interval.

val was an independent risk factor for extremely preterm birth, moderately preterm birth, and neonatal death not due to congenital abnormality. The association occurred even among women whose first pregnancy was a term live birth and persisted after adjustment for maternal age, marital status, height, socioeconomic deprivation category, smoking, previous birth weight vigesimal, and previous caesarean section. The association was specific to preterm birth and neonatal death, as no association existed between a short interpregnancy interval and the risk of delivering a growth restricted infant and the confidence intervals were sufficiently narrow to exclude even a weak association. When we examined the outcome of all first births in relation to the subsequent interpregnancy interval, women with a short interpregnancy interval had a significant excess of intrauterine growth restriction, preterm birth, and perinatal deaths in their first births. Indeed, approximately 10% of women with an interval of less than six months had a first birth that had ended in perinatal death, compared with less than 1% of women with an interval of 18-23 months. These observations are consistent with previous studies and underline the importance of excluding women with complications in their first birth when examining associations between interpregnancy interval and the outcome of the second birth.[11]

An association has previously been shown between maternal age less than 20 years at the time of the second birth and adverse obstetric outcome.[23] In the present study we could show that this association was independent of interpregnancy interval and complications of the first pregnancy. However, the association between maternal age less than 20 years and adverse outcome was attenuated by adjustment for marital status, socioeconomic deprivation category, smoking status, height, previous birth weight vigesimal, and previous caesarean section, although a statistically significant association persisted in multivariate analysis (table 4). We cannot exclude the possibility that maternal age less than 20 years is a marker for some other environmental factor. However, it is unlikely that the associations with a short interpregnancy interval were due to unmeasured or residual confounding. Firstly, after adjustment for maternal age, adjustment for other maternal factors had very little effect (table 4). Secondly, the strength of the association was virtually unchanged when we confined the analysis to married, non-smoking women aged 25 and above. Thirdly, no statistically significant first order interactions occurred between a short interpregnancy interval and other maternal factors. Finally, the association was specific for preterm birth and neonatal death. No association existed between a short interpregnancy interval and delivering a small for gestational age baby. In contrast, a high socioeconomic deprivation category (that is, more deprived) was significantly associated with delivering a small for gestational age baby in multivariate analysis (data not shown).

The lack of association between interpregnancy interval and growth restriction also suggests that the relation between a short interpregnancy interval and other adverse outcomes is unlikely to be due to depletion of maternal nutritional reserves. A specific association between a short interpregnancy interval and preterm birth is biologically plausible. The control of parturition is thought to be mediated by a two step process of activation and stimulation.[24] Activation is defined as the up regulation of expression of a range of contraction associated proteins, such as G protein coupled receptors, in the weeks leading up to term. Stimulation is defined as the process by which synthesis and release of natural agonists for these receptors, such as prostaglandins, initiates uterine contraction. We hypothesise that failure to allow expression of contraction associated proteins to return to prepregnancy levels may be the mechanism by which a short interpregnancy interval predisposes to preterm birth.

We propose that women should be informed of a small but significantly elevated risk of preterm birth

What is already known on this topic

Women with a short interval between pregnancies are at increased risk of obstetric complications

These women also differ in their previous obstetric complications and demographic characteristics

Whether the increased risk of adverse outcome after a short interpregnancy interval is merely due to confounding by obstetric and demographic associations is unclear

What this study adds

Women with short intervals between pregnancies are much more likely to have had complicated first births and to have demographic risk factors for obstetric complications

Even among women with an uncomplicated first birth and after adjustment for maternal demographics, a short interpregnancy interval was associated an increased risk of preterm birth and neonatal death

and perinatal death when they conceive shortly after a birth. Contraceptive advice should be targeted towards women who are most likely to have a subsequent short interpregnancy interval—namely, teenagers and women who have just experienced a perinatal loss.

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Use of time to event analysis to estimate the normal duration of human pregnancy

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BACKGROUND: Current estimates of the average duration of human pregnancy are flawed by inaccurate estimation of the time of conception and by failure to account adequately for the effect of routine elective delivery post-term. METHODS: In this study, 1514 healthy pregnant women were studied in whom the discrepancy between the menstrual history and first trimester crown–rump length estimated gestational age was within –1 to +1 day difference. The duration of gestation was estimated using time to event analysis: non-elective delivery was taken to be the event, and elective delivery was taken to be censoring. RESULTS: The median time to non-elective delivery using the Kaplan–Meier product limit estimate was 283 days after last menstrual period (LMP) and there was no difference comparing male and female fetuses. The median was significantly greater for nulliparous women compared with multiparous women (284 versus 282 days, $P < 0.0001$). Multivariate analysis using Cox's proportional hazards model confirmed the independent effect of nulliparity on duration of pregnancy [hazard ratio, 0.75; 95% confidence interval (CI) 0.67–0.85] and demonstrated no effect of maternal age, previous abortions, fetal sex, high parity, or bleeding before 24 completed weeks of gestation. Bleeding in the third trimester of pregnancy was, however, associated with an earlier onset of spontaneous labour (hazard ratio, 1.38; 95% CI 1.03–1.84). CONCLUSION: This study provides a basis for predicting the probability of labour at a given gestational age at term.

Key words: duration/human/pregnancy/proportional hazards models/survival analysis

Introduction

Attempts to characterize the normal duration of pregnancy extend back through history, because of the importance of establishing paternity. Prior to modern obstetric methods, reference points for conception were taken as the first day of the last menstrual period (LMP) or the date of an isolated act of sexual intercourse (Reid, 1850). The LMP is a poor surrogate of the time of ovulation since, even among women with a regular 28 day cycle, the timing of ovulation is skewed to the second half of the cycle (Lenton and Landgren, 1985). Establishing the date of intercourse is clearly subject to multiple sources of error.

Modern obstetric techniques can be used to provide an unbiased estimate of gestational age. However, modern obstetric practice also involves routine elective delivery post-term (Grant, 1994). When attempting to estimate the duration of pregnancy, the effect of routine elective delivery cannot be avoided using current methods. If these pregnancies are excluded, then there is a systematic exclusion of pregnancies which are prolonged. If they are included, then the average duration of pregnancy includes cases where the end was never fully established.

A range of statistical techniques has been developed to estimate the average time period to the onset of a non-recurrent event, typically death (Hosmer and Lemeshow, 1999). These methods (typically referred to as 'time to event analysis' or 'survival analysis') take into account censored observations, i.e. observation of an individual to a given point until they no longer became at risk of the event. In the present study, it was sought to determine the average duration of human pregnancy among a previously described cohort of normal women (Smith *et al.*, 1998) where gestational age had been confirmed by first trimester ultrasound and where the estimate was adjusted for the effect of elective delivery using time to event analysis. A preliminary account of some of this work has been presented in abstract form (Smith, 2000).

Materials and methods

The results of all ultrasound scans performed between 1985 and 1995 at the Queen Mother's Hospital, Glasgow, UK were entered into a computer database along with details of the woman's medical, gynaecological and obstetric history, antenatal complications and pregnancy outcome. The database included all pregnant women referred for antenatal care because all were scanned at their first antenatal visit. Those women referred early for antenatal care were usually seen after having amenorrhoea for 12 weeks.

Over the 10 year period, 31 269 embryos or fetuses had at least one scan and a known date of delivery. Gestational age at delivery was recorded in 31 259 and birth weight was recorded in 30 789. Of

the 480 infants for whom birth weight was missing, 460 were delivered at <24 weeks.

Any pregnancies with the following (number of cases) were excluded: history of rhesus iso-immunization (279), essential hypertension (324), cardiac disease (128), type 1 diabetes mellitus (115), other medical problems (992), non-viable embryo or fetus at first scan (115), amniocentesis (1259), chorionic villous sampling (929), multiple pregnancy (364), antenatal detection of fetal abnormality (515), therapeutic termination of pregnancy (224), post-natal detection of fetal abnormality (560), intra-uterine contraceptive device seen on ultrasound (42), and second sac seen on ultrasound (85). There were a total of 4568 exclusions (some cases had multiple exclusions).

The crown–rump length was measured by the sonographer using electronic callipers on a frozen image on a monitor. The technique is described elsewhere (Evans *et al.*, 1990). The crown–rump length was recorded as the equivalent number of days gestational age on the basis of an equation [gestational age (weeks) = 8.052 $\sqrt{}$ crown–rump length + 23.73] previously derived at The Queen Mother's Hospital (Robinson and Fleming, 1975). The scans analysed in the present study were performed by real-time ultrasonography using several machines, the majority were trans-abdominal scans through a full bladder.

The inclusion criteria based on the ultrasonography record were a single viable embryo or fetus present at the first ultrasound scan and a crown–rump length at the time of this scan less than the expected size after having amenorrhoea for 13 weeks. A total of 11 314 of the 26 701 non-excluded cases fulfilled these criteria.

The inclusion criteria from the menstrual history were: (i) there was a date recorded for the first day of the last menstrual period and that it was recorded as certain; (ii) there had been no oral contraceptive use in the preceding 3 months, and (iii) the menstrual cycle was 28 days and regular. Of the 11 314 cases with no exclusion criteria who had an early ultrasound scan, 4229 fulfilled the menstrual inclusion criteria and had a birth weight recorded. The study group consisted of 1514 cases where the discrepancy between the estimated gestational age by the menstrual history was within ±1 day of the ultrasound estimate.

Statistical analysis

Delivery by emergency Caesarean section or vaginal birth following non-induced labour were taken to be the event. Elective Caesarean section or any mode of delivery following an induced labour were taken as censoring. The cumulative probability of non-elective delivery at each day of gestation was estimated using the Kaplan–Meier product limit estimate. Univariate comparisons were made using the log rank test. Multivariate modelling was performed using Cox's proportional hazard's method. These techniques are described in detail elsewhere (Hosmer and Lemeshow, 1999). Statistical analysis was performed using Stata version 6.0 (Stata Corporation, College Station, TX, USA).

Results

The basic characteristics of the study group are summarized in Table I. The simple arithmetic median interval from the first day of the LMP to the date of delivery was 281 days.

When the effect of censored observations was taken into account using the Kaplan–Meier product limit estimate, the median time from LMP to non-elective delivery was 283 days (95% confidence interval (CI), 282–284 days). There was no significant difference in the median comparing male and female fetuses and the number of elective deliveries was similar comparing the two sexes (female 23.1%, male = 24.3%). The median time from LMP to non-elective delivery was 2 days longer among nulliparous women compared with multiparous women (Table II and Figure 1) and the difference was highly statistically significant ($P < 0.0001$). The proportion electively delivered was virtually identical comparing the two groups

Table I. Characteristics of study group (n = 1514)

Characteristic	Number (%) or median (IQ range)
Maternal age at booking (years)	28 (25–31)
Gestational age at dating scan (days)	82 (72–87)
Previous births	
0	677 (44.7)
1	558 (36.9)
2	194 (12.8)
>2	85 (5.6)
Previous spontaneous abortions	
0	1155 (76.3)
1	278 (18.4)
2	53 (3.5)
>2	28 (1.8)
Previous therapeutic abortions	
0	1392 (91.9)
1	109 (7.2)
2	11 (0.7)
>2	2 (0.1)
Bleeding in current pregnancy	
First trimester	148 (9.8)
Second trimester	37 (2.4)
Third trimester	72 (4.8)
Induced labour	251 (16.6)
Mode of delivery	
SVD	912 (60.2)
Assisted vaginal	345 (22.8)
Elective Caesarean section	109 (7.2)
Emergency Caesarean section	147 (9.7)
Birth weight of baby (g)	3430 (3100–3740)
Male sex	778 (51.4)
Interval from LMP to delivery (days)	281 (273–286)

IQ = interquartile; SVD = simple vaginal delivery.

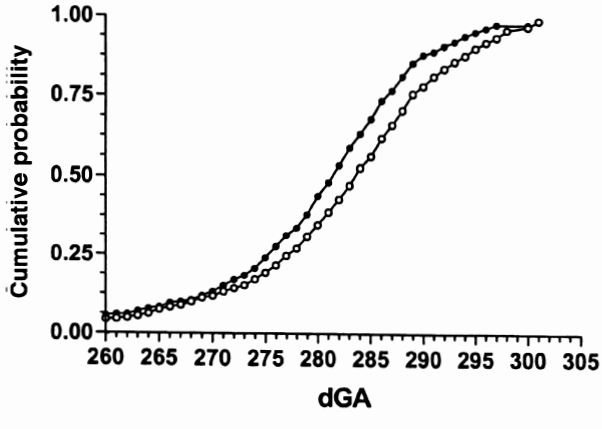

Figure 1. Cumulative probability of non-elective delivery at each day of gestational age (dGA) for multiparous (filled symbols, n = 837) and nulliparous (hollow symbols, n = 677) women. Points are cumulative probability. Comparison of curves: $P < 0.0001$ (log rank test).

Table II. Median time to delivery from Kaplan–Meier product limit estimate

Group	Median duration in days (inter-quartile range)
All women	283 (277–288)
Nulliparous women	284 (278–289)
Multiparous women	282 (276–287)
Male fetus	283 (276–289)
Female fetus	283 (277–288)
Excluding third trimester bleeding	283 (277–288)
Emergency Caesarean section treated as censored	283 (277–289)

Table III. Multivariate proportional hazards model of factors determining onset of labour at term

Characteristic	Hazard ratio (95% CI)	*P* value
Age < 20 years	1.05 (0.76–1.45)	0.75
Age 25–29 years	0.90 (0.76–1.06)	0.22
Age 30–34 years	0.90 (0.76–1.07)	0.24
Age > 34 years	1.06 (0.83–1.37)	0.63
Nulliparous	0.75 (0.66–0.85)	<0.0001
Parity > 2	1.01 (0.77–1.33)	0.93
One previous spontaneous abortion	1.11 (0.96–1.29)	0.16
More than one previous spontaneous abortion	0.98 (0.75–1.29)	0.91
One previous therapeutic abortion	0.99 (0.79–1.23)	0.90
More than one previous therapeutic abortion	0.59 (0.32–1.11)	0.10
First trimester bleeding	0.99 (0.81–1.21)	0.92
Second trimester bleeding	1.20 (0.78–1.83)	0.41
Third trimester bleeding	1.38 (1.03–1.84)	0.03
Male fetal sex	0.95 (0.85–1.07)	0.39

(nulliparous 23.3%, multiparous 24.0%). Excluding women with antepartum haemorrhage and treating emergency Caesarean sections as censored observations had no effect on the estimate of the median duration of pregnancy (Table II).

Multivariate analysis confirmed the independent effect of nulliparity on duration of pregnancy and demonstrated no effect of maternal age, previous abortions, fetal sex, high parity, or bleeding before 24 completed weeks of gestation (Table III). Bleeding in the third trimester of pregnancy was, however, associated with an earlier onset of spontaneous labour. Exclusion of deliveries by emergency Caesarean section had very little effect on the hazard ratios for primparity [0.80 (95% CI, 0.70–0.91)], third trimester bleeding [1.41 (1.03–1.92)] or any of the other covariates (data not shown).

Discussion

One of the most basic descriptive variables of a mammalian species is the average duration of pregnancy. All previous estimates of the average duration of human pregnancy are flawed either by sub-optimal gestational dating or by the failure to correct adequately for the effect of routine elective delivery post-term. The study group in this paper had optimum dating by menstrual history and this was confirmed by close agreement with first trimester ultrasound. This provides the most accurate estimate of gestational age currently possible in spontaneous conceptions (Evans *et al.*, 1990). The effect of elective delivery was addressed in this study by the use of survival time analysis whereby elective deliveries were treated as censored observations. Using survival analysis in this cohort, the overall average duration of pregnancy was 283 days, two days longer than the simple arithmetic median interval from LMP to date of delivery.

Unlike previous studies (Bergsjo *et al.*, 1990), there was no apparent difference in the duration of pregnancy comparing male and female fetuses (Tables II and III). Previous findings of a difference in gestational duration according to fetal sex may reflect a relationship between the timing of fertilization relative to the LMP and fetal sex (James, 1994). The duration of pregnancy was approximately two days longer in nulliparous women. This was not due to a confounding effect of associated variables (maternal age, previous abortions etc) since nulliparity was still associated with later delivery after adjusting for these variables (Table III). The event used in the current analysis was birth, rather than the onset of labour. Labour in nulliparous women is, on average, three hours longer than in multiparous women (Nesheim, 1988). This is clearly not sufficient to explain the observed 2 day difference in duration of pregnancy comparing nulliparous and multiparous women.

The physiological regulation of the onset of parturition in the human is still only partially understood. Current models postulate key roles for the fetal hypothalamo–pituitary–adrenal axis (Nathanielsz *et al.*, 1998) and for the placenta (Majzoub and Karalis, 1999). The observed effect of parity does not exclude a key role for the fetus and placenta since important fetal variables, such as weight, differ between nulliparous and multiparous women (Kramer, 1987).

The clinical significance of this study is that it provides a basis for predicting the probability of labour at a given gestational age at term. This may be useful when planning trials of, for instance, routine induction of labour, or for the timing of procedures such as elective Caesarean section. The present data allow the probability that a woman might go into labour prior to a scheduled date for elective delivery to be estimated. Furthermore, the cumulative probability of delivery tended towards 1.0 at 300 days. However, the increased risk of stillbirth with very advanced gestational age (Yudkin *et al.*, 1987) means that virtually no pregnancy would be allowed to continue into the 43rd week and very high rates of censoring undermine the estimates of the probability of delivery at these advanced gestational ages.

The observation that bleeding in the third trimester was associated with an earlier onset of spontaneous delivery is plausible. However, given the relatively small number of women affected by third trimester bleeding, there was virtually no effect on the median duration of pregnancy when these cases were excluded (Table II). It is likely that a proportion of these cases were due to abruption which can initiate uterine activity. It is likely that labour in these women was initiated before the physiologically determined onset by a pathological process. However, the 'event' was non-elective delivery, i.e. including delivery by emergency Caesarean section. This was done since over 75% of emergency Caesarean sections are performed after the onset of labour (Macara and Murphy,

1994). It might be argued that third trimester bleeding due both to abruption and placenta praevia could lead to emergency Caesarean section before the onset of labour and that the apparent association between third trimester bleeding and early onset of labour may simply reflect an association between bleeding and emergency Caesarean section. However, the hazard ratios associated with both third trimester bleeding and nulliparity were very similar when emergency Caesarean sections were excluded. Treating emergency Caesarean sections as spontaneous births might also be criticized since a small proportion of these will have been performed prior to the onset of labour. Furthermore, when Caesarean section is performed during labour, birth necessarily occurs earlier than if vaginal birth had been awaited. However, the influence of these factors would be expected to be relatively minor and, indeed, treating emergency Caesarean section as censoring had no significant effect on the estimated median duration of pregnancy (Table II).

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Sex, Birth Weight, and the Risk of Stillbirth in Scotland, 1980–1996

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The aim of this study was to determine whether the risk of stillbirth associated with male fetal sex was modified by fetal growth. The study group consisted of all singleton first births weighing greater than 500 g delivered between 28 and 43 weeks gestation in Scotland in 1980–1996 (n = 469,152). Overall, male fetuses were at an increased risk of stillbirth (relative risk = 1.19, 95 percent confidence interval: 1.10, 1.29). There was a significant negative interaction between male sex and increasing birth weight quintile in term, but not preterm, births. The interaction was virtually identical when calculated independently for births in the periods 1980–1987 and 1988–1996. There were linear decreases in the proportion of stillbirths and the proportion of birth weights in the lowest quintile over the period 1980–1996. Adjustment for year of birth did not affect the relation between male sex and stillbirth. However, adjustment for birth weight resulted in a loss of the association between year of birth and risk of stillbirth. The authors concluded that 1) the association between male sex and stillbirth diminishes with increasing birth weight quintile, and 2) there was a fall in the proportion of stillbirths in Scotland between 1980 and 1996, which may have been due to a fall in the proportion of small babies over the same period. *Am J Epidemiol* 2000;151:614–19.

fetal death; gestational age; infant mortality; population surveillance; risk; sex

The risk of mortality differs between males and females in a number of areas of adult human medicine (1–3). Analysis of the mechanisms of such differences is hampered by social and cultural variation in lifestyle between men and women, which may interact with and obscure fundamental sexual differences in human biology (4, 5). Fetal sex has a major effect on a number of aspects of human pregnancy, such as intrauterine growth (6), late fetal death (4, 7–9), preterm birth (10), and necessity for emergency Cesarean delivery (11). These associations allow for the analysis of sex differences in morbidity and mortality in isolation from behavioral and cultural modification and confounding.

It has been suggested previously that the excess of male stillbirths may be related to trauma secondary to the greater average size of males (4). However, animal studies have demonstrated sex differences in the fetal stress response (12–15). Human fetuses that are small for gestational age are at increased risk of late fetal death (16). The aim of this study was to test the hypothesis that the increased risk of stillbirth in males varies with fetal growth.

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Abbreviation: CI confidence interval.

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MATERIALS AND METHODS

Source of data

Data were collected from the Scottish morbidity record (maternity), a national database of pregnancy information that has been greater than 99 percent complete since the late 1970s (17). To eliminate interactions between number of previous pregnancies, birth weight, and risk of stillbirth, we restricted analysis to women having their first baby. There were a total of 478,655 records of singleton and twin first pregnancies. The following exclusions were made (number of records): twins (n = 4,946); missing gestational age (n = 2,416); missing sex (n = 30); missing weight (n = 467); gestational age at delivery of less than 28 or greater than 43 weeks (n = 1,936); and weight less than 500 g (n = 164). The study group was 469,152 (a small number of records had multiple exclusions and/or missing values), which was greater than 99 percent of all singleton births over the period. Gestational age was recorded as completed weeks of gestation and was calculated on the basis of the estimated date of delivery (280 days from the first day of the last menstrual period, corrected to a 28-day menstrual cycle) in the patient's clinical record. Term was defined as 37 weeks' gestation. Fetal death was assumed when a

baby was born that exhibited no signs of life. When a baby exhibited any signs of life, however briefly, it was classified as a livebirth.

Birth weight quintiles and deciles

Analysis of birth weight across a range of gestational ages was performed using birth weight quintiles or deciles. Quintiles were used in the comparison between males and females to increase the number of stillbirths in each group. For births at each week of gestation, the birth weights of males and females were independently classed as quintiles. For example, if 1,000 males and 1,000 females were born in a given week, the pooled quintile would be the smallest 200 boys and the smallest 200 girls. The sex-specific quintiles for all weeks of gestation were then pooled., i.e., the lowest quintile is the smallest 20 percent of boys and smallest 20 percent of girls born at each week of gestation from 28 to 43 weeks. Adjustment of the odds ratio for year of birth for birth weight was performed using birth weight deciles, which were also calculated independently for each week of gestation for males and females and pooled. Year-specific quintiles were also calculated to correct for variation in birth weight over the study period. Quintiles were calculated as above for four periods: 1980–1984, 1985–1988, 1989–1992, and 1993–1996 (inclusive), and then the quintiles from the four time periods were pooled.

Statistical analysis

Dichotomous outcomes were compared by using relative risks. The null hypothesis that the relative risk of being male was the same across strata was tested using the Mantel-Haenszel test of heterogeneity (18). Adjusted odds ratios for factors and interactions were calculated using logistic regression analysis, and the goodness-of-fit was assessed using the Pearson chi-squared test (18). Continuous variables were summarized by the median and interquartile ranges. Statistical analysis was performed using the Stata software package, version 6.0 (Stata Corporation, College Station, Texas). Statistical significance was assumed at the 5 percent level.

RESULTS

There were 1,469 male stillbirths and 239,808 male livebirths, and 1,162 female stillbirths and 226,713 female livebirths (stillbirth male relative risk = 1.19, 95 percent confidence interval (CI): 1.10, 1.29; population attributable fraction, 9.1 percent). The relative risk of stillbirth varied according to birth weight quintile (figure 1). When term and preterm births were analyzed separately, the trend was evident only among term births (figure 2).

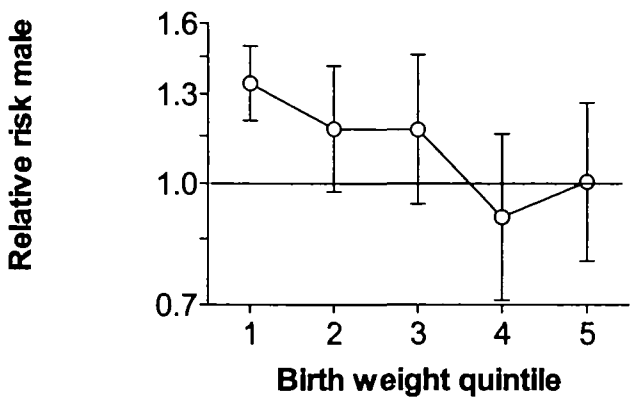

FIGURE 1. Relative risk ($\log_{10}$ scale) of stillbirth associated with male sex related to birth weight quintiles in Scotland, 1980–1996. Mantel-Haenszel test for heterogeneity $\chi^2 = 11.5$, $p = 0.02$. Bars are 95% confidence intervals.

The relation was examined using logistic regression analysis. Preliminary analysis demonstrated that the goodness-of-fit was improved if birth weight quintile was modeled as a series of categorical variables rather than as a continuous variable, indicating that the relation between birth weight quintile and risk of stillbirth is nonlinear. An interaction term between male sex and birth weight quintile demonstrated a significant negative interaction with increasing birth weight quintile. The log-likelihood was virtually unchanged if the interaction between male sex and birth weight quintile was modeled as interactions with each quintile as a categorical variable (log likelihood, −15,645.2) or with quintile as a continuous variable (log likelihood, −15,646.0), and therefore the model with the fewer parameters (the latter) was used (table 1).

Preliminary analyses demonstrated significant interactions between term birth and 1) male sex, 2) birth weight quintile, and 3) the interaction between sex and birth weight quintile. Therefore, further comparison of term and preterm births was made using separate logistic regression models. When confined to term deliveries, the adjusted odds ratio of the interaction between male sex and birth weight quintile was still statistically significant, whereas it was no longer significant when the analysis was confined to preterm deliveries (table 1). The adjusted odds ratio of the interaction for term births between 1980 and 1987 was 0.86 (95 percent CI: 0.76, 0.97) and for births between 1988 and 1996, it was 0.87 (95 percent CI: 0.78, 0.98). The adjusted odds ratio of the interaction for term births using year-specific quintiles (see Materials and Methods) was 0.88 (95 percent CI: 0.81, 0.95).

The number and birth weight of livebirths and stillbirths at each week of gestation are tabulated for males and females (table 2). More males (n = 16,011 at 28–36 weeks vs. 225,266 at term) than females (n = 13,070 at 28–36 weeks vs. 214,805 at term) were delivered preterm (relative risk of preterm delivery for males = 1.16, 95 percent CI: 1.13, 1.18; population attributable fraction, 7.5 percent).

There were linear decreases in the proportion of stillborn babies per year over the period 1980–1996 (yearly fall, 0.007 percent of total annual births; 95 percent CI: 0.003, 0.010) and the proportion of infants in the lowest birth weight quintile over the same period (yearly fall, 0.27 of percent total annual births; 95 percent CI: 0.22, 0.31). The odds ratio for stillbirth associated with male sex was unchanged by adjustment for year of birth, but advancing year of birth was no longer significantly associated with a decreased

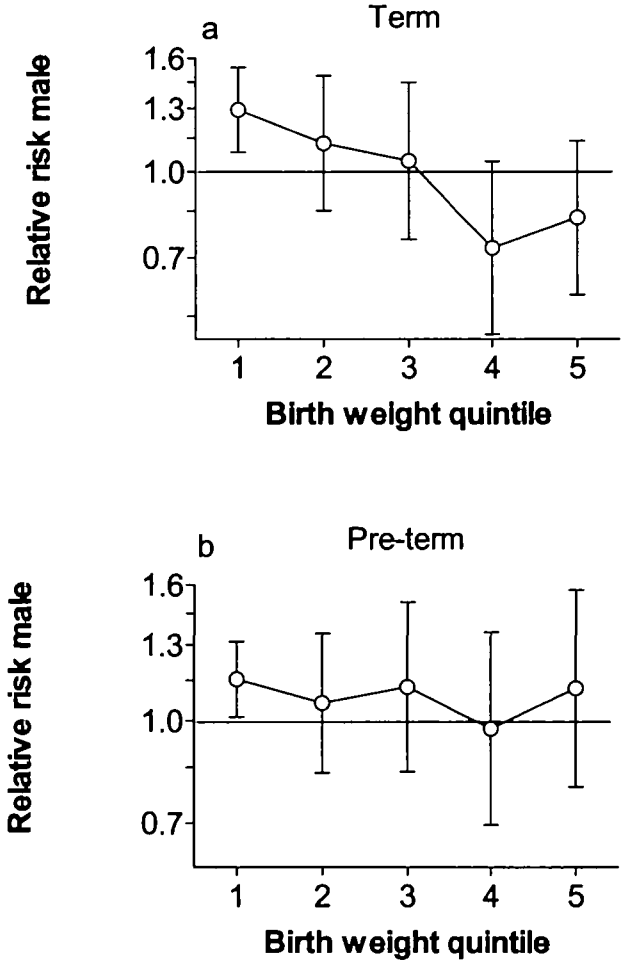

FIGURE 2. Relative risk ($\log_{10}$ scale) of term and preterm stillbirths associated with male sex related to birth weight quintile in Scotland, 1980–1996. *a*, term births (Mantel-Haenszel test for heterogeneity χ^2 = 11.4, p = 0.02); and *b*, preterm births (χ^2 = 1.07, p = 0.9). Bars are 95% confidence intervals.

TABLE 1. Logistic regression analysis of birth weight quintile and fetal sex in determining the risk of stillbirth, Scotland, 1980–1996

Covariates*	All births				Term births				Preterm births			
	No interaction		Interaction†		No interaction		Interaction†		No interaction		Interaction†	
	Adjusted OR‡	95% CI‡	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Male sex	1.20	1.11, 1.30	1.46	1.26, 1.68	1.08	0.96, 1.22	1.47	1.18, 1.83	1.12	1.01, 1.25	1.19	0.98, 1.45
Quintile												
1	4.50	3.97, 5.13	3.72	3.13, 4.42	3.22	2.68, 3.86	2.46	1.93, 3.13	6.77	5.61, 8.17	6.34	4.90, 8.20
2	1.57	1.36, 1.83	1.37	1.15, 1.62	1.28	1.04, 1.58	1.05	0.83, 1.34	1.92	1.55, 2.38	1.83	1.42, 2.35
3	1.12	0.95, 1.31	1.02	0.86, 1.21	0.94	0.75, 1.18	0.83	0.66, 1.05	1.34	1.06, 1.69	1.30	1.02, 1.66
4	0.89	0.76, 1.06	0.85	0.72, 1.01	0.79	0.62, 1.01	0.75	0.59, 0.95	1.01	0.80, 1.29	1.00	0.78, 1.28
Male* quintile§			0.92	0.87, 0.97			0.88	0.81, 0.95			0.97	0.90, 1.05
						Goodness of fit						
χ^2	11.7		1.68		11.5		1.28		1.27		0.75	
df	4		3		4		3		4		3	
p value	0.02		0.64		0.02		0.73		0.87		0.85	

* The reference group for sex was female, and that for birth weight quintile was the highest quintile (5).
† Models were constructed for each group, both with and without an interaction term between male sex and birth weight quintile.
‡ OR, odds ratio; CI, confidence interval.
§ The odds ratio for the interaction is for an increase in birth weight quintile of +1.

TABLE 2. Number and birth weight of livebirths and stillbirths at each week of gestation by infant sex, Scotland, 1980–1996

Week	Males						Females					
	Livebirths			Stillbirths			Livebirths			Stillbirths		
	No.	Median BW* (g)	Interquartile range	No.	Median BW (g)	Interquartile range	No.	Median BW (g)	Interquartile range	No.	Median BW (g)	Interquartile range
28	345	1,170	1,000, 1,300	90	880	765, 1,190	292	1,115	980, 1,242	63	860	690, 1,100
29	389	1,340	1,140, 1,500	78	1,020	830, 1,200	319	1,220	1,040, 1,400	67	936	680, 1,250
30	501	1,485	1,250, 1,680	93	1,150	900, 1,500	371	1,400	1,160, 1,560	70	1,050	800, 1,400
31	597	1,650	1,440, 1,830	100	1,290	982, 1,680	486	1,530	1,290, 1,740	61	1,250	930, 1,585
32	999	1,840	1,595, 2,046	92	1,375	1,160, 1,760	823	1,750	1,490, 2,000	77	1,280	960, 1,675
33	1,235	2,075	1,810, 2,310	88	1,630	1,422, 1,992	932	1,940	1,700, 2,220	64	1,562	1,330, 1,860
34	2,102	2,270	2,010, 2,520	102	1,800	1,400, 2,150	1,759	2,190	1,930, 2,430	79	1,710	1,410, 2,041
35	3,000	2,490	2,220, 2,740	90	1,975	1,640, 2,500	2,494	2,410	2,160, 2,670	57	1,700	1,380, 2,130
36	5,970	2,700	2,430, 2,960	140	2,280	1,820, 2,635	4,959	2,630	2,353, 2,900	97	2,250	1,850, 2,680
37	10,894	2,930	2,660, 3,220	108	2,515	2,068, 2,860	9,500	2,840	2,570, 3,120	78	2,555	2,200, 2,950
38	25,869	3,150	2,860, 3,430	127	2,780	2,460, 3,100	23,421	3,040	2,760, 3,320	102	2,725	2,360, 3,150
39	44,637	3,310	3,040, 3,600	103	2,960	2,600, 3,320	41,948	3,200	2,930, 3,460	109	2,950	2,580, 3,310
40	81,194	3,460	3,180, 3,740	153	3,200	2,810, 3,600	79,221	3,320	3,060, 3,600	134	3,119	2,600, 3,470
41	48,986	3,590	3,300, 3,880	80	3,340	3,030, 3,795	47,957	3,450	3,180, 3,740	80	3,402	2,980, 3,630
42	12,599	3,670	3,380, 3,980	22	3,440	2,950, 3,820	11,817	3,530	3,240, 3,820	21	3,520	3,190, 3,920
43	491	3,685	3,400, 4,000	3			414	3,555	3,230, 3,827	3		

* BW, birth weight.

risk of stillbirth after adjustment for birth weight (table 3).

DISCUSSION

The main finding of this study is that the increased risk of stillbirth associated with male sex progressively diminished with increasing birth weight (figure 1). These data suggest that the increased risk of stillbirth among males may be related, at least in part, to a greater risk of stillbirth in the face of a given degree of growth impairment. This sexual difference may be mediated by physiologic variation at the level of the maternal response to the conceptus, at the placenta, or may be related to sexual differences in fetal physiology (12–15). The biologic basis of the association warrants investigation.

Further epidemiologic studies might determine whether the effect is observed in other populations. If the association does represent an impaired response of males to growth restriction, it might be expected that the excess of male stillbirths would be more marked in racial groups with higher incidences of growth restriction and stillbirth, such as African Americans (19). Interestingly, falling proportions of stillbirths in Britain in the 20th century have been associated with a fall in the ratio of male to female stillbirths (20).

Males are generally larger than females, but the use of quintiles specific for sex and gestational age corrected for this effect. It is possible that the association merely represents the delayed expulsion of male fetuses, i.e., that males are more likely to be macerated than are females. The database did not have information on whether stillbirths were macerated. This seems an unlikely explanation, however, since the relation was strong at term, when prenatal visits occur at weekly intervals and the chance of intrauterine death being undetected for a prolonged period is lowest.

TABLE 3. Logistic regression analysis of sex, year of birth, and birth weight decile in determining the risk of stillbirth, Scotland, 1980–1996

Logistic regression model*	Year of birth		Male sex	
	OR†	95% CI†	OR	95% CI
Univariate	0.987	0.980, 0.995	1.20	1.11, 1.29
Year and male sex	0.987	0.979, 0.995	1.20	1.11, 1.29
Year, male sex, and birth weight decile	0.994	0.986, 1.001	1.20	1.11, 1.30

* The reference group for male sex was female. Year was entered as a continuous variable, and the odds ratio is for a change in year of birth of +1 year. Birth weight decile was modeled as a series of categorical variables. Goodness of fit: model of year and sex, $p = 0.86$; model of year, sex, and birth weight decile, $p = 0.17$.

† OR, odds ratio; CI, confidence interval.

The database does not record the individual estimates of gestational age on the basis of ultrasound (where performed) and menstrual history. The gestational age at delivery is recorded in the database on the basis of the estimated date of delivery as recorded in the patient's clinical record. Where ultrasound was performed, clinical judgment of gestational age depends on the gestational age at the time of ultrasound, the reliability of the menstrual history, and the degree of discrepancy between the menstrual and ultrasound estimates. Published criteria exist in Britain that attempt to standardize the corrections (21). It seems unlikely that any error arising from these issues may result in a systematic male-female bias, as male fetuses are no more likely to deviate from their expected size at dating ultrasound examination than are female fetuses (22).

The data cover a period of 17 years. The proportion of cases in which the estimated date of delivery is adjusted on the basis of ultrasound measurements is likely to have increased over this period, and other changes in obstetric practice have occurred that might affect the number of stillbirths and the ability to detect poor fetal growth. Such changes are unlikely to explain the association between male sex and risk of stillbirth, since the odds ratio for male sex was not changed by adjustment for year of birth (table 3) and the interaction between male sex and birth weight quintile was virtually identical when 1980–1987 and 1988–1996 were compared.

Over the study period, there was a fall in the proportion of babies with a birth weight in the lowest quintile. The latter finding is consistent with previous studies in Scotland that have demonstrated an increase in average birth weights between 1980 and 1992, and the factors that might have mediated this change have been discussed in detail elsewhere (23). The interaction between male sex and lowest birth weight quintile in determining the risk of stillbirth is unlikely to be an artifact of this variation over the study period, since the interaction was of a similar magnitude and statistical significance when the birth weight quintiles were calculated for 4- to 5-year periods and then pooled.

There was also a fall in the proportion of stillbirths over the study period (figure 1 and table 2). Interestingly, adjustment for birth weight decile resulted in a loss of the association between year of birth and risk of stillbirth. This suggests that the fall in the number of stillbirths over the study period may be due to the reduction in the number of smaller babies, which is consistent with the observation that being small for gestational age is associated with an increased risk of stillbirth (16).

The relation between birth weight quintile and sex was less marked when confined to babies born preterm. However, when preterm deliveries are analyzed, the birth weight quintiles necessarily refer to babies born preterm. Since some premature births are associated with preceding growth restriction (22) it follows that the size of liveborn, preterm babies may not be representative of the size of ongoing pregnancies in utero. Since the population that is at risk of fetal death is all ongoing pregnancies, rather than just that fraction of pregnancies that deliver (24), the loss of the association in preterm babies may reflect the difficulty in categorizing birth weight in preterm babies rather than a real biologic difference. Furthermore, as has been previously demonstrated (10), more males than females were delivered preterm, which further complicates the reference group.

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A population study of birthweight and the risk of caesarean section: Scotland 1980–1996

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Objectives 1. To describe the relation between birthweight and risk of emergency caesarean section at term; 2. to determine whether the relation between birthweight and caesarean section differed between male and female babies; and 3. to determine what proportion of the increased rates of caesarean section could be related to greater birthweights.

Design Retrospective population study.

Setting Data collected from Scottish Morbidity Record 1980 to 1996.

Population All first singleton deliveries by emergency caesarean section and non-elective vaginal birth of live babies at 40 weeks of gestation (n = 120,854).

Main outcome measure Delivery by emergency caesarean section.

Results There was a U-shaped relation between birthweight and the risk of caesarean section, with the lowest risk associated with weights in the range 3000–3500 g. Overall, males were more likely to be delivered by caesarean section (relative risk = 1·2, 95% CI 1·2–1·3). The association between male sex and increased risk of caesarean section persisted after adjusting for birthweight, but only males weighing < 4000 g were at increased risk of caesarean section compared with similarly sized females. Between 1980 and 1996, there were linear increases in the rate of caesarean section (from 7·1% to 10·7%, $r^2 = 0·8$, $P < 0·001$) and median birthweight (from 3360 g in 1980 to 3420 g in 1996, $r^2 = 0·8$, $P < 0·001$). The population attributable fraction of caesarean sections related to year of delivery 1981–1996 was not significantly altered by adjusting for birthweight (22·3% *vs* 21·6%).

Conclusions There is no evidence to suggest that increasing birthweights have contributed to increasing rates of caesarean section in Scotland between 1980 and 1996 among singleton first births non-electively delivered at 40 weeks of gestation.

INTRODUCTION

Rates of caesarean section have risen dramatically in both the United Kingdom and the United States over the past two decades[1]. The reasons behind this are complex and not fully understood, but the principal mediators of the increase are thought to be changes in obstetric practice[2], which are at least potentially modifiable. However, it has been suggested that a significant proportion of the increased rate of caesarean delivery is due to increasing birthweights[3]. This conclusion was reached by describing the relation between birthweight and the risk of caesarean section in data collected between 1987 and 1990 and standardising the rate of caesarean section from 1987 to 1990 for values of birthweight from 1970. The importance of the association between birthweight and caesarean delivery is that this relation is not easily amenable to reduction. Indeed, attempts to reduce the number of caesarean deliveries in the face of a true biologically-based reason for the increase could be potentially hazardous.

There are a number of weaknesses in previous studies relating birthweight and the risk of caesarean section. Firstly, birthweight is a continuous variable. All major studies of the effect of birthweight on the risk of caesarean section utilise arbitrary strata of weight[3–5] or quartiles[6]. Treating continuous variables in this manner, although convenient, results in a loss of information[7]. Secondly, male and female fetuses are not considered separately. Given that males are on average 4% heavier at term than females[8], it seems plausible that the relation between birthweight and caesarean delivery might be modified by gender. Finally, the effect of increases in birthweight on the risk of caesarean section have been proposed on the basis of extrapolation[3] (i.e. the hypothesis has not been tested on longitudinally collected data).

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The Scottish Morbidity Record (Maternity)[9] has collected basic information on all births in Scotland with greater than 99% completeness since the late 1970 s. Between 1980 and 1992 there was an increase in average birthweights in Scotland[8]. The aims of this study were: 1. to describe the relation between birthweight and the risk of caesarean section; 2. to determine whether the relation differed between males and females; and 3. to quantify the extent, if any, that increasing rates of caesarean section might be explained by increasing birthweights. These aims were addressed in singleton first live births which were delivered at 40 weeks of gestation by emergency caesarean section or delivered vaginally following spontaneous labour.

METHODS

A total of 478,655 records of first pregnancies were available from the Scottish Maternity Record (Maternity, SMR2) from 1980 to 1996. The following were missing: gestational age at delivery in 2416 (0·5%), mode of delivery in 253 (0·05%), and whether labour was induced in 98 (0·02%). From the 475,912 records without these missing values (99·4% of total), 121,079 records were selected where a single fetus was delivered at 40 weeks of gestational age, labour was not induced, and delivery was not by elective caesarean section. Cases were excluded that had missing values for birthweight (n = 67), gender (n = 3), where the birthweight was recorded as < 500 g (n = 1) or where the baby was stillborn (n = 154) leaving a study group of 120,854, which was 99·8% of eligible cases.

Definitions and data quality

The data recorded in the SMR2 have been intermittently audited. The last audit was performed in 1992 and involved comparison of the coded record with the clinical case record in 2% of pregnancies nationally over a six month period. This demonstrated that the coded record was accurate in more than 98% of cases in the major fields (Dr J. Chalmers, Information and Statistics Division, National Health Service, Scotland, personal communication).

First pregnancies were defined as a pregnancy in a woman who had not previously had a live birth or stillbirth. Gestational age was defined as the number of completed weeks of pregnancy on the basis of the accepted date of delivery from the patient's clinical record. Emergency caesarean section was defined as a caesarean section that was not planned.

Statistical analysis

The risk of caesarean section was compared between different groups using relative risks and 95% CI. The null hypothesis that the relative risk of being male was the same across birthweight strata was tested using the Mantel-Haenszel test of homogeneity[10]. Adjusted odds ratios for factors and interactions were calculated using logistic regression analysis[10]. Adjustment for birthweight in logistic regression models was performed using weight as a centred variable (i.e. weight–median weight) and also a quadratic of the centred term (i.e. [weight–median weight]^2)[7]. Adjusted attributable fractions following logistic regression were calculated using the method described by Greenland and Drescher[11]. Statistical analysis was performed using the Stata software package (Stata Corporation, College Station, Texas, USA), version 6·0. Statistical significance was assumed at the 5% level.

RESULTS

The proportion of babies born by emergency caesarean section varied in relation to both sex and birthweight (Table 1). There was a U-shaped relation between birthweight and the risk of caesarean section (Fig. 1) with the lowest risk in the range 3000–3500 g. Overall, the relative

Table 1. Numbers of emergency caesarean sections and vaginal deliveries following spontaneous labour in singleton first births (live) in Scotland, 1980–1996 by gender and weight group. Values are given as n or n (%).

	Female		Male	
Weight group	Caesarean section	Vaginal delivery	Caesarean section	Vaginal delivery
< 2000 g	10 (26·3)	28	10 (31·2)	22
2000–2499 g	120 (12·4)	850	108 (16·9)	532
2500–2999 g	731 (6·8)	10,095	651 (9·0)	6544
3000–3499 g	1854 (6·6)	26,221	2015 (8·0)	23,107
3500–3999 g	1571 (9·4)	15,069	2256 (10·4)	19,387
4000–4499 g	500 (16·4)	2550	922 (16·3)	4738
4500–4999 g	84 (29·8)	198	158 (26·2)	446
> 5000 g	13 (59·1)	9	25 (45·4)	30
TOTAL	4883 (8·2)	55,020	6145 (10·1)	54,806

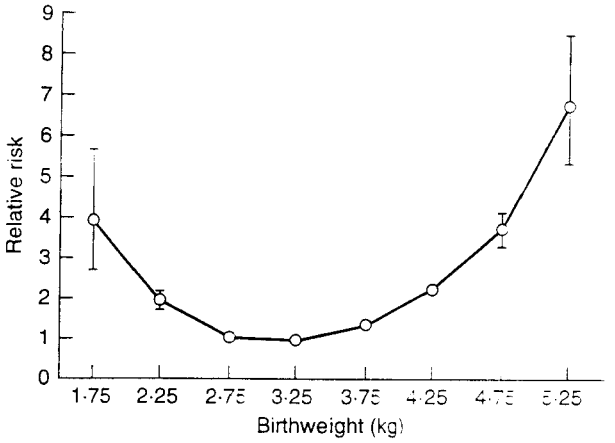

Fig. 1. Relative risk of emergency caesarean section related to birthweight among primiparous singleton pregnancies non-electively delivered at 40 weeks of gestation. Bars are 95% confidence intervals. The groups employed were the same as in Table 1. The relative risk of caesarean section in each group was related to the risk of caesarean section among babies in the birthweight range 3000–3499 g.

risk of caesarean section associated with male sex was 1·2 (95% CI 1·2–1·3) and the population attributable fraction was 10·7% (95% CI 8·9–12·4). The population attributable fraction associated with male sex adjusted for birthweight (as a centred continuous variable with a quadratic term) was 7·4% (95% CI 5·6–9·2). When males and females were compared within a series of birthweight strata, it was found that only males with a birthweight < 4000 g were at increased risk of emergency caesarean section compared with similarly sized females (Fig. 2).

There were strong positive correlations between year of delivery and proportion of deliveries by emergency caesarean section (Fig. 3 a), median birthweight (Fig. 3 b), and proportion with a birthweight > 4000 g (Fig. 3 c). There was a strong negative correlation between year of delivery and proportion with a birthweight < 2500 g (Fig. 3 d).

Logistic regression demonstrated little effect of adjusting for birthweight and the interaction between weight and sex on the risk of caesarean section associated with advancing year over the study period (Fig. 4). Similarly, the sum of the population attributable fractions for years of delivery 1981 to 1996 adjusted only for sex was 22·3% (95% CI 15·9–28·2) and the same value adjusted for sex, birthweight and interactions between birthweight and sex was 21·6% (95% CI 15·2–27·5).

DISCUSSION

Many previous studies have demonstrated that very large babies are at increased risk of caesarean section[2]. What has been less appreciated in epidemiological studies is that the relation between birthweight and caesarean section is U-shaped and virtually symmetrical (Fig. 1) (i.e. the risk of caesarean section increases as babies get both bigger and smaller than the average). One practical consequence of this is that when trying to estimate the effect of shifts in average birthweights on rates of caesarean section, the beneficial effect of a reduced number of small babies must be taken into account. The indication for caesarean section was not obtained from the database, but it seems likely that the increased risk of caesarean section among small babies is due to an increased risk of fetal distress, and that the increased risk of caesarean section among large babies will be due to obstructed labour.

No previous study of the effect of birthweight has determined whether the relation between birthweight and caesarean section risk was the same for males and females. Previous studies have demonstrated that males are at an increased risk of caesarean section for failure to progress, an association which is due to the greater average size of males. Males are also at an increased risk of caesarean section for fetal distress[5]. Interestingly, it was observed in the present study that the association between male fetal sex and increased risk of caesarean section became progressively stronger as birthweight decreased below 4000 g (Fig. 2). This interaction between male sex and birthweight suggests that the risks of male sex and growth restriction may act synergistically to increase the risk

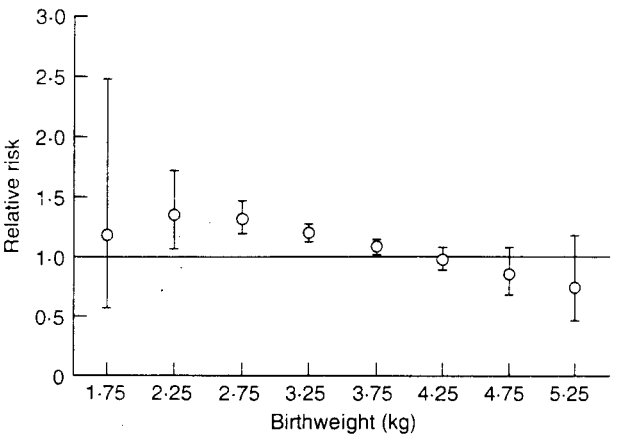

Fig. 2. Mantel-Haenszel analysis of interaction between sex and weight in determining risk of emergency caesarean section among primiparous singleton pregnancies non-electively delivered at 40 weeks of gestation. The same groups were employed as in Fig. 1 and Table 1. For each weight range, the relative risk of a male having an emergency caesarean section was calculated with reference to a female. Mantel-Haenszel test for homogeneity χ^2 32·5, $P < 0{\cdot}001$. Where the bars exclude 1, a significant difference between males and females is assumed within the given stratum. Because the homogeneity test is statistically significant, a valid adjusted combined relative risk associated with male sex cannot be calculated.

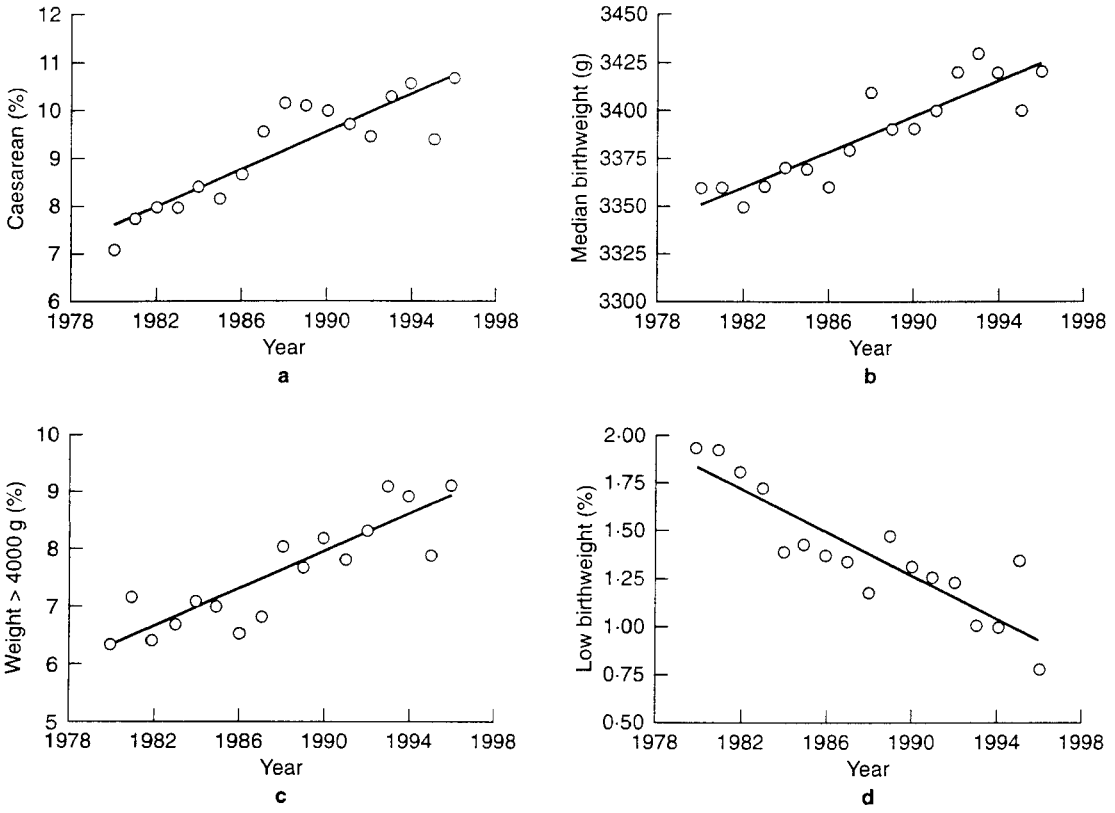

Fig. 3. Regression analysis of effect of year of birth on obstetric outcomes among primiparous singleton pregnancies non-electively delivered at 40 weeks of gestation. Lines fitted using least squares method. (a) proportion delivered by emergency caesarean delivery, $r^2 = 0{\cdot}8$, $P < 0{\cdot}001$; (b) median birthweight, $r^2 = 0{\cdot}8$, $P < 0{\cdot}001$; (c) proportion birthweight > 4000 g, $r^2 = 0{\cdot}8$, $P < 0{\cdot}001$; (d) proportion low birthweight (< 2500 g), $r^2 = 0{\cdot}8$, $P < 0{\cdot}001$.

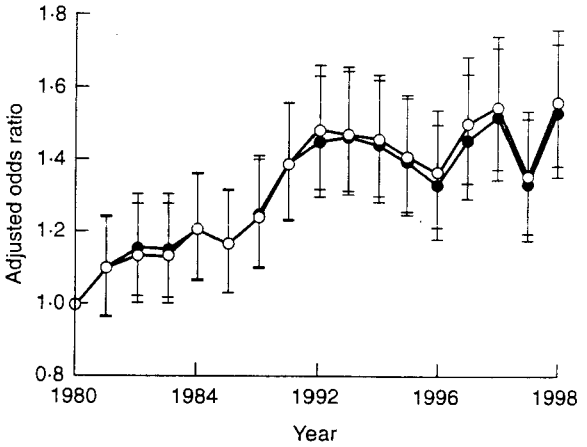

Fig. 4. Adjusted odds ratios associated with year of delivery derived from two logistic regression models among primiparous singleton pregnancies non-electively delivered at 40 weeks of gestation: 1. adjusted for male sex alone (○); and 2. adjusted for male sex, birthweight and the interaction between sex and birthweight (●). Birthweight was modelled as a centred quadratic expression (i.e. the difference between the birthweight and the median birthweight (birthweight – 3360 g) and the same parameter squared (birthweight – 3360 g)^2). Interaction terms with male sex were male* (birthweight – 3360 g), male* (birthweight – 3360 g)^2 (l). Points are adjusted odds ratios and bars are 95% confidence intervals.

of fetal distress. Interestingly, a similar interaction exists with respect to the risk of stillbirth: male sex is associated with an increased risk of stillbirth with decreasing birthweight[12]. These observations suggest the possibility of some fundamental sexual differences in the fetal response to intrauterine stress. This possibility is consistent with animal studies which have demonstrated differences in the metabolism of adrenal medullary and cortical hormones comparing male and female fetuses[13–15].

Data collected over the period 1980 to 1996 confirmed the previously described increase in average birthweights in Scotland[8]. The change in median birthweight (Fig. 3 b) was mirrored by an increase in the proportion of babies with a birthweight > 4000 g (Fig. 3 c) and a decrease in the proportion with birthweights < 2500 g (Fig. 3 d). As discussed above, even without considering sex, these changes would be expected to have opposite effects on the rate of caesarean section. Furthermore, the increased proportion of babies > 4000 g would be expected to reduce the number of caesareans due to male fetal sex. Since 10% of all caesarean sections could be attributed to male sex, modification of the effect of sex by birthweight

could have a significant effect on the overall rate of caesarean section.

From the above, therefore, it is by no means obvious that increasing average birthweight would be expected to increase the rate of caesarean section. The SMR2 database contains longitudinally collected data over a period where a significant increase in average birthweights was observed. It allowed the hypothesis that increasing average birthweight in a population would lead to increased rates of caesarean section to be tested directly. This was performed using logistic regression analysis, where each year of birth was entered as a variable and 1980 was used as a reference. Two models were created, one where the risk associated with each year was adjusted simply for the proportion of boys and girls, and a second model where the risk associated with each year was also adjusted for birthweight and the interaction between birthweight and fetal sex. If increasing birthweight accounted for the increased rate of caesarean section over the study period, one would have observed that the odds ratio associated with advancing year of birth would be significantly decreased after adjusting for birthweight. In fact, the odds ratios from the two models were virtually superimposed (Fig. 4). Furthermore, the population attributable fraction was used to summarise the effect of the increased rate of caesarean section over the period between 1981 and 1996. From the first model, it was estimated that 22·3% of caesarean sections would have been prevented had the rate stayed at the 1980 level. Had a significant proportion of this increase been due to increasing birthweights, the population attributable fraction for 1981–1996 would have been substantially reduced after adjusting for birthweight. In fact, the figure was virtually unaltered after adjusting for birthweight (21·6%). It is concluded that increasing birthweight did not result in an increased risk of caesarean section among singleton first pregnancies, non-electively delivered at 40 weeks of gestation. It must be concluded that other factors are responsible for the increased rates of caesarean section among this group. However, this study cannot exclude effects of increases in birthweight on multiparous women or women who had labour induced.

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Articles

Caesarean section and risk of unexplained stillbirth in subsequent pregnancy

Gordon C S Smith, Jill P Pell, Richard Dobbie

Summary

Background Caesarean section is associated with an increased risk of disorders of placentation in subsequent pregnancies, but effects on the rate of antepartum stillbirth are unknown. We aimed to establish whether previous caesarean delivery is associated with an increased risk of antepartum stillbirth.

Methods We linked pregnancy discharge data from the Scottish Morbidity Record (1980–98) and the Scottish Stillbirth and Infant Death Enquiry (1985–98). We estimated the relative risk of antepartum stillbirth in second pregnancies using time-to-event analyses.

Findings For 120 633 singleton second births, there were 68 antepartum stillbirths in 17 754 women previously delivered by caesarean section (2·39 per 10 000 women per week) and 244 in 102 879 women previously delivered vaginally (1·44; p<0·001). Risk of unexplained stillbirth associated with previous caesarean delivery differed significantly with gestational age (p=0·04); the excess risk was apparent from 34 weeks (hazard ratio 2·23 [95% CI 1·48–3·36]). Risk was not attenuated by adjustment for maternal characteristics or outcome of the first pregnancy (2·74 [1·74–4·30]). The absolute risk of unexplained stillbirth at or after 39 weeks' gestation was 1·1 per 1000 women who had had a previous caesarean section and 0·5 per 1000 in those who had not. The difference was due mostly to an excess of unexplained stillbirths among women previously delivered by caesarean section.

Interpretation Delivery by caesarean section in the first pregnancy could increase the risk of unexplained stillbirth in the second. In women with one previous caesarean delivery, the risk of unexplained antepartum stillbirth at or after 39 weeks' gestation is about double the risk of stillbirth or neonatal death from intrapartum uterine rupture.

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Introduction

Rates of caesarean section have risen substantially in recent years.[1] The causal factors are complex and incompletely understood.[2,3] Concerns have been expressed about potential adverse effects, especially in relation to short-term morbidity in the mother and child.[4,5] Studies on the effects of previous caesarean section on future pregnancies have focused mainly on the maternal and fetal risks of scar rupture associated with vaginal birth.[6,7] However, it has also been noted that placental complications, such as abruption and placenta praevia, are more common in women who have previously undergone caesarean section,[8,9] and the association with abruption has been observed in women with no previous history of abruption and is independent of obvious confounders.[10] The effect of previous caesarean delivery on the risk of antepartum perinatal death in subsequent pregnancies is not known. We did a large-scale, retrospective, cohort study to establish whether caesarean delivery in a first pregnancy was associated with an increased risk of antepartum stillbirth in the second.

Methods

Data sources

The Scottish Morbidity Record (SMR2) collects information on clinical and demographic characteristics and outcomes for all patients discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been more than 99% complete since the late 1970s.[11] A quality assurance exercise was done in 1996–97 in which 5% of case records (n=1414) were compared with the SMR2 database during a 6-month period. All fields used in the present study had fewer than 2% errors, with the exception of maternal height (4·4%), estimated gestation (5·6%), induction of labour (6·4%), and duration of labour (13·5%) (Chalmers J, Consultant in Public Health, Information and Statistics Division of the National Health Service [NHS], personal communication).

We identified records from the SMR2 between 1980–98 and linked them to records from the Scottish Stillbirth and Infant Death Enquiry (1985–98)—a national register in which all perinatal deaths in Scotland are classified. Coding of the cause of death is done by one individual (the Scottish coordinator) in the Information and Statistics Division of the NHS on the basis of clinical information obtained from local coordinators and pathologists. Cases are identified through registration of stillbirths and neonatal deaths with the General Registrar's Office, which is a legal requirement for a perinatal death. The register is almost 100% complete and has been described in detail.[12,13]

Study population

We identified all second births in Scotland between 1992–98. We selected this range because smoking status was not included in the SMR2 database before 1992. Study exclusion criteria were multiple pregnancy, delivery outside 24–43 weeks' gestation, birthweight less than 500 g, and perinatal deaths due to congenital anomaly or rhesus isoimmunisation. We also excluded records with missing values. We linked records from the second pregnancy to

records from the first pregnancy in the same woman using a probability-based matching approach.[14] We excluded first pregnancy records using the same criteria as second pregnancy records, and excluded pairs of records if the interpregnancy interval was negative or implausibly short or if there was a discrepancy between the documented method of delivery in the first record and the previous caesarean delivery field in the second record.

Definitions of maternal and obstetric characteristics

We adjusted the risk of unexplained antepartum stillbirth for socioeconomic deprivation, smoking, maternal age, and maternal height. Postcode of residence was used to derive Carstairs socioeconomic deprivation scores.[15] Scores were based on 1991 Census data on car ownership, unemployment, overcrowding, and social class within postcode sectors of residence that contain, on average, around 1600 residents. The deprivation scores were used to categorise women by quintile of socioeconomic deprivation. Higher quintiles indicate a greater degree of deprivation. Smoking was defined as the smoking status of the woman at the time of first attendance for antenatal care. Maternal age was defined as the age of the mother at the time of birth. Maternal height was measured in cm and the value used was that recorded in every woman's clinical record. Gestational age at birth was defined as completed weeks of gestation on the basis of the estimated date of delivery in every woman's clinical record. Gestational age has been confirmed by ultrasound in the first half of pregnancy in more than 95% of women in the UK since the early 1990s.[16] Extremely and moderately preterm birth were defined as occurring between 24–32 and 33–36 weeks' gestation, respectively. Birthweight was categorised into 20 sex-specific and gestational-age-specific percentiles derived from livebirths in the whole population. A small-for-gestational-age baby was defined as a liveborn baby with a birthweight in the smallest percentile (ie, the 0–5th percentile). Interpregnancy interval was defined as the number of days from the first birth until the estimated date of the last menstrual period of the second. The estimated date of the last menstrual period was calculated by subtracting the estimated gestational age from the date of delivery.

Definition of stillbirths

We classified stillbirths as antepartum and intrapartum. Deaths caused by congenital anomaly were defined as any structural or genetic defect incompatible with life, or potentially treatable but causing death. The cause of antepartum stillbirth was classified according to a modified version of the Wigglesworth hierarchical system.[13,17] Stillbirths were classified according to a hierarchy of direct obstetric causes (in order): toxaemia, haemorrhage (antepartum), mechanical, maternal, miscellaneous, and unexplained. Mechanical included death caused by uterine rupture. The hierarchy dictates that a perinatal death in which there was severe pre-eclampsia complicated by abruption would be classified as being due to toxaemia, since toxaemia is above haemorrhage in the hierarchy. The cause of perinatal death in the first pregnancy was categorised into unexplained antepartum stillbirth and all other perinatal deaths. If the first birth had occurred between 1980–84, all perinatal deaths were classified as "all other perinatal deaths".

Statistical analyses

We summarised continuous variables as medians and IQRs, and compared groups using the Mann-Whitney U test. χ^2 tests were used for univariate comparisons of dichotomous data (more than five observations expected in all cells) or Fisher's exact test (five or fewer expected observations in one or more cells). The p values for all hypothesis tests were two-sided and significance was set at $p<0{\cdot}05$. The risk of stillbirth was compared between groups using time-to-event analyses in which week of gestation was used as the timescale, antepartum stillbirth due to the specified cause was defined as the event, and all other

	No previous caesarean (n=102 879)	Previous caesarean (n=17 754)	p*
Maternal characteristics			
Age, years (median [IQR])	28 (25–32)	30 (26–33)	<0·001
Height, cm (median [IQR])	162 (158–167)	160 (156–165)	<0·001
Deprivation quintile, n (%)			
1 (least deprived)	20 175 (19·6%)	3610 (20·3%)	
2	19 826 (19·3%)	3568 (20·1%)	
3	20 711 (20·1%)	3501 (19·7%)	
4	20 184 (19·6%)	3481 (19·6%)	
5 (most deprived)	21 983 (21·4%)	3594 (20·2%)	0·001
Smoking status			
Non-smoker, n (%)	64 391 (62·6%)	11 807 (66·5%)	
Ex-smoker, n (%)	7472 (7·3%)	1329 (7·5%)	
Smoker, n (%)	31 016 (30·2%)	4618 (26·0%)	<0·001
Outcome second pregnancy			
Interpregnancy interval, days (median [IQR])	829 (499–1365)	841 (515–1338)	0·24
Gestational age at delivery, weeks (median [IQR])	40 (39–41)	39 (38–40)	<0·001
Gestational age at delivery			
24–32 weeks, n (%)	749 (0·7%)	183 (1·0%)	
33–36 weeks, n (%)	3472 (3·4%)	789 (4·4%)	
37–43 weeks, n (%)	98 658 (95·9%)	16 782 (94·5%)	<0·001
Birthweight, g (median [IQR])	3480 (3150–3810)	3420 (3060–3760)	<0·001
Birthweight			
<5th percentile, n (%)	3304 (3·2%)	722 (4·1%)	<0·001
>95th percentile, n (%)	6669 (6·5%)	1493 (8·4%)	<0·001
Antepartum stillbirth, n (%)	244 (0·2%)	68 (0·4%)	<0·001
Outcome first pregnancy†			
Gestational age at delivery, weeks (median [IQR])	40 (39–41)	40 (38–41)	<0·001
Gestational age at delivery			
24–32 weeks, n (%)	968 (1·1%)	535 (3·5%)	
33–36 weeks, n (%)	3632 (4·1%)	1184 (7·7%)	
37–43 weeks, n (%)	83 823 (94·8%)	13 648 (88·8%)	<0·001
Birthweight, g (median [IQR])	3340 (3020–3650)	3370 (2920–3770)	<0·001
Birthweight			
<5th percentile, n (%)	4922 (5·6%)	1163 (7·6%)	<0·001
>95th percentile, n (%)	2438 (2·8%)	998 (6·5%)	<0·001
Perinatal death			
Unexplained stillbirth, n (%)	371 (0·4%)	3 (0·02%)	<0·001
Other, n (%)	568 (0·6%)	175 (1·1%)	

*By Mann-Whitney U, χ^2, or Fisher's exact test as appropriate. †n for no previous caesarean=88 423; n for previous caesarean=15 367.

Table 1: **Maternal characteristics and obstetric outcome in relation to previous caesarean section in 120 633 second births**

	No previous caesarean (n=102 879)		Previous caesarean (n=17 754)		p*
	Number	Incidence†	Number	Incidence†	
Cause of stillbirth					
All causes	244‡	0·144	68	0·239	0·0001
Toxaemia	14	0·008	3	0·011	0·71
Haemorrhage	46	0·027	10	0·035	0·46
Mechanical	3	0·002	2	0·007	0·08
Miscellaneous	9	0·005	3	0·011	0·28
Maternal	8	0·005	7	0·025	0·0004
Maternal (excluding diabetes)	6	0·004	3	0·011	0·11
Unexplained	163	0·096	43	0·151	0·004

*Log rank test. †Per 1000 women per week. ‡One death in this group was unclassified.

Table 2: **Risk of antepartum stillbirth after 24 weeks' gestation in relation to previous caesarean section in 120 633 second births**

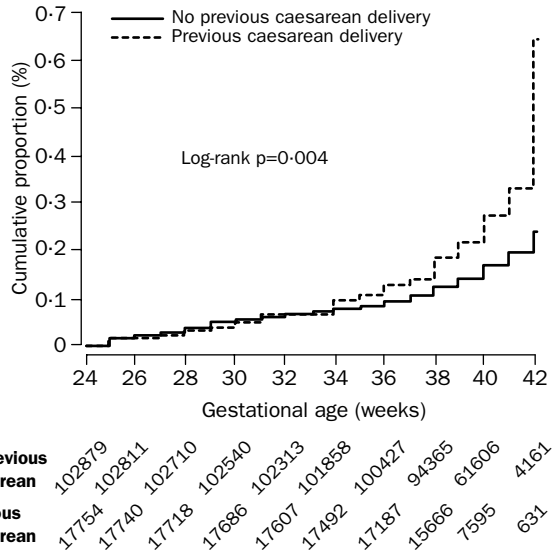

Figure 1: **Cumulative proportion of unexplained stillbirths per week of gestation**

Hazard ratio for women with previous caesarean delivery relative to women with a previous vaginal birth=1·64 (95% CI 1·17–2·30).

births were treated as censored. In this method, ongoing pregnancies are the denominator,[18] but censoring due to birth is accounted for and multivariate analysis can be done.[19] This approach allows assessment of the relative risk accounting for variation in the duration of pregnancy, and is appropriate for situations in which not all individuals would ultimately experience the event.[20] Survival data were plotted as cumulative percentage with event as recommended for rare outcomes,[21] and univariate statistical comparisons were by log-rank test. Crude and adjusted hazard ratios were estimated with a proportional hazards model.[22] The proportional hazards assumption was tested using the global test of Grambsch and Therneau.[23] The absolute risk of stillbirth was assessed using the prospective risk of stillbirth—ie, the number of stillbirths at or after a given week of gestation divided by the total number of births at or after a given week.[24] The risks of preterm birth and of extremes of birthweight percentile were assessed with multivariate logistic regression analysis. All continuous covariates in regression models were categorised. The significance of interaction terms was assessed with the likelihood ratio test and significance set at p<0·01. All analyses were done with Stata software, version 7.0.

Results

There were 411 685 singleton births in Scotland between 1992 and 1998, excluding deaths due to fetal abnormality or rhesus isoimmunisation; 144 202 (35%) were second births. Of these, 408 (0·3%) did not have information for gestational age or birthweight, or these values were outside 24–43 weeks or less than 500 g, respectively. Of the remaining 143 794 records, data were missing for previous caesarean delivery in 14 (<0·1%), height in 12 866 (9·0%), deprivation category in 448 (0·3%), smoking status in 13 395 (9·3%), and maternal age in one (<0·1%). In total, 23 161 (16·1%) records had one or more missing values, leaving a study group of 120 633 women.

There was a record for the first pregnancy in 105 930 (87·8%) of the study group. 31 (<0·1%) were excluded because the interpregnancy interval was less than 28 days. Of the remaining 105 899, mode of delivery in the first pregnancy was not noted in 40 (<0·1%) women, and there was a discrepancy between the mode of delivery field in the first record and the previous caesarean section field in the second record in 1617 (1·5%). Of the remaining 104 242 first pregnancy records, 448 (0·4%) had no note of gestational age or birthweight, or these values were outside 24–43 weeks or less than 500 g, respectively. Four (<0·1%) records were excluded because of a missing value for fetal sex, leaving a subgroup of 103 790 births with complete data on both pregnancies—86·0% of the study group. Of these births, 2812 (2·7%) of first births had occurred between 1980 and 1984, predating the Scottish Stillbirth and Infant Death Enquiry, and the causes of 16 perinatal deaths that occurred in this group during the first pregnancy had not been classified.

Women who had previously been delivered by caesarean section were older, shorter, less likely to smoke, and less likely to live in an area of high socioeconomic deprivation (table 1). Women whose first delivery was by caesarean section were more likely to have had complications in the first pregnancy. They had an excess of moderate and extreme prematurity, an excess of very small and very large for gestational age babies, and fewer unexplained stillbirths but an excess of other perinatal deaths. On univariate analysis of second pregnancy outcomes, women who had had a previous caesarean section delivered earlier, delivered smaller neonates, and were more likely to have an antepartum stillbirth than women who had previously delivered vaginally (table 1).

The main determinant of the excess of stillbirths in women who had had a previous caesarean section was unexplained stillbirth (table 2). For all gestational ages, the hazard ratio for unexplained stillbirth in women with previous caesarean delivery was 1·64 (95% CI 1·17–2·30), p=0·004. However, the hazards associated with previous vaginal birth and previous caesarean section were significantly non-proportional during gestational age 24–42 weeks (p=0·04). The excess risk associated with previous caesarean delivery became apparent from

	No previous caesarean section					Caesarean section in first pregnancy				
	Ongoing pregnancies (n)	Stillbirths (n)	Other births (n)	Weekly rate*	Cumulative rate*	Ongoing pregnancies (n)	Still-births (n)	Other births (n)	Weekly rate*	Cumulative rate*
Week of gestation										
34	101 858	7	540	0·07 (0·02–0·12)	0·07 (0·02–0·12)	17 492	4	122	0·23 (0·00–0·45)	0·23 (0·00–0·45)
35	101 311	3	881	0·03 (0·00–0·06)	0·10 (0·05–0·18)	17 366	2	177	0·12 (0·00–0·28)	0·35 (0·16–0·77)
36	100 427	12	1757	0·12 (0·05–0·19)	0·22 (0·14–0·33)	17 187	4	401	0·24 (0·00–0·47)	0·58 (0·31–1·08)
37	98 658	14	4279	0·15 (0·07–0·22)	0·36 (0·26–0·50)	16 782	2	1114	0·12 (0·00–0·29)	0·70 (0·40–1·24)
38	94 365	16	11 726	0·18 (0·09–0·27)	0·54 (0·42–0·72)	15 666	7	4390	0·52 (0·13–0·90)	1·22 (0·78–1·92)
39	82 623	13	21 004	0·18 (0·08–0·28)	0·73 (0·57–0·93)	11 269	4	3670	0·42 (0·01–0·84)	1·65 (1·08–2·51)
40	61 606	17	35 311	0·39 (0·20–0·57)	1·11 (0·88–1·40)	7595	4	4180	0·73 (0·01–1·44)	2·37 (1·56–3·60)
41	26 278	7	22 110	0·46 (0·12–0·80)	1·57 (1·20–2·06)	3411	2	2778	0·99 (0·00–2·36)	3·36 (2·03–5·55)
42	4161	2	4091	0·95 (0·0–2·26)	2·51 (1·46–4·34)	631	2	615	6·20 (0·00–14·80)	9·52 (3·82–23·62)

*Per 1000 ongoing pregnancies.

Table 3: **Number of events and life table analysis of unexplained stillbirths at or after 34 weeks' gestation in second pregnancies in relation to previous caesarean delivery (n=119 350)**

	Risk relative to women with no previous caesarean					
	Crude OR (95% CI)	p	Adjusted OR 1 (95% CI)†	p	Adjusted OR 2 (95% CI)‡	p
Outcome of first pregnancy						
Unexplained stillbirth ⩾34 weeks*	2·48 (1·61–3·85)	<0·001	2·65 (1·70–4·13)	<0·001	2·74 (1·74–4·30)	<0·001
Birthweight <5th percentile	1·28 (1·17–1·40)	<0·001	1·17 (1·07–1·29)	0·001	1·15 (1·04–1·26)	0·005
Birthweight >95th percentile	1·33 (1·25–1·42)	<0·001	1·47 (1·38–1·57)	<0·001	1·07 (0·99–1·14)	0·07
Delivery 24–32 weeks	1·45 (1·21–1·73)	<0·001	1·45 (1·21–1·74)	<0·001	1·08 (0·89–1·30)	0·46
Delivery 33–36 weeks	1·39 (1·28–1·51)	<0·001	1·38 (1·26–1·50)	<0·001	1·15 (1·05–1·26)	0·002

OR=odds ratio. *These values are crude and adjusted hazard ratios rather than odds ratios. †Adjusted for maternal age, height, social deprivation quintile, and smoking status. Birthweight outcomes were also adjusted for an interaction term between smoking and age. ‡Adjusted for all covariates as in 1, but also for interpregnancy interval and features of the first pregnancy: moderate and extreme preterm birth, birthweight percentile, unexplained stillbirth, and other perinatal death.

Table 4: **Risk of adverse pregnancy outcome in second pregnancies in relation to previous caesarean delivery adjusted for outcome of first pregnancy (n=103 790)**

34 weeks' gestation (figure 1). There was no evidence of non-proportionality of the hazards before 34 weeks' (p=0·79) and at or after 34 weeks' gestation (p=0·96). The hazard ratio associated with previous caesarean delivery was 0·97 (0·52–1·78), p=0·91, before 34 weeks' and 2·23 (1·48–3·36), p<0·001 at or after 34 weeks' gestation. Therefore, we included births only at or after 34 weeks' gestation in subsequent analyses.

Table 3 shows the actual number of events at each week of gestation. The excess rate of stillbirths in the previous caesarean group is not merely a result of excess risk at or after 41 weeks' gestation, since if births were censored at 39 weeks' gestation a significant excess of deaths remained in this group (log-rank p=0·02). Adjustment for maternal demographic or obstetric characteristics did not attenuate the association between previous caesarean birth and unexplained stillbirth (table 4). Exclusion of women whose first birth had occurred before 1985 had no effect on the association between previous caesarean delivery and unexplained stillbirth (adjusted hazard ratio 2·56 [1·61–4·08], p<0·001). Previous caesarean delivery, other maternal characteristics, and the outcome of the first pregnancy did not interact significantly in determining the risk of unexplained stillbirth in the second pregnancy.

The association between previous caesarean and stillbirth was similar if the analysis was confined to women who had delivered at term in their first birth (adjusted hazard ratio 2·74 [1·92–5·48], p<0·001) or at or after 40 weeks' gestation in their first birth (3·45 [2·01–5·94], p<0·001). We analysed the 96 737 women whose first pregnancy was

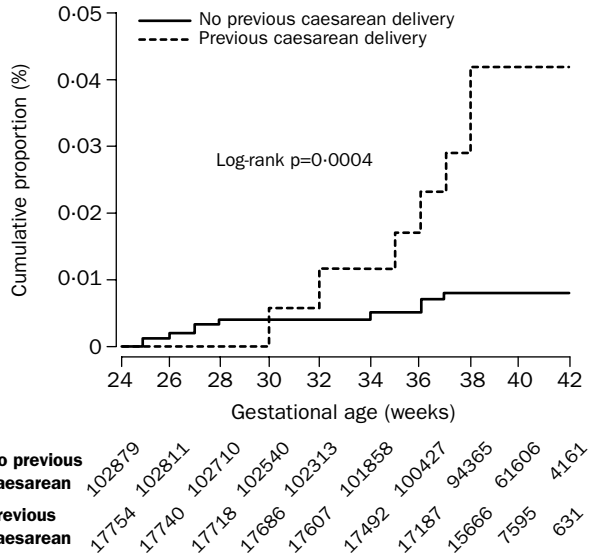

Figure 2: **Cumulative proportion of stillbirths due to maternal disease per week of gestation**

Hazard ratio for women with previous caesarean delivery relative to women with a previous vaginal birth=5·12 (95% CI 1·85–14·12).

delivered at term to establish whether the association between previous caesarean delivery and the risk of unexplained stillbirth might be accounted for by the original indication for caesarean section. The risk of unexplained stillbirth in the second pregnancy did not significantly differ (p=0·67) between women who had caesarean section before labour started (n=5364, hazard ratio 1·99 [0·94–4·20]), women whose first labour had lasted 1–9 h before caesarean (n=3258, hazard ratio 2·92 [1·33–6·45]), and women whose labour had lasted 10 h or more before first caesarean delivery (n=4906, hazard ratio 2·90 [1·47–5·73]).

If we included only women delivered at term by intrapartum caesarean section in their first birth (n=8164), there was no association between the duration of labour in the first birth (expressed as a continuous variable in hours) and the risk of unexplained stillbirth in their second pregnancy (adjusted hazard ratio 1·02 [0·94–1·10], p=0·66). There was no association between operative vaginal delivery in the first birth (forceps or vacuum extraction, n=21 740) and unexplained stillbirth in the second pregnancy (adjusted hazard ratio 1·05 [0·62–1·79], p=0·84).

For unexplained stillbirths at or after 34 weeks' gestation, the median birthweight in women with a previous caesarean delivery was smaller than in women whose first birth was vaginal (2820 g [IQR 2240–3062] *vs* 3110 [2540–3480], respectively, p=0·04), and more were at or below the fifth percentile for gestational age (12 [39%] of 31 *vs* 15 [16%] of 91, respectively, p=0·01). Also, there was a non-significant trend towards fewer babies in the upper quintile of birthweight for gestational age (three [10%] of 31 *vs* 19 [21%] of 91, respectively, p=0·19) which was significant if restricted to stillbirths at term and post term (one [5%] of 21, *vs* 18 [26%] of 69, respectively, p=0·04). The overall autopsy rate in the 206 unexplained stillbirths in the whole study group was 77·2%. There was no difference in the rate of autopsies between women who had not had a previous caesarean section (129 of 163) and those previously delivered by caesarean section (30 of 43, p=0·19).

We estimated the absolute risk of stillbirth associated with previous caesarean delivery using the prospective risk of stillbirth.[24] The prospective risk of stillbirth, from 34 weeks' gestation, was 1·77 per 1000 for women who had had a previous caesarean delivery, and 0·89 for other women; the risk difference was 0·88 (0·23–1·53). For antepartum stillbirths between 34 and 38 weeks (to estimate the additional risk among women who have a planned repeat caesarean section at the start of the 39th week) the risk was 1·09 per 1000 for women who had had a previous caesarean delivery, and 0·51 per 1000 for other women; the risk difference was 0·58 per 1000 (0·07–1·08). The prospective risk of stillbirth from 39 weeks' gestation was 1·06 per 1000 for women with a previous caesarean delivery and 0·47 per 1000 for other women.

Significant associations between previous caesarean delivery and intrauterine growth restriction and preterm

birth persisted in multivariate analysis (table 4). Women who had been delivered by caesarean section in their first pregnancy also had significantly more stillbirths attributed to maternal disease (figure 2). If deaths due to diabetes were excluded from the analyses, the association between previous caesarean section and stillbirth due to maternal disease was no longer significant (table 2). The univariate hazard ratio for unexplained stillbirth associated with previous caesarean section was very similar if women with missing values were included (hazard ratio 1·98 [1·36–2·89], p<0·001).

Discussion

Our results show that women whose first birth was by caesarean section were at significantly increased risk of having an antepartum stillbirth in their second pregnancy, mainly because of increased risk of unexplained stillbirth. The association with unexplained stillbirth was not attenuated by adjustment for maternal age, height, smoking status, social deprivation, and interpregnancy interval, or for key outcomes of the first pregnancy: birthweight percentile, preterm delivery, and perinatal death.

Our results are of relevance for women considering caesarean delivery who are planning further pregnancies. The absolute risk of perinatal death associated with vaginal breech delivery at term is around 8·3 per 1000 births.[25] Caesarean section reduces the risk of perinatal morbidity and mortality associated with vaginal breech birth.[26] The overall excess risk of stillbirth in a second pregnancy that was associated with a previous caesarean delivery was below one per 1000, which is unlikely to influence the decision to have a caesarean section for breech presentation in a first pregnancy. However, if women are being counselled about caesarean birth with no clear obstetric advantage, such as caesarean section for maternal request, the possible effect on the risk of unexplained stillbirth in future pregnancies should be discussed.

Our results are also of relevance for women who have previously been delivered by caesarean section who are considering mode of delivery in a subsequent pregnancy. Previous studies have focused on the risk of perinatal death caused by intrapartum uterine rupture; we have estimated the absolute risk of this event as 0·45 per 1000.[7] However, from 39 weeks' gestation onwards, the absolute risk of unexplained stillbirth in women who had had a previous caesarean delivery was greater than double this risk at 1·06 per 1000. The current data suggest that an additional benefit of planned repeat caesarean delivery at 39 weeks' gestation may be to reduce the risk of unexplained stillbirth. This issue should be discussed with women who have had a previous caesarean delivery when considering mode of delivery in the second pregnancy. Although induction of labour at 39 weeks' gestation would also address this risk, it is associated with an increased risk of scar rupture.[6] However, it is not known whether induction of labour is associated with an increased risk of perinatal death due to uterine rupture.

The increased risk of antepartum stillbirth in women previously delivered by caesarean section is unlikely to be due to a confounding effect of some unmeasured risk factor. Unlike deaths from maternal disease, the association with previous caesarean delivery became evident from 34 weeks' gestation onwards, and persisted at term and post term. If our results were biased by other complications of pregnancy, this difference would have been expected to be greater before term, since women who have had a previous caesarean and complications of an earlier pregnancy are more likely to be delivered by planned repeat caesarean section at term.[6] Time-to-event analysis corrects for censoring for elective delivery, which clearly will differ between women who have and have not had a previous caesarean birth.

The association between previous caesarean delivery and unexplained stillbirth in the second pregnancy was not attenuated by restricting the analysis to women who gave birth at or after 40 weeks' gestation in their first pregnancy. If the association were the result of some unmeasured confounding association with major complications in the first pregnancy, we would have anticipated a weaker association in this group. Moreover, the association was unaltered by adjustment for maternal factors or obstetric history. 50% of emergency caesarean sections in first pregnancies are for dystocia—ie, failure to progress.[27] The strength of the association was similar whether the first caesarean section was antepartum or intrapartum, and did not vary with the duration of labour before the first caesarean section, indicating that the association was independent of the indication for caesarean delivery. Furthermore, the association between first caesarean birth and stillbirth in the second pregnancy is unlikely to be due to a confounding factor associated with difficult labour, since there was no an association between operative vaginal birth (forceps or vacuum extraction) in the first pregnancy and the risk of unexplained stillbirth in the second.

The database did not include information on maternal weight, and it was not possible to adjust for maternal body-mass index. Obesity is associated with a doubling in risk of late fetal death in parous women.[28] Also, some study results have suggested that obese women are at increased risk of caesarean section,[29] although results are inconsistent.[30] Our results might be accounted for by a confounding effect of obesity, but this is unlikely for several reasons. First, stillbirths in the previous caesarean group were less likely to be large and more likely to be small for gestational age, which is the opposite of the pattern expected with obesity. Second, after adjustment for first pregnancy outcome, previous caesarean section and delivering a large for gestational age baby were not associated (table 4), but the association with unexplained stillbirth persisted. Third, the association between previous caesarean birth and stillbirth was stronger than that described for a body-mass index greater than 30.[28] Moreover, if the excess of antepartum stillbirths in the previous caesarean delivery group was caused by a confounding effect of a known risk factor, it was not being addressed; these deaths occurred at term, when elective caesarean delivery has little risk of neonatal death.[7]

Although the association between previous caesarean delivery and the risk of unexplained stillbirth is unlikely to be due to an unmeasured confounder, we cannot exclude this possibility. However, interventional trials are unlikely to be able to resolve this issue. The largest randomised controlled trial of caesarean delivery, to our knowledge, was the term breech trial, which had around 1000 participants in each group.[26] Even if all these women were followed up and all women had a subsequent pregnancy, an analysis of these data would have less than 3% power to detect the increased risk of unexplained stillbirth that we have observed. Furthermore, this power calculation does not account for the fact that 43% of women randomised to vaginal birth were actually delivered by caesarean section.[26]

The strengths of the dataset that we used are that it combined obstetric and demographic variables with almost complete perinatal death data, including the timing and cause of death; and that women had free access to obstetric care. Case-control studies could allow for adjustment for more maternal factors, but would introduce recall bias.

Women previously delivered by caesarean section were also at increased risk of stillbirth due to maternal disease as a

result of an excess of deaths attributed to diabetes (table 2). Diabetes increases the risk of caesarean section and antepartum stillbirths;[31] the association with stillbirths attributed to maternal disease probably indicates a confounding effect of diabetes. Unlike the risk of unexplained stillbirth, the association between previous caesarean delivery and stillbirth caused by maternal disease was only apparent preterm (figure 2). With respect to gestational age, this pattern supports our interpretation that confounding by a known risk factor for antepartum stillbirth would be expected to cause an increased risk preterm that would not be apparent at term and post term. The patterns of association indicate that our results are unlikely to be due to misclassification of stillbirths as unexplained that were in fact due to maternal disease. Moreover, we saw no effect of adjustment for age or any interaction between maternal age and previous caesarean section that might suggest confounding by maternal disease.

It was not a prior hypothesis that the association between previous caesarean delivery and unexplained stillbirth would vary with gestational age. The separation into before and after 34 weeks' gestation was done as a result of our analysis. Further studies will be required to confirm this finding. However, non-proportionality of the hazards was confirmed by a formal statistical test. Moreover, the association between previous caesarean section and unexplained stillbirth was still highly significant across the whole range of gestation.

The association between unexplained stillbirth and previous caesarean section is biologically plausible. It is possible that intentional or inadvertent ligation of major uterine vessels at the time of first caesarean section could affect uterine blood flow in future pregnancies. Furthermore, previous caesarean delivery is also known to be associated with an increased risk of abnormal placentation leading to abruption, placenta praevia, and morbid adherence of the placenta.[8–10] Stillbirth is associated with a high resistance pattern of uterine artery and umbilical artery blood flow, which may indicate maldevelopment of the villous tree.[32–34] The association between previous caesarean and stillbirth might be, therefore, another manifestation of abnormal placentation caused by a uterine scar. Consistent with this interpretation, stillbirths in women with a previous caesarean section were more likely to be small for gestational age than stillbirths in other women. Previous caesarean section was also associated with an increased risk of preterm birth and delivering a liveborn small for gestational age infant. This association might also be due to uteroplacental dysfunction or to the association between previous caesarean birth and abruption—since abruption is associated both with fetal growth restriction and with preterm birth.[35] We are not aware of any studies in which the effects have been assessed of caesarean delivery on uterine blood flow and mechanisms of placentation in future pregnancies. Such work could identify the biological basis for our results.

Contributors

G C S Smith formed the hypothesis, did the analysis, interpreted the results, and drafted the paper. J P Pell interpreted the results and contributed to the draft of the paper. R Dobbie did the linkage and extracted the data. All authors edited and approved the final version of the paper.

Conflict of interest statement

None declared.

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Original Contribution

Previous Preeclampsia, Preterm Delivery, and Delivery of a Small for Gestational Age Infant and the Risk of Unexplained Stillbirth in the Second Pregnancy: A Retrospective Cohort Study, Scotland, 1992–2001

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Women with a previous stillbirth are known to be at increased risk of stillbirth in subsequent pregnancies. However, few studies have addressed the association between other complications of pregnancy and the future risk of stillbirth. Using linkage of national pregnancy and perinatal death registries, the authors performed a retrospective cohort study of 133,163 women having a second birth in Scotland between 1992 and 2001 whose first infant was liveborn. The risk of unexplained stillbirth was increased among women with a previous preterm birth (adjusted hazard ratio (HR) = 2.04, 95% confidence interval (CI): 1.34, 3.11), previous delivery of a small for gestational age (SGA) infant (HR = 2.14, 95% CI: 1.59, 2.87), and previous preeclampsia (HR = 1.68, 95% CI: 1.07, 2.62). The associations were similar after adjustment for maternal age, height, marital and smoking status, and interpregnancy interval. There was a statistically significant positive interaction between previous delivery of a SGA infant and previous preeclampsia ($p = 0.01$): Women with this combination in their first pregnancy had an approximately fivefold risk of unexplained stillbirth in the second pregnancy (HR = 4.95, 95% CI: 2.63, 9.32). Associations were stronger with SGA unexplained stillbirths. The authors conclude that complicated first births of liveborn infants are associated with an increased risk of unexplained stillbirth in the next pregnancy.

pregnancy complications; risk; stillbirth

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD, *International Classification of Diseases*; OR, odds ratio; SGA, small for gestational age.

Antepartum stillbirth is death of the fetus before the onset of labor. It accounts for two thirds of all perinatal deaths and affects approximately one in 200 pregnancies (1). Approximately two thirds of antepartum stillbirths have no direct cause and are referred to as ''unexplained.'' The risk of both unexplained stillbirth and other pregnancy complications is associated with indicators of placental function, such as low levels of pregnancy-associated plasma protein A (2, 3), high levels of maternal serum alpha-fetoprotein (4), and a high resistance pattern of uterine artery Doppler flow velocimetry (5). Consequently, it is plausible that unexplained stillbirth and other complications of pregnancy are different clinical manifestations of a common problem in placentation.

It is well recognized that specific pregnancy complications, such as spontaneous preterm delivery and abruption, are likely to recur (6, 7). It is likely that this reflects, at least in part, a persistent predisposition to impaired placentation. Given that unexplained stillbirth and other pregnancy

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complications appear to have common placental determinants, we hypothesized that women who had pregnancies complicated by preeclampsia, preterm birth, or intrauterine growth restriction may be at increased risk of unexplained stillbirth in their subsequent pregnancies. Here we report the relation between complications in a first livebirth and the risk of unexplained stillbirth in 133,163 second pregnancies.

MATERIALS AND METHODS

Data sources

The Scottish Morbidity Record 2 collects information on clinical and demographic characteristics and outcomes for all patients discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been greater than 99 percent complete since the late 1970s (8). A quality assurance exercise was performed in 1996–1997, where 5 percent of case records were compared with the Scottish Morbidity Record 2 database over a 6-month period ($n = 1{,}414$). This exercise demonstrated that all fields used in the present study had less than 2 percent errors with the exception of the following (percent errors in parentheses): maternal height (4.4 percent) and estimated gestation (5.6 percent). *International Classification of Diseases* (ICD) diagnostic codes were found to be 80–90 percent accurate for the first four diagnoses and 70–80 percent accurate for the remainder (9).

Records of singleton births from the Scottish Morbidity Record 2 between 1985 and 2001 were identified and linked to records from the Scottish Stillbirth and Infant Death Enquiry (a national register that routinely classifies all perinatal deaths in Scotland) by use of a probability-based matching approach, which has been shown to match correctly approximately 98 percent of records (10). Coding of the cause of death is performed by a single medically qualified individual (the Scottish coordinator) in the Information and Statistics Division of the National Health Service on the basis of clinical information obtained from local coordinators and pathologists. Cases are identified through registration of stillbirths and neonatal deaths with the General Registrar's Office, which is a legal requirement following a perinatal death. The register is 100 percent complete when compared with the death certificate database and has been described in detail elsewhere (11, 12). Approval for the record linkage was provided by the Privacy Advisory Committee of the Information and Statistics Division of the National Health Service Scotland.

Study cohort

The population studied consisted of all second births in Scotland between 1992 and 2001, where there was a record for the first birth in the linked database. The analysis focused on second births after 1991, since smoking status was included only in the Scottish Morbidity Record 2 database from 1992 onward. Women were excluded whose first record had missing data for gestation or for infant's sex or birth weight; where the gestational age at delivery was outside the range of 24–43 weeks; and where the infant was stillborn. Women were excluded whose second record had missing data for gestation, infant's sex, birth weight, or any of the other maternal characteristics. Records were also excluded where the second infant died during the perinatal period as the result of congenital abnormality or rhesus isoimmunization or where delivery was outside the range of 24–43 weeks. Women were also excluded where the pair of records yielded an interpregnancy interval that was negative or implausibly short and where there was a discrepancy between the documented mode of delivery in the first record and the previous cesarean delivery field in the second record.

Definitions of maternal and obstetric characteristics

In the comparison of risk of unexplained antepartum stillbirth, the following demographic factors were considered as possible confounders: socioeconomic deprivation, smoking, maternal age, maternal height, and marital status. The postcode of residence was used to derive Carstairs socioeconomic deprivation scores (13). These are based on 1991 census data on car ownership, unemployment, overcrowding, and social class within postcode sectors of residence that contain, on average, around 1,600 residents. The deprivation scores were then used to assign women to categories of socioeconomic deprivation within the study cohort. Higher numbers indicate a greater degree of deprivation. ''Smoking'' was defined as the smoking status of the woman at the time of first attendance for antenatal care. ''Maternal age'' was defined as the age of the mother at the time of birth. Maternal height was measured in centimeters, and the value used was that documented in each woman's clinical record. ''Gestational age at birth'' was defined as the completed weeks of gestation on the basis of the estimated date of delivery in each woman's clinical record. Gestational age has been confirmed by ultrasound in the first half of pregnancy in more than 95 percent of women in the United Kingdom since the early 1990s (14). ''Preterm birth'' was defined as birth before 37 weeks of gestation. Birth weight was classified into sex- and gestational age-specific percentiles on the basis of 1,002,834 singleton livebirths between 1985 and 2001 entered into the Scottish Morbidity Record 2. ''Small for gestational age (SGA) birth weight'' was defined as a birth weight in the smallest 10 percent for sex and gestation. ''Interpregnancy interval'' was defined as the number of days from the first birth until the estimated date of the last menstrual period of the second. The estimated date of the last menstrual period was calculated by subtracting the estimated gestational age from the date of delivery. ''Preeclampsia'' was defined as the presence of an appropriate diagnostic code (ICD, Ninth Revision, code 642.4 or 642.5 or ICD, Tenth Revision, code O140, O141, or O149) in the delivery record.

Definition of stillbirths

Stillbirths were classified as antepartum (deaths before the onset of labor) and intrapartum (deaths during labor). ''Deaths caused by congenital anomaly'' were defined as any structural or genetic defect incompatible with life or potentially treatable but causing death. The cause of antepartum stillbirth was classified in the Scottish Stillbirth and Infant

Death Enquiry according to a modified version of the Wigglesworth hierarchical system (15), which is described in detail elsewhere (12). Stillbirths were classified according to direct obstetric causes (in order): toxemia (i.e., pre-eclampsia or eclampsia), hemorrhage (antepartum), mechanical, maternal, miscellaneous, and unexplained. Unexplained stillbirths included those that were SGA. The hierarchy dictates that a perinatal death where there was severe pre-eclampsia complicated by abruption would be classified as being due to toxemia, since toxemia is above hemorrhage in the hierarchy.

Statistical analyses

Continuous variables were summarized by the median and interquartile range, and comparisons between groups were made by the Mann-Whitney U test. Univariate comparisons of dichotomous data were made by use of the chi-square test and the test for trend, as appropriate. The p values for all hypothesis tests were two sided, and statistical significance was set at $p < 0.05$. The risk of stillbirth was compared between groups by time-to-event analyses (Kaplan-Meier and Cox proportional hazard model) in which the week of gestation was used as the time scale, antepartum stillbirth due to the specified cause was defined as the event, and all other births were treated as censored. This method uses ongoing pregnancies as the denominator, as previously suggested (16), but accounts for censoring due to birth, allows multivariate analysis (17), and can be used in situations where not all individuals would ultimately experience the event (18). This analytical approach allows assessment of the relative risk accounting for variation in the duration of pregnancy. Survival data were plotted as the cumulative percentage with event as recommended for rare outcomes (19), and univariate statistical comparisons were made with the log-rank test. Crude and adjusted hazard ratios were estimated by use of the proportional hazards model (20). The statistical significance of interactions between first pregnancy outcomes was assessed with the likelihood ratio test. The proportional hazards assumption was tested with the test of Grambsch and Therneau (21) as previously described for the analysis of stillbirth risk (9, 22). Logistic regression analysis was used to estimate adjusted odds ratios within given gestational windows. In these analyses, the number of antepartum stillbirths within the given range was the numerator, and the number of all births at the given or later gestations was the denominator. All statistical analyses were performed with STATA, version 8.2, software (StataCorp LP, College Station, Texas).

RESULTS

The Scottish Morbidity Record 2 contained 196,842 records of second singleton births between 1992 and 2001. Of these, 166,552 (84.6 percent) could be linked to a record for the first birth; 33,389 of these records (20.0 percent) were excluded (figure 1), leaving a study group of 133,163. There were 357 (0.3 percent) antepartum stillbirths not due to fetal abnormality or rhesus isoimmunization: 105 (29.4 percent) were explained (toxemia, hemorrhage, mechanical, maternal, and miscellaneous), and 252 (70.6 percent) were unexplained. Women whose second pregnancy ended in antepartum stillbirth were more likely in their first pregnancy to have delivered a SGA infant, delivered preterm, had a diagnosis of preeclampsia, and delivered by cesarean section (table 1). The interpregnancy interval varied in relation to whether the second pregnancy was an antepartum stillbirth, with a greater proportion of these women experiencing very prolonged intervals. Women experiencing a stillbirth were shorter and, at the time of the second pregnancy, were more likely to live in an area of high socioeconomic deprivation, to smoke, and to be unmarried.

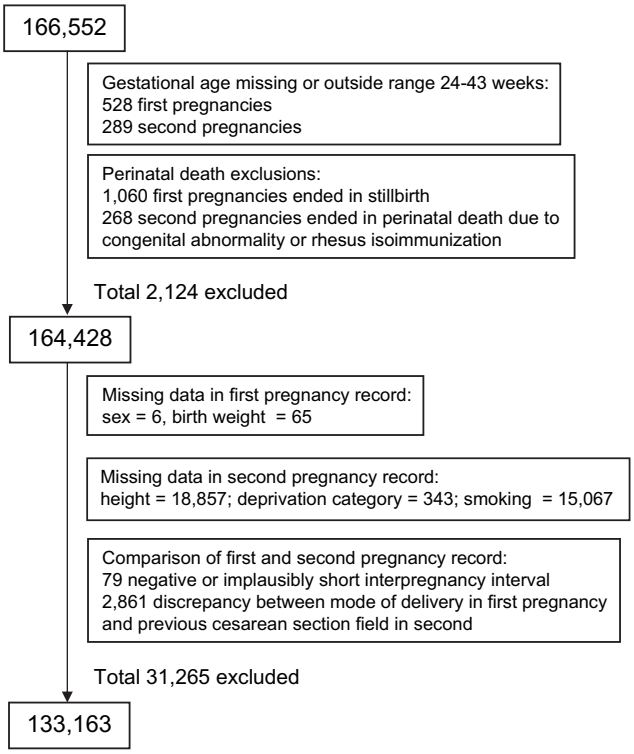

FIGURE 1. Selection of study cohort from all second singleton births in Scotland recorded in the Scottish Morbidity Record 2, 1992–2001.

Preterm birth, delivery of a SGA infant, and preeclampsia in the first pregnancy were each associated with an approximately two- to threefold risk of stillbirth in the second pregnancy (table 2). The risk of explained stillbirth was approximately sixfold among women with a previous preterm delivery and approximately threefold among women with previous delivery of a SGA infant or with preeclampsia. When analyzed by cause of stillbirth, previous preterm birth was associated with a sixfold risk of stillbirth due to preeclampsia, a fourfold risk of stillbirth due to abruption, and a 16-fold risk of stillbirth due to maternal disease. Previous delivery of a SGA infant was associated with sixfold risk of stillbirth due to preeclampsia and a fourfold risk of stillbirth due to abruption. Previous preeclampsia was associated with an 11-fold risk of stillbirth due to preeclampsia and a sixfold risk of stillbirth due to maternal disease.

TABLE 1. Maternal characteristics and outcome by occurrence of antepartum stillbirth in the second pregnancy, Scotland, 1992–2001

	Not antepartum stillbirth ($n = 132,806$)		Antepartum stillbirth ($n = 357$)		p value*
	No.	%	No.	%	
First pregnancy outcome					
Small for gestational age infant					
No	116,673	87.9	272	76.2	<0.001
Yes	16,133	12.2	85	23.8	
Gestation at birth					
Term	125,165	94.3	307	86.0	<0.001
Preterm	7,641	5.8	50	14.0	
Preeclampsia					
No	125,747	94.7	320	89.6	<0.001
Yes	7,059	5.3	37	10.4	
Cesarean section					
No	112,582	84.8	264	74.0	<0.001
Yes	20,224	15.2	93	26.1	
Second pregnancy characteristics					
Interpregnancy interval					
<6 months	5,242	4.0	15	4.2	0.02
6–11 months	13,828	10.4	29	8.1	
12–23 months	37,997	28.6	94	26.3	
24 months–5 years	58,140	43.8	152	42.6	
6–10 years	16,301	12.3	60	16.8	
>10 years	1,298	1.0	7	2.0	
Age, years (median (interquartile range))	29	25, 32	28	23, 32	0.1
Height, cm (median (interquartile range))	162	158, 167	161	157, 165	<0.001
Deprivation category					
1 (least deprived)	8,253	6.2	9	2.5	<0.001
2	18,606	14.0	43	12.0	
3	28,650	21.6	67	18.8	
4	32,293	24.3	87	24.4	
5	20,373	15.3	75	21.0	
6	15,920	12.0	46	12.9	
7 (most deprived)	8,711	6.6	30	8.0	
Smoking status					
Never	85,288	64.2	193	54.1	<0.001
Current	37,595	28.3	149	41.7	
Former	9,923	7.5	15	4.2	
Marital status					
Married	92,521	69.7	214	59.9	<0.001
Other	40,285	30.3	143	40.1	

* Mann-Whitney *U*, chi-square test for trend, or chi-square test as appropriate.

Preterm birth, delivery of a SGA infant, and preeclampsia in the first pregnancy were each associated with an approximately twofold risk of unexplained stillbirth. The strength of association was very similar when the analysis was confined to previous spontaneous preterm birth (hazard ratio (HR) = 1.92, 95 percent confidence interval (CI): 1.14, 3.23).

In relation to the risk of unexplained stillbirth, there were no statistically significant interactions between previous

TABLE 2. First pregnancy outcome and the risk of explained and unexplained stillbirth in the second pregnancy, Scotland, 1992–2001

Cause of stillbirth	Gestation of previous birth					Birth weight of previous infant					Previous preeclampsia				
	Preterm ($n = 7,691$)	Term ($n = 125,472$)	Hazard ratio	95% confidence interval	*p* value*	Small for gestational age ($n = 16,218$)	Appropriate for gestational age ($n = 116,945$)	Hazard ratio	95% confidence interval	*p* value*	Preeclampsia ($n = 7,096$)	No preeclampsia ($n = 126,067$)	Hazard ratio	95% confidence interval	*p* value*
All causes	50	307	3.10	2.30, 4.18	<0.001	85	272	2.32	1.82, 2.96	<0.001	37	320	2.12	1.51, 2.99	<0.001
Toxemia†	4	12	5.98	1.93, 18.58	<0.001	7	9	5.70	2.12, 15.31	<0.001	6	10	10.87	3.95, 29.91	<0.001
Hemorrhage†	11	46	4.29	2.22, 8.30	<0.001	19	38	3.67	2.12, 6.37	<0.001	3	54	1.01	0.32, 3.23	>0.9
Mechanical†	1	5	4.00	0.46, 34.48	0.2	1	5	1.50	0.18, 12.85	0.7	1	5	3.73	0.44, 31.93	0.2
Maternal†	9	10	15.77	6.40, 38.84	<0.001	2	17	0.86	0.20, 3.72	0.8	5	14	6.43	2.32, 17.85	<0.001
Miscellaneous†	1	6	3.47	0.41, 29.12	0.2	0	7				1	6	3.16	0.38, 26.24	0.3
All explained†	26	79	5.97	3.83, 9.32	<0.001	29	76	2.81	1.83, 4.30	<0.001	16	89	3.28	1.92, 5.56	<0.001
Unexplained†	24	228	2.04	1.34, 3.11	<0.001	56	196	2.14	1.59, 2.87	<0.001	21	231	1.68	1.07, 2.62	0.02

* Log-rank test.
† Numbers and hazard ratios exclude all other causes of stillbirth.

FIGURE 2. Kaplan-Meier plot of cumulative probability of unexplained stillbirth (expressed per 1,000 pregnancies) in the second birth in relation to the outcome of the first birth, Scotland, 1992–2001. A, comparison of women whose first birth was at term (dashed line) with those who had previously delivered preterm (solid line); B, comparison of women who delivered an appropriate for gestational age infant and had no diagnosis of preeclampsia in their first pregnancy (dashed line) with women who delivered a small for gestational age (SGA) infant and had a documented diagnosis of preeclampsia in their first pregnancy (solid line).

preterm delivery and previous delivery of a SGA infant ($HR_{interaction} = 1.10$, 95 percent CI: 0.41, 2.95; $p = 0.85$) or between previous preterm birth and previous preeclampsia ($HR_{interaction} = 0.48$, 95 percent CI: 0.15, 1.59; $p = 0.21$). However, there was a statistically significant interaction between previous preeclampsia and previous delivery of a SGA infant ($HR_{interaction} = 3.37$, 95 percent CI: 1.34, 8.45; $p = 0.01$). All subsequent analysis of the risk of unexplained stillbirth examined combinations of previous delivery of a SGA infant and previous preeclampsia. The risk of unexplained stillbirth was approximately 60 percent higher among women with a previous preterm birth (figure 2A; table 3). The risk of unexplained stillbirth was

TABLE 3. Unadjusted and adjusted hazard ratios for unexplained stillbirth in the second pregnancy, Scotland, 1992–2001

Maternal and obstetric characteristics	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	*p* value*	Hazard ratio	95% confidence interval	*p* value*
First pregnancy predictors						
Gestation at birth						
Term	Referent			Referent		
Preterm	2.04	1.34, 3.11	<0.001	1.62	1.04, 2.51	0.04†
Small for gestational age or preeclampsia						
Not small for gestational age or preeclampsia	Referent		<0.001	Referent		<0.001
Small for gestational age alone	1.83	1.32, 2.53		1.67	1.20, 2.33	
Preeclampsia alone	1.02	0.54, 1.93		0.88	0.46, 1.68	
Small for gestational age and preeclampsia	6.83	3.72, 12.55		4.95	2.63, 9.32	
Previous cesarean section						
No	Referent			Referent		
Yes	1.95	1.46, 2.60	<0.001	1.75	1.30, 2.37	<0.001†
Second pregnancy predictors						
Interpregnancy interval						
<6 months	0.98	0.52, 1.88	0.07‡	0.88	0.45, 1.70	0.3
6–11 months	0.72	0.45, 1.16		0.72	0.44, 1.16	
12–23 months	0.82	0.62, 1.12		0.85	0.62, 1.16	
24 months–5 years	Referent			Referent		
6–10 years	1.15	0.80, 1.67		1.08	0.74, 1.58	
>10 years	2.42	1.06, 5.49		2.06	0.89, 4.77	
Age, years						
<20	1.35	0.65, 2.79	0.04	1.33	0.61, 2.88	0.2
20–24	1.41	1.00, 1.99		1.32	0.92, 1.90	
25–29	Referent			Referent		
30–34	1.09	0.79, 1.50		1.1	0.81, 1.56	
35–39	1.47	0.96, 2.25		1.48	0.96, 2.28	
>39	2.99	1.30, 6.86		2.93	1.27, 6.79	
Deprivation category						
1 (least deprived)	0.37	0.16, 0.85	0.2‡	0.40	0.17, 0.92	0.3
2	0.84	0.54, 1.28		0.89	0.57, 1.37	
3	0.95	0.66, 1.36		0.99	0.69, 1.43	
4	Referent			Referent		
5	1.12	0.76, 1.64		1.08	0.73, 1.58	
6	1.02	0.67, 1.57		0.96	0.63, 1.47	
7 (most deprived)	1.20	0.73, 1.98		1.06	0.63, 1.76	
Height, cm						
<155	1.29	0.83, 2.00	0.049‡	1.06	0.68, 1.65	0.3
155–159	1.59	1.14, 2.21		1.47	1.05, 2.05	
160–164	Referent			Referent		
165–169	1.06	0.74, 1.51		1.12	0.78, 1.60	
170–174	0.89	0.55, 1.44		0.97	0.60, 1.58	
>174	0.99	0.48, 2.06		1.15	0.55, 2.39	
Smoking						
Never	Referent		0.03	Referent		0.2
Current	1.34	1.03, 1.74		1.07	0.80, 1.44	
Former	0.74	0.42, 1.30		0.67	0.38, 1.18	
Marital status						
Married	Referent			Referent		
Other	1.37	1.06, 1.77	0.02	1.20	0.89, 1.62	0.2

* *p* value is test for heterogeneity except where otherwise noted.
† $p < 0.01$ for test of proportional hazards assumption (Biometrika 1994;81:515–26 (21)).
‡ $p < 0.05$ for linear trend.

TABLE 4. Relation between first pregnancy outcome and small for gestational age and appropriate for gestational age unexplained stillbirth, Scotland, 1992–2001*

Outcome of first pregnancy	Small for gestational age			Appropriate for gestational age		
	Hazard ratio	95% confidence interval	*p* value	Hazard ratio	95% confidence interval	*p* value
Gestation at first birth						
Preterm	3.38	1.87, 6.11	<0.001	1.39	0.75, 2.57	0.3
Small for gestational age or preeclampsia						
Small for gestational age alone	2.73	1.65, 4.49	<0.001	1.42	0.92, 2.20	0.1
Preeclampsia alone	1.30	0.47, 3.59	0.6	0.89	0.39, 2.02	0.8
Small for gestational age and preeclampsia	5.91	1.85, 18.85	0.003	7.25	3.54, 14.82	<0.001
Mode of delivery						
Cesarean	3.34	2.15, 5.19	<0.001	1.38	0.93, 2.04	0.1

* The referent category for preterm was previous term birth, for small for gestational age and/or preeclampsia was women who had neither outcome, and for mode of delivery was any form of vaginal delivery.

approximately 70 percent higher among women with a previous delivery of a SGA infant in the absence of a diagnosis of preeclampsia. A previous diagnosis of preeclampsia was not associated with the subsequent risk of unexplained stillbirth if the infant was appropriate for gestational age. However, the risk of unexplained stillbirth was fivefold among women with the combination of previous preeclampsia and delivery of a SGA infant (figure 2B; table 3). The association between previous preterm birth and previous cesarean section significantly varied across the range of 24–43 weeks (table 3). The association with previous preterm birth was strong at 24–32 weeks (odds ratio (OR) = 2.71, 95 percent CI: 1.56, 4.71) and not statistically significant at 33–36 weeks (OR = 1.34, 95 percent CI: 0.52, 3.47) or 37–43 weeks (OR = 0.39, 95 percent CI: 0.12, 1.24).

We found an association between cesarean delivery in the first pregnancy and the risk of unexplained stillbirth in the second (table 4), which is consistent with our previous study (9). However, there would have been considerable overlap between the patients in our previous study (eligible second births in Scotland in 1992–1998) and those in the present study. We repeated the analysis of previous cesarean delivery confined to the 32,628 births from 1999 to 2001, that is, in women who were not included in our previous analysis. The hazard ratio for unexplained stillbirth associated with previous cesarean delivery in births from 1999 to 2001 was 2.27 (95 percent CI: 1.38, 3.73; $p = 0.001$).

We analyzed the relation between the outcome of the first pregnancy and the risk of unexplained stillbirth, dividing the outcome into those that were SGA and those that were appropriate for gestational age. Associations tended to be stronger for unexplained stillbirth where the birth weight was SGA (table 4).

The main analysis was then performed in the approximately 31,000 women excluded because of missing data in relation to the second pregnancy. This addressed whether the cohort studied may have been unrepresentative of the whole population; for example, it may have systematically excluded women who delivered without booking for prenatal care, leading to biases. Among these women, the unadjusted hazard ratio for unexplained stillbirth was 2.57 (95 percent CI: 1.27, 5.18) for women with a prior history of preterm birth, 2.08 (95 percent CI: 1.18, 3.67) for women with previous delivery of a SGA infant, and 1.91 (95 percent CI: 0.91, 4.00) for women with previous preeclampsia. The strength of the associations did not significantly differ from those observed among women with complete data ($p = 0.7$, 0.9, and 0.8, respectively).

DISCUSSION

It is well recognized that women who have a stillbirth in one pregnancy are at increased risk of stillbirth in future pregnancies (23). These women are typically offered additional fetal surveillance and early elective delivery at term. The key finding of the present study is that women who experienced preterm birth, delivery of a SGA infant, or preeclampsia in a first birth of a liveborn infant were also at increased risk of unexplained stillbirth in the second. Moreover, there was a synergistic association between previous delivery of a SGA infant and previous preeclampsia: This combination carried a fivefold risk of unexplained stillbirth in the second pregnancy.

Previous preterm birth, previous delivery of a SGA infant, and previous preeclampsia were also associated with an increased risk of explained stillbirth. These observations are likely to reflect, at least in part, the recurrence of specific complications, such as abruption and preeclampsia. The association between prior complications and the risk of explained stillbirth in the second pregnancy may also reflect common associations among preexisting maternal disease, obstetric complications, and stillbirth. For example, women with insulin-dependent diabetes mellitus are at increased

risk of preterm birth and preeclampsia (24). The increased risk of explained stillbirth among women with previous complicated births is, therefore, plausible but probably merely reflects the known recurrence risk of obstetric complications and common associations among maternal disease, obstetric complications, and stillbirth.

There has been only one large-scale study, to our knowledge, that has previously addressed the association between previous obstetric complications and the future risk of stillbirth (25). The major weakness of that study was that they lacked data on the cause of stillbirth. Therefore, antepartum and intrapartum stillbirths were pooled, as were explained and unexplained stillbirths. That study demonstrated an approximately twofold risk of stillbirth associated with both previous preterm birth and previous delivery of a SGA infant. No data were reported on previous preeclampsia. It was unclear from that study whether these associations were explained by simply recurrence of complications (abruption and preeclampsia) or by common associations with maternal disease, as discussed above. In the present study, we show that prior pregnancy complications are associated with the risk of both explained and unexplained antepartum stillbirth.

The current findings are biologically plausible. Previous studies have shown that the same biochemical or biophysical measurements of placental function in early pregnancy are associated with both unexplained stillbirth and other adverse obstetric outcomes (2–5). Although the determinants of poor placentation remain obscure, it is known that placentally related complications tend to recur (6). Furthermore, women with elevated levels of maternal serum alpha-fetoprotein (an indicator of placental permeability) in one pregnancy are more likely to have elevated levels of this protein in the next pregnancy (26). The current findings suggest that women who have a tendency to impaired placentation may manifest this with different complications in different pregnancies. The factors that determine which complications arise in a given pregnancy remain unclear. Consistent with this interpretation, the association that we found between previous pregnancy complications and the risk of unexplained stillbirth tended to be stronger for unexplained stillbirths where the infant was SGA. Previous studies have shown associations between placental function and SGA unexplained stillbirths but not those with birth weight appropriate for gestational age (3).

We had previously demonstrated an association between cesarean delivery in the first pregnancy and the risk of unexplained stillbirth in the second (9). We observed a very similar association in the current analysis. However, the current data expand on our previous analysis in two ways. First, we now show that the association is similar after adjustment for a diagnosis of preeclampsia in the first pregnancy. Second, we repeated the analysis confined to births between 1999 and 2001 (our previous study had examined second births in Scotland between 1992 and 1998, and many of these would also have been included in the present study). We found a very similar strength of association between previous cesarean delivery in the first pregnancy and the risk of unexplained stillbirth in the second in births between 1999 and 2001. Thus, it is unlikely that this association is a chance finding.

In conclusion, women with previous placentally related complications in a livebirth are at increased risk of unexplained stillbirth. The association is particularly strong among those with the combination of previous preeclampsia and previous delivery of a SGA infant, which suggests that the underlying defect in placentation leading to that combination may be similar to the defect predisposing to stillbirth.

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Section 2. Delivery-related complications in special situations (multiple pregnancy and among women attempting vaginal birth after caesarean section)

ORIGINAL CONTRIBUTION

Risk of Perinatal Death Associated With Labor After Previous Cesarean Delivery in Uncomplicated Term Pregnancies

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Context Trial of labor after previous cesarean delivery is associated with increased risk of uterine rupture. However, no reliable data exist on the effect of a trial of labor on the risk of perinatal death in otherwise uncomplicated term pregnancies.

Objective To determine the risk of intrapartum stillbirth or neonatal death not related to congenital abnormality among women with uncomplicated term pregnancies who had a trial of labor after previous cesarean delivery, compared with women having a planned repeat cesarean delivery, and multiparous and nulliparous women at term not delivered by planned cesarean method.

Design and Setting Population-based, retrospective cohort study of data from the linked Scottish Morbidity Record and Stillbirth and Neonatal Death Enquiry encompassing births in Scotland between January 1, 1992, and December 31, 1997.

Population A total of 313 238 singleton births between 37 and 43 weeks' gestational age in which the fetus was in a cephalic presentation.

Main Outcome Measure Delivery-related perinatal death, defined as intrapartum stillbirth or neonatal death unrelated to congenital anomaly, compared among the 4 groups.

Results Among women who had a trial of labor following previous cesarean delivery (n=15 515), the overall rate of delivery-related perinatal death was 12.9 (95% confidence interval [CI], 7.9-19.9) per 10 000 women. This was approximately 11 times greater (odds ratio [OR], 11.6; 95% CI, 1.6-86.7) than the risk associated with planned repeat cesarean delivery (n=9014), more than twice (OR, 2.2; 95% CI, 1.3-3.5) the risk associated with other multiparous women in labor (n=151 549), and similar to the risk among nulliparous women in labor (n=137 160; OR, 1.3; 95% CI, 0.8-2.1). The associations were not explained by differences in maternal height, smoking status, socioeconomic status, age, fetal growth, or week of gestation at delivery. Among women having a trial of labor, the rate of death due to mechanical causes, including uterine rupture, was 4.5 (95% CI, 1.8-9.3) per 10 000 women. This was more than 8 times greater than other multiparous women (OR, 8.5; 95% CI, 3.2-22.3) and nulliparous women (OR, 8.8; 95% CI, 3.2-24.2).

Conclusions The absolute risk of perinatal death associated with trial of labor following previous cesarean delivery is low. However, in our study, the risk was significantly higher than that associated with planned repeat cesarean delivery, and there was a marked excess of deaths due to uterine rupture compared with other women in labor.

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INCREASING RATES OF CESAREAN delivery are a major cause for concern in almost all developed countries.[1] A number of strategies have been proposed that aim to reduce the overall proportion of cesarean deliveries, including trial of labor after previous cesarean deliveries.[2] Observational studies[3,4] suggest that trial of labor is associated with a significantly increased risk of uterine rupture. A meta-analysis reported an increased risk of perinatal death associated with trial of labor[5] but included premature births between 28 and 36 weeks' gestation and breech deliveries.[6] There is no large-scale study of the relative and absolute risks of perinatal death among women previously delivered by cesarean method but with an uncomplicated pregnancy at term. In the present study, we sought to address this by linking national registers of pregnancy discharge data and perinatal deaths.

METHODS

The analysis was designed to determine the risk of intrapartum stillbirth or neonatal death unrelated to congenital abnormality among women with an uncomplicated term pregnancy who had a trial of labor following at least 1 previous cesarean delivery. Trial of labor was defined as any vaginal or emergency (unplanned) cesarean delivery

See also p 2627 and Patient Page.

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occurring at or beyond 37 weeks' gestation in a woman who had previously been delivered by cesarean method. These women were compared with 3 groups: (1) women having planned repeat cesarean delivery, (2) other multiparous women at term not delivered by planned cesarean method, and (3) nulliparous women at term not delivered by planned cesarean method. Nulliparous women were women with no previous pregnancies or whose previous pregnancies all ended in abortion.

Population

The Scottish Morbidity Record (SMR2) collects information on clinical and demographic characteristics and outcomes for all patients discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been more than 99% complete since the late 1970s.[7] An analysis of 1414 records from 1996 through 1997 demonstrated that the register was free of significant errors in more than 98% of records in all the fields used in the present analysis, with the exception of postcode (94.0%), height (96.2%), estimated gestation (94.4%), and method of induction of labor (93.6%) (Jim Chalmers, MBChB, Information and Statistics Division, National Health Service, Edinburgh, Scotland, written communication, April 2001). The SMR2 records were linked to records from the Scottish Stillbirth and Neonatal Death Enquiry. This national register has routinely classified all perinatal deaths in Scotland since 1983. It is almost 100% complete and has been described in detail elsewhere.[8]

Study Group

The study group consisted of all births in Scotland between January 1, 1992, and December 31, 1997. The exclusion criteria for the study group were multiple pregnancy, noncephalic presentation, delivery outside the range of 37 to 43 weeks' gestation, perinatal deaths due to congenital anomaly, antepartum stillbirth not due to congenital anomaly, and deliveries by planned cesarean method, except among women who had been delivered by cesarean method in a previous pregnancy.

The main outcome of this study was delivery-related perinatal death, defined as intrapartum stillbirth or neonatal death not caused by congenital anomaly. Stillbirths were defined as newborns that showed no signs of life following delivery. Stillbirths were subdivided into antepartum (deaths before the onset of labor) and intrapartum (deaths during labor). Neonatal death was defined as death during the first 4 weeks of life in a live newborn. Deaths caused by congenital anomaly were defined as any structural or genetic defect incompatible with life or potentially treatable but causing death.

In the comparison of risk of perinatal death among groups of women, the following factors were considered as possible confounders: socioeconomic deprivation, smoking, maternal age, maternal height, gestational age, and birth weight. Postcode of residence was used to derive Carstairs socioeconomic deprivation scores.[9] These are based on 1991 census data on car ownership, unemployment, overcrowding, and social class within postcode sectors of residence that contain, on average, approximately 1600 residents. The deprivation scores were then used to categorize women into quintiles of socioeconomic deprivation within the study cohort. Higher quintiles indicate a greater degree of deprivation. Smoking was defined as the smoking status of the woman at the time of first attendance for antenatal care. Maternal age was defined as the age of the mother at the time of birth. Maternal height was measured in centimeters, and the value used was that documented in each woman's clinical record. Height is generally measured using a free-standing or wall-mounted height measure. Gestational age at birth was defined as completed weeks of gestation on the basis of the estimated date of delivery in each woman's clinical record. Gestational age has been confirmed by ultrasound in the first half of pregnancy in more than 95% of women in the United Kingdom since the early 1990s.[10] Birth weight was categorized into sex- and gestational age-specific deciles, using a method previously described in detail.[11] Low birth weight was defined as birth weight of less than 2500 g.

The cause of perinatal death was classified according to a hierarchical system that is described in detail elsewhere.[12] Deaths were initially classified according to the following direct obstetric causes (in order): toxemia, hemorrhage, mechanical, maternal, and none of these obstetric causes. Mechanical was defined as death from uterine rupture, cord compression (including prolapse), birth trauma, or asphyxia associated with disproportion. In the absence of any of the listed direct obstetric causes, the deaths were classified by the pediatric diagnoses and these were grouped into intrapartum anoxia, other (pulmonary causes, intracranial hemorrhage, infection, other hemorrhage, and miscellaneous), and unexplained. The hierarchy dictates that a perinatal death where there was severe preeclampsia complicated by abruption would be classified as being due to toxemia because toxemia is above both hemorrhage and intrapartum anoxia in the hierarchy.

Statistical Analyses

Continuous variables were summarized by the median and interquartile range, and comparisons between groups were performed using the Mann-Whitney *U* test. Univariate comparisons of dichotomous data were performed using the χ^2 test (>5 observations in all cells) or Fisher exact test (≤ 5 observations in ≥ 1 cells). Ordinal data were compared using the χ^2 test for trend. The *P* values for all hypothesis tests were 2-sided and .05 was the significance level. Adjusted rates were obtained using direct standardization. Crude and adjusted odds ratios (ORs) were obtained using logistic regression analysis. Cases with missing values were excluded from the multivariate analysis. The statistical significance of interaction terms was assessed using the likelihood ratio test. Model goodness-of-fit was assessed using the Hosmer-Lemeshow test based on deciles of probability.[13] All statistical analyses were performed using version

7.0 of the Stata software package (Stata Corp, College Station, Tex).

RESULTS

Of the SMR2 records with a perinatal death documented, 97.8% could be linked to a corresponding record in the Stillbirth and Neonatal Death Enquiry. From 1992 through 1997, there were 356 958 records of singleton births in Scotland in the SMR2 database. Among these records, there were 697 (0.2%) with missing values for gestational age, 4873 (1.4%) with missing values for presentation at delivery, and 8 (<0.1%) with missing values for number of previous cesarean deliveries. A total of 5564 records had 1 or more missing values, leaving 351 394 records. Among this group, there were 16 427 fetuses (4.7%) with a noncephalic presentation, 621 perinatal deaths (0.2%) related to congenital anomaly, 1479 antepartum stillbirths (0.4%) unrelated to congenital anomaly, 20 628 births (5.9%) outside the range of 37 to 43 weeks' gestational age, and 9827 births (2.8%) by planned cesarean method where the women had not had a previous cesarean delivery. A total of 38 156 records had 1 or more exclusion criteria, resulting in a study group of 313 238 (87.8% of all singleton births during the study period).

The study group was subdivided into 15 515 women previously delivered by cesarean method who had a trial of labor, 9014 women who had previously been delivered by cesarean method who delivered by planned cesarean method in the current pregnancy, 137 160 nulliparous women who were not delivered by planned cesarean method, and 151 549 multiparous women who had not had a previous cesarean delivery and did not deliver by planned cesarean method in the current pregnancy. Within the study group, there were missing values for maternal height in 26 825 women (8.6%), for smoking status in 29 730 (9.5%), for deprivation quintile in 4975 (1.6%), for birth weight in 61 (<0.1%), and for 5-minute Apgar score in 36 (<0.1%).

The study group characteristics and basic outcome data are given in TABLE 1. The highest rate of perinatal death (12.9 per 10 000 women) was seen among women having a trial of labor (TABLE 2). The risk of a delivery-related perinatal death among women having a trial of labor was more than 11 times (OR, 11.6; 95% confidence interval [CI], 1.6-86.7) that of women having a planned repeat cesarean delivery (TABLE 3). The risk of death associated with a trial of labor was similar when compared with nulliparous women in labor (OR, 1.3; 95% CI, 0.8-2.1) but was more than twice that of other multiparous women in labor (OR, 2.2; 95% CI, 1.3-3.5). When delivery-related perinatal deaths among all women who had previously been delivered by cesarean method were analyzed, it was estimated that 91% (95% CI, 36%-99%) could be attributed to the increased risk of death associated with a trial of labor.

Statistical comparison with the planned repeat cesarean delivery group was problematic because there was only

Table 1. Study Group Characteristics and Crude Outcome Data by Method of Delivery and Obstetric History*

	Previous Cesarean Delivery			No Previous Cesarean Delivery			
Characteristics	Trial of Labor (n = 15 515)	Planned Repeat Cesarean Delivery (n = 9014)	*P* Value†	Nulliparous (n = 137 160)	*P* Value†	Multiparous (n = 151 549)	*P* Value†
Age, median (IQR), y	30 (26-33)	31 (27-34)	<.001	26 (21-29)	<.001	29 (26-32)	<.001
Height, median (IQR), cm	161 (157-165)	159 (154-163)	<.001	163 (158-167)	<.001	162 (158-167)	<.001
Deprivation quintile							
1 (Least deprived)	2776 (18.2)	1860 (21.0)		25 031 (18.6)		27 734 (18.6)	
2	3069 (20.1)	1680 (18.9)		25 718 (19.1)		28 814 (19.3)	
3	2970 (19.4)	1617 (18.2)	.02	26 816 (19.9)	.59	29 543 (19.8)	.64
4	3154 (20.7)	1788 (20.1)		28 099 (20.8)		30 085 (20.2)	
5 (Most deprived)	3298 (21.6)	1935 (21.8)		29 245 (21.7)		33 031 (22.1)	
Missing data	248	134		2251		2342	
Smoking status, No. (%)							
Nonsmoker	8423 (60.1)	5524 (67.4)		74 589 (59.8)		82 338 (60.3)	
Ex-smoker	980 (7.0)	588 (7.2)	<.001	13 098 (10.5)	<.001	9247 (6.8)	.85
Current	4620 (33.0)	2079 (25.4)		36 960 (29.7)		45 062 (33.0)	
Missing data	1492	823		12 513		14 902	
Gestation, median (IQR), wk	40 (39-41)	38 (38-39)	<.001	40 (39-41)	<.001	40 (39-41)	.03
Birth weight, median (IQR), g	3460 (3120-3800)	3380 (3062-3720)	<.001	3390 (3080-3700)	<.001	3500 (3190-3830)	<.001
Low birth weight, No. (%)	455 (2.9)	249 (2.8)	.45	3649 (2.7)	.05	2570 (1.7)	<.001
5-Minute Apgar score <4, No. (%)	105 (0.68)	40 (0.44)	.02	816 (0.60)	.21	918 (0.61)	.28
Intrapartum death, No. (%)	7 (0.05)	0 (0)	.05	39 (0.03)	.23	31 (0.02)	.08
Neonatal death, No. (%)	13 (0.08)	1 (0.01)	.02	96 (0.07)	.52	59 (0.04)	.02

*IQR indicates interquartile range.
†Statistical comparison with trial of labor. Continuous data compared using Mann-Whitney *U* test, categorical data compared using Fisher exact test or χ^2 test as appropriate (see "Methods" section), and ordinal data compared using χ^2 test for trend.

a single death among the 9014 women. All the records with missing values were among the 9013 survivors and, therefore, excluding missing records resulted in a weaker association between trial of labor and perinatal death compared with planned repeat cesarean delivery simply by reducing the denominator in the latter group (Table 3). However, among the cases with nonmissing values, adjusting for maternal age, smoking status, height, deprivation quintile, gestational age at birth, and birth weight decile strengthened the association between trial of labor and perinatal death when compared with elective repeat cesarean delivery (OR, 11.7; 95% CI, 1.4-101.6). When women having a trial of labor were compared with nulliparous and other multiparous women, adjusting for maternal age, smoking status, height, deprivation quintile, gestational age at birth, and birth weight decile had no effect on the ORs (Table 3).

When the analyses were confined to births at or after 40 weeks' gestation, the results were similar (Table 2). Although there were no deaths among the 1064 planned repeat cesarean deliveries at or after 40 weeks' gestation, the numbers were too small to be statistically significantly lower than the trial of labor group. Among births at or after 40 weeks' gestation, the risk of death associated with a trial of labor was similar when compared with nulliparous women in labor (OR, 1.2; 95% CI, 0.6-2.2) but higher when compared with other multiparous women in labor (OR, 2.7; 95% CI, 1.4-5.2).

Among women previously delivered by cesarean method, 369 (2.4%) of those having a trial of labor had more than 1 previous cesarean delivery, whereas 2962 (32.9%) of those delivered by planned cesarean method had more than 1 previous cesarean delivery. Of the 20 perinatal deaths among women having a trial of labor, 19 women (95%) had only 1 previous cesarean delivery. Among women previously delivered by cesarean method, 5206 (33.6%) of those having a trial of labor had previously had a vaginal birth, whereas 988 (11.0%) of those delivered by planned cesarean method had previously had a vaginal birth. Of the 20 perinatal deaths among women having a trial of labor, 5 women (25%) had previously had a vaginal birth. Among the trial of labor group, there were 12 perinatal deaths among 3945 neonates born by emergency cesarean delivery and 8 deaths among 11 570 neonates delivered vaginally ($P = .001$).

The rates of perinatal death due to different causes differed among the 4 groups (TABLE 4). Compared with other multiparous women, women having a trial of labor had more than 8 times the risk of a perinatal death due to a mechanical cause (OR, 8.5; 95% CI, 3.2-22.3) and almost 3 times the risk of a perinatal death due to intrapartum anoxia (OR,

Table 2. Rates of Perinatal Death in Relation to Previous Cesarean Delivery and Mode of Delivery*

Outcomes	Previous Cesarean Delivery			No Previous Cesarean Delivery			
	Trial of Labor	Planned Repeat Cesarean Delivery	*P* Value†	Nulliparous Labor	*P* Value†	Multiparous Labor	*P* Value†
All births							
No. of deaths/births	20/15 515	1/9014	.001	135/137 160	.29	90/151 549	.004
Rate per 10 000 (95% CI)	12.9 (7.9-19.9)	1.1 (0.0-6.1)		9.8 (8.3-11.6)		5.9 (4.8-7.3)	
Births at or after 40 weeks' gestation							
No. of deaths/births	11/9574	0/1064	.62	89/90 496	.61	41/95 596	.006
Rate per 10 000 (95% CI)	11.5 (5.7-20.5)	0 (0.0-34.6)‡		9.8 (7.9-12.1)		4.3 (3.1-5.8)	
Records with no missing values (all term births)							
No. of deaths/births	13/12 904	1/7648	.02	113/113 359	.88	69/124 987	.06
Rate per 10 000 (95% CI)	10.1 (5.4-17.2)	1.3 (0.0-7.3)		10.0 (8.2-12.0)		5.5 (4.3-7.0)	
Standardized rate (95% CI)§	9.9 (4.3-15.6)	0.4 (0.0-1.1)‖		10.0 (8.0-12.0)		5.5 (4.1-6.8)	

*CI indicates confidence interval.
†Fisher exact test comparison with trial of labor group.
‡One-sided 97.5% CI.
§Standardized for maternal age, smoking, height, and social deprivation against whole study group.
‖The standardized rate should be interpreted with caution since there was only a single event.

Table 3. Crude and Adjusted Odds Ratio for Delivery-Related Perinatal Death Associated With Trial of Labor*

Comparison	1 or More Missing Values		No Missing Values			
	Crude OR (95% CI)	*P* Value	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)†	*P* Value
Trial of labor vs planned repeat cesarean delivery‡	11.6 (1.6-86.7)	.02	7.7 (1.0-59.0)	.05	11.7 (1.4-101.6)	.03
Trial of labor vs other multiparous women	2.2 (1.3-3.5)	.002	1.8 (1.0-3.3)	.05	1.7 (1.0-3.2)	.07
Trial of labor vs nulliparous women	1.3 (0.8-2.1)	.26	1.0 (0.6-1.8)	.97	0.9 (0.5-1.7)	.79

*Goodness-of-fit models were as follows (Hosmer-Lemeshow test): $P = .98$, $P = .98$, and $P = .23$, respectively. No statistically significant interactions in any model between previous cesarean delivery and the following: maternal age, smoking status, height, socioeconomic deprivation, use of prostaglandin E_2 to induce labor, gestational age at birth, and birth weight decile for gestational age. OR indicates odds ratio; CI, confidence interval.
†The ORs were adjusted for maternal age, smoking status, height, deprivation quintile, gestational age at birth, and birth weight decile for gestational age.
‡Number of deaths in reference category too small to yield stable estimates.

2.8; 95% CI, 1.3-6.5). When compared with nulliparous women, women having a trial of labor had an increased risk of perinatal death due to mechanical causes alone (OR, 8.8; 95% CI, 3.2-24.2).

Women undergoing a trial of labor were less likely to have a prostaglandin E_2 (PGE_2) induction, had shorter labors, had lower rates of operative vaginal delivery, and had higher rates of emergency cesarean delivery than nulliparous women (TABLE 5). Women undergoing a trial of labor were more likely to have a PGE_2 induction, had longer labors, and had higher rates of both operative vaginal and cesarean delivery than other multiparous women. Among women having a trial of labor, there were 3 perinatal deaths among 2395 women induced with PGE_2 and 17 deaths among 13 120 women not treated with PGE_2 ($P>.99$).

In addition to the 15 515 women who fulfilled the criteria for trial of labor at term, there were 35 women who fulfilled the same criteria except that the newborn was an antepartum stillbirth not caused by congenital abnormality at term. Fifteen of these women delivered before 39 weeks, 10 delivered in the 39th week of gestation, and 10 delivered at or after 40 weeks' gestation.

Table 4. Rates of Different Causes of Perinatal Death in Relation to Previous Cesarean Delivery and Mode of Delivery*

	Previous Cesarean Delivery			No Previous Cesarean Delivery			
Cause of Death	Trial of Labor (n = 15 515)	Planned Additional Cesarean Delivery (n = 9014)	*P* Value†	Nulliparous Labor (n = 137 160)	*P* Value†	Multiparous Labor (n = 151 549)	*P* Value†
Toxemia							
No. of deaths	1	0	>.99	6	.53	2	.25
Rate per 10 000 (95% CI)	0.6 (0.0-3.6)	0.0 (0.0-4.1)‡		0.4 (0.0-1.0)		0.1 (0.0-0.5)	
Hemorrhage							
No. of deaths	1	0	>.99	9	>.99	14	>.99
Rate per 10 000 (95% CI)	0.6 (0.0-3.6)	0.0 (0.0-4.1)‡		0.7 (0.3-1.2)		0.9 (0.5-1.6)	
Mechanical							
No. of deaths	7	0	.05	7	<.001	8	<.001
Rate per 10 000 (95% CI)	4.5 (1.8-9.3)	0.0 (0.0-4.1)‡		0.5 (0.2-1.1)		0.5 (0.2-1.0)	
Maternal							
No. of deaths	1	1	>.99	14	>.99	7	.54
Rate per 10 000 (95% CI)	0.6 (0.0-3.6)	0.6 (0.0-6.2)		1.0 (0.6-1.7)		0.5 (0.2-1.0)	
Intrapartum anoxia							
No. of deaths	7	0	.05	71	.85	24	.02
Rate per 10 000 (95% CI)	4.5 (1.8-9.3)	0.0 (0.0-4.1)‡		5.2 (4.0-6.5)		1.6 (1.0-2.4)	
Other pediatric							
No. of deaths	2	0	.53	18	>.99	14	.66
Rate per 10 000 (95% CI)	1.3 (0.2-4.6)	0.0 (0.0-4.1)‡		1.3 (0.8-2.1)		0.9 (0.5-1.6)	
Unexplained							
No. of deaths	1	0	>.99	10	>.99	21	.72
Rate per 10 000 (95% CI)	0.6 (0.0-3.6)	0.0 (0.0-4.1)‡		0.7 (0.4-1.3)		1.4 (0.9-2.1)	

*CI indicates confidence interval.
†Fisher exact test comparison with trial of labor group.
‡One-sided 97.5% CI.

Table 5. Management of Labor by Parity and Obstetric History*

	Previous Cesarean Delivery Trial of Labor (n = 15 515)	No Previous Cesarean Delivery			
		Nulliparous (n = 137 160)	*P* Value†	Multiparous (n = 151 549)	*P* Value†
Prostaglandin E_2 induction, No. (%)	2395 (15.4)	24 878 (18.1)	<.001	21 130 (13.9)	<.001
Duration of labor, median (IQR), h	7 (4-10)	9 (6-12)	<.001	5 (3-7)	<.001
Mode of delivery, No. (%)					
Spontaneous	9076 (58.5)	88 864 (64.8)	<.001	143 079 (94.4)	<.001
Assisted vaginal delivery	2494 (16.1)	31 128 (22.7)		4821 (3.2)	
Emergency cesarean delivery	3945 (25.4)	17 168 (12.5)		3649 (2.4)	
Timing of perinatal death, wk					
<39	3	21	.62	32	.06
≥39	17	114		58	

*IQR indicates interquartile range.
†Statistical comparison with trial of labor group. Continuous data compared using Mann-Whitney *U* test, and categorical data compared using Fisher exact test or χ^2 test as appropriate (see "Methods" section).

COMMENT

The ideal means to determine the risks and benefits of trial of labor vs planned repeat cesarean delivery would be a randomized controlled trial. In practice, this would be difficult to perform because many women would be unhappy to have such a decision made in a random manner and large numbers of women would be required for a study powered to detect differences in such rare outcomes as uterine rupture and perinatal death. In the absence of randomized controlled trial evidence, analysis of observational data must be used to estimate the risks of these rare outcomes. A recent observational study[4] has reported on the relative and absolute risks of uterine rupture associated with trial of labor. Herein, we report the risk of perinatal death associated with trial of labor among women at term with a singleton pregnancy in a cephalic presentation.

In the present study, the risk of delivery-related perinatal death among women having a trial of labor was more than 11 times that of women having a planned repeat cesarean delivery. Women having a planned repeat cesarean delivery experienced the lowest death rate among any of the groups. The low rate of death was explained by the absence of any risk of intrapartum stillbirth and a significantly lower risk of neonatal death. The risk associated with planned repeat cesarean delivery at term was so low that only a single death occurred in Scotland during the 6 years of the study period. Multivariate statistical comparison among groups is problematic when the number of events is so small, and larger studies will be required to analyze adequate numbers of deaths following planned cesarean delivery. However, selection bias is unlikely to explain the lower risk of death among women having a planned repeat cesarean delivery, because they are more likely to have medical and obstetric complications than women offered a trial of labor.[4] Consistent with this, adjusting for maternal age, smoking status, height, deprivation quintile, gestational age at birth, and birth weight decile for gestational age strengthened the association between trial of labor and perinatal death when compared with women having a planned repeat cesarean delivery, though the CIs were wide because of the small number of cases.

Our observed rate of perinatal death associated with planned repeat cesarean delivery, 1.1 per 10 000 women, is much lower than previously cited.[5] However, previously published perinatal mortality figures for both trial of labor and planned cesarean delivery did not exclude breech presentations and preterm newborns delivered between 28 and 36 weeks' gestation.[6] Since prematurity and breech presentation are associated with an excess of perinatal mortality,[14,15] these data are unhelpful in informing women who reach term with a fetus presenting cephalically. This group accounted for 84% of women with a previous cesarean delivery in our study.

When compared with other multiparous women in labor, women having a trial of labor had approximately twice the rate of delivery-related perinatal death. This finding was due to an increased risk of death due to mechanical causes, including uterine rupture, and death due to intrapartum anoxia not related to uterine rupture. The overall rate of delivery-related perinatal death among women having a trial of labor was not significantly greater than nulliparous women in labor. The increased number of deaths due to mechanical causes among women having a trial of labor compared with nulliparous women was offset by a lower rate of death due to other causes. The observation that the level of risk of nonmechanical perinatal death among women having a trial of labor was intermediate between other multiparous and nulliparous women probably reflects the fact that approximately one third of women having a trial of labor had previously had a vaginal birth. There are other possible factors that could contribute to differences in outcome among the groups that were not recorded in the database, such as epidural anesthesia, use of electronic fetal monitoring, and details of maternal medical and obstetric complications. Further studies will be required to determine whether systematic variation in any of these variables may contribute to differences in the risk of delivery-related perinatal death among these groups.

The data presented in this article are collected nationally and form an extract of a larger data set, which is reported in detail elsewhere.[12] Overall, the statistics were comparable with previous analyses of perinatal deaths. The overall rate of intrapartum stillbirth unrelated to congenital abnormality of 2.5 per 10 000 births was comparable with previous studies from Scandinavia,[16] and the total proportion of all stillbirths that were classified as intrapartum was 11%, which is similar to national data from England.[17] The number of neonatal deaths observed in our study was lower than a report from Wales,[18] which described 7.4 neonatal deaths attributable to an intrapartum event per 10 000 births. However, that study included neonates of all gestational ages, using a birth-weight cutoff of more than 1499 g, which would have included a significant proportion of preterm births.

Current recommendations are that planned cesarean delivery should be performed in the 39th week of gestation to reduce the risk of neonatal respiratory morbidity.[19] It could be argued that uterine rupture may occur in earlier weeks of gestation and that the apparent protective effect of planned cesarean delivery is exaggerated. However, 85% of delivery-related perinatal deaths at term among women having a trial of labor occurred at or after 39 weeks' gestation. This is consistent with the observation that approximately 15% of multiparous women will undergo labor between the start of the 37th week and the start of the 39th week of gestation.[20] Therefore, it seems likely that most deaths could have been avoided by planned cesarean delivery at the start of the 39th week of gestation. Moreover, planned cesarean delivery at this time would also avoid exposure to the

risk of antepartum stillbirth while awaiting the onset of labor. There were 20 antepartum stillbirths among women having a trial of labor at or after 39 weeks' gestation and a proportion of these may also have been prevented by planned cesarean delivery at the start of the 39th week of gestation. Therefore, the potential protective effect on perinatal death of planned cesarean delivery over trial of labor may be greater than estimated in the present study of intrapartum stillbirths and neonatal deaths.

The definition of a trial of labor used in this study was that a woman who had previously been delivered by cesarean method was delivered at term by a method other than planned cesarean. However, it is likely that a small proportion of these women were due to have a planned cesarean delivery but presented in labor before their scheduled date and an emergency cesarean delivery was performed in early labor. Moreover, the database did not include information on the nature of the incision used in the previous cesarean delivery. For this reason, we repeated the analysis confined to births at or after 40 weeks' gestation. By this time, all women scheduled for planned cesarean delivery should have had the procedure, including any women who had previously had a classic cesarean delivery. The risks of perinatal death were virtually unchanged, suggesting that our results are robust. The outcome of trial of labor was comparable with previous studies: 75% had a vaginal delivery, which was almost identical to an analysis of more than 17 000 trials of labor from Switzerland.[6]

Our data provide essential information for women to make an informed choice about a trial of labor. Overall, the point estimate of the risk of a perinatal death associated with a trial of labor is 1 in 775, and the 95% CIs indicate that the risk is unlikely to be higher than 1 in 500. The point estimate of the risk of a perinatal death due to uterine rupture associated with a trial of labor is 1 in 2200, and the 95% CIs indicate that the risk is unlikely to be higher than approximately 1 in 1000.

Considerable caution should be applied when extrapolating these data to considering possible benefits of planned cesarean delivery among women who have not previously had a cesarean birth. More than one third of delivery-related perinatal deaths among multiparous women who had not previously been delivered by cesarean method were observed before 39 weeks of gestation. Scheduling planned cesarean delivery for the start of the 39th week of gestation may have failed to prevent many of these deaths. Moreover, we present no data on the risk of perinatal death following planned cesarean delivery among nulliparous women.

Obstetricians have faced pressure from government and health care insurers to advocate vaginal birth after cesarean delivery as one strategy to reduce the overall rate of cesarean delivery. However, this pressure has been exerted in the absence of any reliable information on the risks to the newborn for most women. This study is the first to our knowledge that is adequately powered and analyzed to provide information on the risks of perinatal death associated with the management of women with a history of cesarean delivery but an otherwise uncomplicated pregnancy at term.

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Analysis and interpretation of data: Smith, Pell, Cameron.
Drafting of the manuscript: Smith, Pell.
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Papers

Factors predisposing to perinatal death related to uterine rupture during attempted vaginal birth after caesarean section: retrospective cohort study

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Abstract

Objective To determine the factors associated with an increased risk of perinatal death related to uterine rupture during attempted vaginal birth after caesarean section.
Design Population based retrospective cohort study.
Setting Data from the linked Scottish Morbidity Record and Stillbirth and Infant Death Survey of births in Scotland, 1985-98.
Participants All women with one previous caesarean delivery who gave birth to a singleton infant at term by a means other than planned repeat caesarean section (n = 35 854).
Main outcome measures All intrapartum uterine rupture and uterine rupture resulting in perinatal death (that is, death of the fetus or neonate).
Results The overall proportion of vaginal births was 74.2% and of uterine rupture was 0.35%. The risk of intrapartum uterine rupture was higher among women who had not previously given birth vaginally (adjusted odds ratio 2.5, 95% confidence interval 1.6 to 3.9, P < 0.001) and those whose labour was induced with prostaglandin (2.9, 2.0 to 4.3, P < 0.001). Both factors were also associated with an increased risk of perinatal death due to uterine rupture. Delivery in a hospital with < 3000 births a year did not increase the overall risk of uterine rupture (1.1, 0.8 to 1.5, P = 0.67). However, the risk of perinatal death due to uterine rupture was significantly higher in hospitals with < 3000 births a year (one per 1300 births) than in hospitals with ≥ 3000 births a year (one per 4700; 3.4, 1.0 to 14.3, P = 0.04).
Conclusion Women who have not previously given birth vaginally and those whose labour is induced with prostaglandin are at increased risk of uterine rupture when attempting vaginal birth after caesarean section. The risk of consequent death of the infant is higher in units with lower annual numbers of births.

Introduction

Uterine rupture during attempted vaginal birth after a previous caesarean section is a rare event that affects about one in 200 women,[1] and consequent death of the infant is even rarer, affecting about one per 2000.[2] Analysis of the factors determining perinatal death due to uterine rupture therefore requires data from large numbers of women. Most large scale databases of births lack detailed information on the cause of perinatal death and the obstetric characteristics of the population. Consequently, we know of no reports of the risk factors for perinatal death due to uterine rupture during attempted vaginal birth after previous caesarean section. We linked national registries of pregnancy discharge data and perinatal death to determine the factors associated with this event.

Methods

The inclusion criteria for the study were that a woman had previously had one caesarean section and was delivered in her current pregnancy by a means other than planned caesarean section. We excluded women with more than one previous caesarean, those with multiple gestations, those delivering before 37 weeks' gestation, and those delivering beyond 43 weeks' gestation. We also excluded cases in which the infant died from causes other than intrapartum uterine rupture.

Data sources—The Scottish Morbidity Record (SMR2) collects information on clinical and demographic characteristics and outcomes for all patients discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been > 99% complete since the late 1970s.[3] The register collects both specific obstetric data and up to six ICD-9 (international classification of diseases, ninth revision) or ICD-10 (10th revision) diagnostic codes relating to the admission. In 1996-7 a quality assurance analysis comparing 1414 records with the clinical notes showed that the register was free from significant errors in > 98% of records in all the specific fields used in the present analysis. Exceptions were postcode (94.0%), height (96.2%), estimated gestation (94.4%), and method of induction of labour (93.6%). The previous caesarean section field was 99.7% accurate. ICD diagnostic codes were found to be 80-90% accurate for the first four diagnoses and 70-80% accurate for the remainder (Jim Chalmers, personal communication). SMR2 records were linked to records from the Scottish Stillbirth and Infant Death Survey. This national register routinely classifies all perinatal deaths in Scotland. Coding of the cause of death is performed by a single medically qualified individual, and the survey is described in detail elsewhere.[4]

Definitions—We defined trial of labour as a singleton delivery at term by a means other than planned caesarean section in women with only one previous caesarean delivery. The definition of perinatal death due to uterine rupture was that the obstetric cause of death was coded as "mechanical" under the modified Wigglesworth classification[5] and that the ICD-9 diagnostic code for intrapartum uterine rupture (665.1) was listed under the specific diagnoses. Intrapartum uterine ruptures that did not result in perinatal death were identified with ICD-9 and ICD-10 diagnostic codes 665.1 and O711, respectively, from the

diagnostic fields in the SMR2 record related to hospital discharge after delivery. Hospital throughput was defined as the total number of births recorded in the SMR2 database for the given hospital over the given year. Hospital throughput was categorised into above or below the median (3000 births). Other maternal characteristics were defined as previously described.[2]

Statistical analyses—We summarised continuous variables with medians and interquartile ranges and used the Mann-Whitney U test for comparisons between groups and Fisher's exact test for univariate comparisons of dichotomous data. P values for all hypothesis tests were two sided. Multivariate analysis was performed using logistic regression analysis. The significance of interaction terms was assessed with the likelihood ratio test. The goodness of fit of models was assessed with the Hosmer and Lemeshow test based on tenths of probability.[6] Because of the rarity of the event we used exact logistic regression to model the risk of perinatal death due to uterine rupture.[7] When we treated annual number of births as a continuous variable in the exact model, we rounded it to the nearest 50 to make the model computationally feasible. All statistical analyses were performed with the Stata software package version 8.2 (StataCorp, College Station, TX), except for exact logistic regression, which was performed with LogXact version 5.0 (Cytel Software Corporation, Cambridge, MA).

Results

There were 871 283 SMR2 birth records for Scotland for 1985-98. In total 39 729 (4.6%) women had had one previous caesarean delivery and were delivered by a means other than planned caesarean section. There were 452 (1.1%) multiple births, 3462 (8.7%) births outside the range of 37-43 weeks' gestation, and 543 (1.4%) perinatal deaths due to causes other than intrapartum uterine rupture. We excluded a further 32 (<0.1%) records because the women were documented as being primigravid, despite having had a previous caesarean delivery. We therefore excluded 3875 (9.8%) records (some cases were excluded in more than one category), leaving a study group of 35 854. We compared the demographic and obstetric characteristics of the study group according to whether there was a perinatal death due to uterine rupture (table 1).

There was no association between the annual number of deliveries and the risk of emergency caesarean delivery (odds ratio 1.00, 95% confidence interval 0.98 to 1.01, P=0.58) or uterine rupture overall (0.98, 0.86 to 1.11, P=0.70), but there was a significant negative association with the risk of perinatal death due to uterine rupture (0.68, 0.46 to 0.99, P=0.04) (figure).

On univariate analysis, with the 35 854 women who attempted vaginal birth as the denominator, the risk of uterine rupture was higher in women who had not previously given birth vaginally and in women who had been induced with prostaglandin but not with other methods of induction (table 2). Though delivery in a hospital with <3000 births a year was not associated with the risk of uterine rupture overall, the other associations remained highly significant in multivariate analysis and the point estimates were similar (table 3). There were enough uterine ruptures for us to test the goodness of fit of the model and to examine interactions between the variables. The goodness of fit was adequate (P>0.05), and there were no significant first order interactions between any of the variables with each other or with the year of birth.

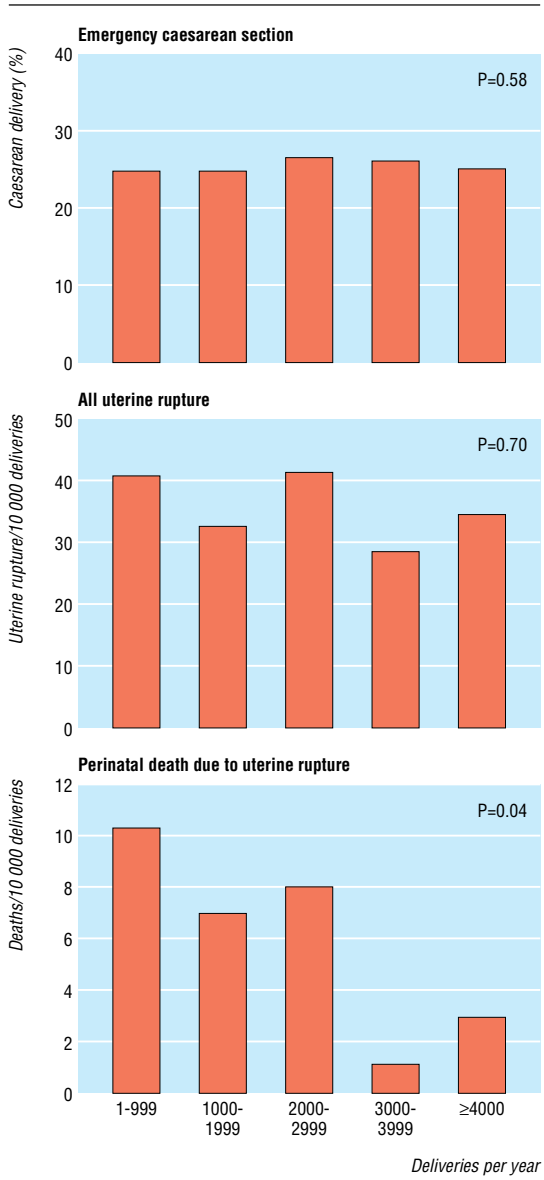
The risk of perinatal death due to uterine rupture was also higher in women who had not previously given birth vaginally and in women who had been induced with prostaglandins but not with other methods of induction (table 2). However, in addition, delivery in a hospital with <3000 births a year was associated with a significantly increased risk of perinatal death due to uterine rupture. The risk of perinatal death was about one in 1300 in hospitals with <3000 births a year and one in 4700 in hospitals with ≥3000 births a year. Because of the small number of deaths caused by uterine rupture, significance was generally attenuated in multivariate analysis (table 3). However, the point estimates were similar to those from the univariate analysis, indicating that the associations seen in univariate analysis were not due to confounding by the factors included in the model. There were too few events for us to assess goodness of fit or first order interactions.

Among the 124 cases of uterine rupture, there were 17 (13.7%) intrapartum stillbirths or neonatal deaths. There were 63 uterine ruptures in hospitals delivering <3000 women per year and 13 (20.6%) resulted in perinatal death. In hospitals delivering ≥3000 women a year there were 61 uterine ruptures and four (6.6%) resulted in perinatal death (P=0.03). Among women with uterine rupture, the relative risk of perinatal death in a hospital with <3000 births a year was about threefold (table 4).

Table 1 Maternal demographic and obstetric characteristics in relation to perinatal death due to uterine rupture. Figures are numbers (percentages) unless stated otherwise

	No perinatal death* (n=35 837)	Perinatal death (n=17)	P value†
Median (IQR) age (years)	29 (26-32)	27 (25-31)	0.61
Median (IQR) height (cm)	161 (157-165)	158 (153-163)	0.13
Height data missing	2927 (8.2)	2 (11.8)	0.64
Marital status:			
Married	28 548 (79.7)	15 (88.2)	>0.9
Other	7 289 (20.3)	2 (17.8)	
Fifth of deprivation distribution:			
1 (least deprived)	6 418 (17.9)	2 (11.8)	0.82
2	6 731 (18.8)	3 (17.6)	
3	6 854 (19.1)	2 (11.8)	
4	7 219 (20.1)	5 (29.4)	
5 (most deprived)	8 182 (22.8)	5 (29.4)	
Missing	433 (1.2)	0 (0.0)	
No of previous vaginal births			
None	23 176 (64.7)	15 (88.2)	0.04
One or more	12 661 (35.3)	2 (11.8)	
No of spontaneous abortions:			
None	27 574 (76.9)	12 (70.6)	0.57
≥1	8 263 (23.1)	5 (29.4)	
No of therapeutic abortions:			
None	32 202 (89.9)	16 (94.1)	>0.9
≥1	3 635 (10.1)	1 (5.9)	
Year of delivery:			
<1992	17 539 (48.9)	9 (52.9)	0.74
≥1992	18 298 (51.1)	8 (47.1)	
Median (IQR) No of deliveries in hospital in given year	3120 (1794-4 129)	2154 (1681-2718)	0.05
Sex of infant:			
Female	17 594 (49.1)	11 (64.7)	0.23
Male	18 243 (50.9)	6 (35.3)	
Median (IQR) weight (g) of infant	3445 (3118-3780)	3242 (3150-3840)	0.76

IQR=interquartile range.
*Includes 35 730 women who did not have uterine rupture documented and 107 women who had uterine rupture documented but it did not result in stillbirth or neonatal death of infant.
†Mann-Whitney U test or Fisher's exact test, as appropriate.



Proportions of emergency caesarean section, all uterine rupture, and perinatal death due to uterine rupture, in relation to size of hospital

When we confined the analysis to births ≥40 weeks' gestation, the risk of uterine rupture was significantly associated with no previous vaginal birth (odds ratio 2.0, 95% confidence interval 1.2 to 3.4, P=0.009) and induction of labour with prostaglandin (2.2, 1.4 to 3.5, P=0.001). Formal tests of interaction between each of these variables and gestation ≥40 weeks showed that the strength of the associations did not significantly differ before and after 40 weeks (P=0.2 and 0.3, respectively). Among the 22 170 births ≥40 weeks' gestation, there were seven deaths out of 10 602 births in hospitals with <3000 births a year and one death out of 11 568 births in hospitals with ≥3000 births a year (P=0.02).

Of the 12 633 women who had previously given birth vaginally, 1499 (11.8%) were induced with prostaglandin compared with 2976 of the 20 215 (12.8%) women who had not done so (P=0.006). We used a logistic regression model to estimate the absolute risk of uterine rupture (including cases in which the infant survived and cases in which the infant died) in relation to different combinations of parity and induction of labour with prostaglandin in relation to 1998 rates. Among women who had not previously given birth vaginally, the risk of uterine rupture without induction of labour with prostaglandin was one in 210 and with induction of labour with prostaglandin was one in 71. Among women with a previous vaginal birth, the risk of uterine rupture without induction of labour with prostaglandin was one in 514 and with induction of labour with prostaglandin was one in 175.

Discussion

We found that after a previous caesarean section women who had not previously given birth vaginally and those who had labour induced with prostaglandin were at increased risk of uterine rupture. The same two factors were associated with the risk of perinatal death due to uterine rupture. In contrast, delivering in a hospital with low throughput was not associated with uterine rupture overall but was associated with an increased risk of perinatal death due to uterine rupture. We found that uterine rupture was three times more likely to result in death of the infant if the delivery took place in a hospital with <3000 births a year. Confining trials of labour to larger obstetric units may therefore reduce the risk of perinatal death associated with uterine rupture during a trial of labour.

The finding that units with high throughput had lower rates of perinatal death due to uterine rupture is plausible. Hospitals with greater throughput are more likely to have resident obstetric, anaesthetic, and neonatal services as well as a dedicated obstetric operating theatre. These factors would allow a faster response to fetal distress due to uterine rupture, which in turn would allow more rapid delivery and resuscitation of the neonate. We did not have information on the structure of services at each unit over the period of study. However, the factors are likely to be highly correlated and interdependent. A

Table 2 Univariate obstetric associations with uterine rupture and perinatal death due to uterine rupture. Figures are numbers (percentages) unless stated otherwise

	Uterine rupture				Perinatal death due to uterine rupture			
Characteristics	Yes (n=124)	No (n=35 730)	Relative risk (95% CI)	P value*	Yes (n=17)	No† (n=35 837)	Relative risk (95% CI)	P value*
<3000 births a year	63 (50.8)	16 930 (47.4)	1.1 (0.8 to 1.6)	0.47	13 (76.5)	16 980 (47.4)	3.6 (1.2 to 11.1)	0.03
No previous vaginal birth	102 (82.3)	23 089 (64.6)	2.5 (1.6 to 4.0)	<0.0001	15 (88.2)	23 176 (64.7)	4.1 (0.9 to 17.9)	0.04
Induction of labour without prostaglandin‡	13 (10.5)	4416 (12.4)	1.1 (0.6 to 2.0)	0.75	2 (11.8)	4427 (12.4)	1.2 (0.3 to 5.6)	0.68
Induction of labour with prostaglandin‡	39 (31.4)	4436 (12.4)	3.3 (2.2 to 4.8)	<0.0001	5 (29.4)	4470 (12.5)	3.0 (1.0 to 8.8)	0.05
Gestation >41 weeks	8 (6.4)	1867 (5.2)	1.2 (0.6 to 2.6)	0.54	0 (0.0)	1875 (5.2)	—	>0.9

*Fisher's exact test (two sided).
†Includes 35 730 women who did not have uterine rupture documented and 107 women who had uterine rupture documented but it did not result in stillbirth or neonatal death.
‡Same reference category for both: all women in whom labour was not induced.

Table 3 Multivariate analysis (with odds ratios and 95% confidence intervals) of risk of uterine rupture and perinatal death due to uterine rupture

	All uterine rupture		Perinatal death due to uterine rupture	
Characteristics	**Adjusted OR (95% CI)*†**	**P value**	**Adjusted OR (95% CI)***	**P value**
<3000 births a year	1.1 (0.8 to 1.5)	0.67	3.4 (1.0 to 14.3)	0.04
No previous vaginal birth	2.5 (1.6 to 3.9)	<0.001	4.1 (0.9 to 36.6)	0.06
Induction of labour with prostaglandin	2.9 (2.0 to 4.3)	<0.001	2.5 (0.7 to 7.7)	0.17

*Adjusted for each of other factors.
†Also adjusted for year of delivery.

unit with no resident obstetric or anaesthetic cover is unlikely to have a dedicated obstetric operating theatre or a resident experienced neonatologist. Therefore, even if these data were available, it would be extremely difficult to determine the independent contributions of each of these factors in reducing the risk of death. Therefore, the total number of births is a useful composite measure of the level of support and has the pragmatic advantage of being easy to define.

Study strengths and weaknesses

Previous large scale analyses of the factors determining uterine rupture could not reliably distinguish between asymptomatic dehiscence of the previous caesarean section scar and clinically significant, symptomatic uterine rupture.[1 8 9] The failure to define the event may lead to ascertainment bias. As asymptomatic dehiscence of the scar will generally be identified during a subsequent caesarean section, there will be increased ascertainment of uterine rupture for any exposure that is associated with an increased risk of caesarean delivery. As we were able to study perinatal death due to uterine rupture, this allowed us to identify catastrophic rupture that would be ascertained irrespective of the mode of delivery. We conclude that the associations between uterine rupture and no previous vaginal birth and induction of labour with prostaglandin are unlikely to be explained by ascertainment bias. Previous studies have suggested that the protective effect of a previous vaginal birth is observed whether it preceded or followed the first caesarean delivery.[10]

Findings are comparable with previous studies

The estimates of absolute risk in the present analysis are comparable with those from previous studies. The overall rate of successful vaginal delivery of 74.2% is similar to the generally quoted overall figure of 75%.[11] The overall rate of uterine rupture of 0.35% is consistent with that reported in a previous large scale Swiss study.[9] The overall risk of perinatal death due to uterine rupture (one in 2100) is similar to the one in 2600 reported in a study from Washington State, USA.[1] The risk among large obstetric units (one per 4700) is similar to a case series from a large obstetric centre in California (one per 4200).[12] Although the total number of perinatal deaths in our study was relatively small (17), this is almost three times more than reported in a recent meta-analysis of all previous studies.[13] Guise et al commented that the risk of death in Scotland, as cited from our previous report,[2] was 10 times higher than reported in other studies.[13] However, the figure they quoted was for perinatal death due to all causes related to delivery. The absolute risk of death due to uterine rupture in our previous study (4.5 per 10 000) was similar to the overall risk in our current analysis. Both fall within the 95% confidence intervals of the meta-analysis. We believe that the current data give the best estimate of the absolute risk of perinatal death among women attempting vaginal birth after caesarean.

A previous population based study had shown an association between induction of labour with prostaglandin and uterine rupture.[1] This finding led the American College of Obstetricians and Gynecologists to recommend avoidance of prostaglandin in women with a previous caesarean section. However, the number of women was small (366) and this was less than 2% of the study population. In the present study, we had data on 4475 women who had labour induced with prostaglandin, which was 12.5% of our cohort. Our analyses confirmed that induction of labour with prostaglandin, but not other methods, was independently associated with an increased risk of uterine rupture, including catastrophic rupture leading to perinatal death. It remains to be determined whether this is due to a specific pharmacological effect or whether the use of prostaglandin is merely a marker for a woman with an unfavourable cervix.

We defined trial of labour as any woman who had a single previous caesarean birth who was delivered at term by a means other than planned caesarean section. The cohort studied probably includes some women who were due for planned repeat caesarean section but attended in early labour, had an emergency caesarean delivery, and did not truly attempt vaginal birth. However, women delivering at or after 40 weeks are unlikely to have requested planned repeat caesarean section. We found that the nature and strength of associations in the present study were similar when we confined analyses to births at or after 40 weeks' gestation, and misclassification of attempted vaginal birth is unlikely to have significantly affected our results.

Conclusion

In summary, we have shown that the risk of uterine rupture is increased among women who have not previously given birth vaginally and those undergoing induction of labour with prostaglandin. Our data show that the risk of consequent death of the infant is lower in obstetric units with higher throughput. Although other interpretations could be made, we believe the most plausible explanation for these findings is that the facilities generally available at larger obstetric units reduce the risk of

Table 4 Factors associated with perinatal death among women with documented uterine rupture. Figures are numbers (percentages) unless stated otherwise

Characteristics	**Uterine rupture led to perinatal death (n=17)**	**Uterine rupture did not lead to perinatal death (n=107)**	**Relative risk (95% CI)**	**P value***	**†Adjusted odds ratio (95% CI)**	**P value†**
<3000 births a year	13 (76.5)	50 (46.7)	3.1 (1.1 to 9.1)	0.03	3.9‡ (1.2 to 12.8)	0.03
No previous vaginal birth	15 (88.2)	87 (81.3)	1.6 (0.4 to 6.6)	0.73	1.7 (0.4 to 8.3)	0.79
Induction of labour with prostaglandin†	5 (29.4)	34 (31.8)	0.9 (0.3 to 2.4)	>0.9	0.8 (0.2 to 2.6)	0.85

*Fisher's exact test.
†From exact logistic regression.
‡Univariate odds ratio=3.7. Higher value of adjusted odds ratios compared with relative risk is due to relatively high incidence of event in group.

What is already known on this topic

Attempting vaginal birth after previous caesarean section (VBAC) carried the risk of uterine rupture, which may result in perinatal death

No studies to date have examined the factors associated with perinatal death due to uterine rupture during attempted VBAC

No studies to date have examined the organisation of health care and the risk of perinatal death due to uterine rupture during attempted VBAC

What this study adds

For women attempting VBAC, no previous vaginal birth and induction of labour with prostaglandin were associated with uterine rupture resulting in perinatal death

The risk of perinatal death due to uterine rupture was greater in hospitals with lower annual numbers of deliveries

perinatal death in the event of uterine rupture. The same is probably true of other obstetric emergencies. Perinatal deaths could, therefore, potentially be reduced by confining high risk births to large obstetric units or by providing additional facilities at smaller units.

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Predicting Cesarean Section and Uterine Rupture among Women Attempting Vaginal Birth after Prior Cesarean Section

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Abbreviations: ALLR, adjusted log likelihood ratio; CI, confidence interval; ICD, International classification of disease; IQR, interquartile range; OR, odds ratio; ROC, receiver operating characteristic; SMR2, Scottish Morbidity Record

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ABSTRACT

Background

There is currently no validated method for antepartum prediction of the risk of failed vaginal birth after cesarean section and no information on the relationship between the risk of emergency cesarean delivery and the risk of uterine rupture.

Methods and Findings

We linked a national maternity hospital discharge database and a national registry of perinatal deaths. We studied 23,286 women with one prior cesarean delivery who attempted vaginal birth at or after 40-wk gestation. The population was randomly split into model development and validation groups. The factors associated with emergency cesarean section were maternal age (adjusted odds ratio [OR] = 1.22 per 5-y increase, 95% confidence interval [CI]: 1.16 to 1.28), maternal height (adjusted OR = 0.75 per 5-cm increase, 95% CI: 0.73 to 0.78), male fetus (adjusted OR = 1.18, 95% CI: 1.08 to 1.29), no previous vaginal birth (adjusted OR = 5.08, 95% CI: 4.52 to 5.72), prostaglandin induction of labor (adjusted OR = 1.42, 95% CI: 1.26 to 1.60), and birth at 41-wk (adjusted OR = 1.30, 95% CI: 1.18 to 1.42) or 42-wk (adjusted OR = 1.38, 95% CI: 1.17 to 1.62) gestation compared with 40-wk. In the validation group, 36% of the women had a low predicted risk of caesarean section (<20%) and 16.5% of women had a high predicted risk (>40%); 10.9% and 47.7% of these women, respectively, actually had deliveries by caesarean section. The predicted risk of caesarean section was also associated with the risk of all uterine rupture (OR for a 5% increase in predicted risk = 1.22, 95% CI: 1.14 to 1.31) and uterine rupture associated with perinatal death (OR for a 5% increase in predicted risk = 1.32, 95% CI: 1.02 to 1.73). The observed incidence of uterine rupture was 2.0 per 1,000 among women at low risk of cesarean section and 9.1 per 1,000 among those at high risk (relative risk = 4.5, 95% CI: 2.6 to 8.1). We present the model in a simple-to-use format.

Conclusions

We present, to our knowledge, the first validated model for antepartum prediction of the risk of failed vaginal birth after prior cesarean section. Women at increased risk of emergency caesarean section are also at increased risk of uterine rupture, including catastrophic rupture leading to perinatal death.

Introduction

Encouraging women with a prior cesarean delivery to attempt vaginal birth in subsequent pregnancies is a strategy that has been employed to address rising rates of cesarean delivery. However, a series of retrospective studies published in the last five to ten years have indicated an increased risk of serious adverse outcomes among women who attempted vaginal birth compared with those who had a planned repeat cesarean delivery [1–3]. A recent large-scale prospective study has shown that among women with a prior cesarean delivery, the rates of maternal complications are highest among women who attempt vaginal birth and fail (14.1%), intermediate among women who have a planned cesarean delivery (3.6%), and lowest among women who attempt vaginal birth and succeed (2.4%) [4]. Therefore, the balance of risks and benefits of trial of labor versus planned repeat cesarean section itself depends on the risk of emergency cesarean section should labor be attempted.

Many studies have addressed methods for identifying women at low and high risk of failure of an attempted vaginal birth after a prior cesarean. A recent systematic review reported that only two of the six available tools had been validated [5]. Both of these incorporated data that would only be available when a women presented in labor, such as the results of electronic fetal monitoring and cervical dilatation on admission [6,7]. Currently, therefore, there is no validated antepartum tool to predict the risk of a failed attempt at vaginal birth among women with a prior cesarean delivery. Moreover, there are no data on whether women at increased risk of cesarean section are also at increased risk of uterine rupture. We sought to develop a simple, validated model to predict the risk of emergency cesarean section among women attempting vaginal birth and to determine whether women at increased risk of cesarean section were also at increased risk of uterine rupture, including catastrophic rupture leading to death of the infant.

Methods

Population

The Scottish Morbidity Record (SMR2) collects information on clinical and demographic characteristics and outcomes for all patients discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been more than 99% complete since the late 1970s [8]. A quality assurance analysis compared 1,414 records in 1996–1997 with the clinical notes. This analysis demonstrated that the register was free from significant errors in more than 98% of records in all the specific fields used in the present analysis, with the exception of postcode (94.0%), height (96.2%), estimated gestation (94.4%), and method of induction of labor (93.6%). The previous cesarean section field was 99.7% accurate. International classification of disease (ICD) diagnostic codes were found to be 80%–90% accurate for the first four diagnoses and 70%–80% accurate for the remainder [9]. SMR2 records were linked to records from the Scottish Stillbirth and Neonatal Death Enquiry. This national register has routinely classified all perinatal deaths in Scotland since 1983. It is virtually 100% complete and has been described in detail elsewhere [10]. The predictors of cesarean section employed in the current study were those that were recorded in the SMR2 and which had been identified in previous studies as possible risk factors for emergency cesarean delivery.

Study Group

The population was drawn from all term singleton births to women with one prior cesarean section in Scotland between 1985 and 2001, inclusive. The exclusion criteria for the study group were preterm birth, perinatal deaths due to congenital anomaly, antepartum stillbirth due to any cause, deliveries by planned cesarean section, and women documented as being primigravid despite also being documented as having had a prior cesarean delivery. The primary analysis was confined to women who delivered at or after 40-wk gestation.

Definitions

Emergency cesarean section was defined as any non-planned cesarean delivery. Maternal age was defined as the age of the mother at the time of birth. Maternal height was measured in centimeters, and the value used was that documented in each woman's clinical record. Gestational age at birth was defined as completed wk of gestation on the basis of the estimated date of delivery in each woman's clinical record. Gestational age has been confirmed by ultrasound in the first half of pregnancy in more than 95% of women in the United Kingdom since the early 1990s [11]. Hospital throughput was defined as the total number of births recorded in the SMR2 database for the given hospital over the given year and was categorized into above or below the national median (3,000 births).[9]

Perinatal deaths were classified on the basis of data from the Scottish Stillbirth and Neonatal Death Enquiry [10]. Death caused by congenital anomaly was defined as any structural or genetic defect incompatible with life or potentially treatable but causing death. The registry subclassifies stillbirths into antepartum (deaths before the onset of labor) and intrapartum (deaths during labor). A death was taken to be due to intrapartum uterine rupture if it was an intrapartum stillbirth or neonatal death, when the cause of death was documented as intrapartum anoxia, when the obstetric cause of death was coded as "mechanical" under the modified Wigglesworth classification [12], and when the ICD9 code for intrapartum uterine rupture (665.1) was listed as a specific diagnosis. Intrapartum uterine ruptures not resulting in perinatal death were identified using ICD9 and ICD10 diagnostic codes 665.1 and O711, respectively, from the diagnostic fields in the SMR2 record related to hospital discharge following delivery.

Statistical Analyses

Continuous variables were summarized by the median and interquartile range (IQR), and comparisons between groups were performed using the Mann-Whitney U test. Univariate comparisons of categorical data were performed using Fisher's exact test. The p values for all hypothesis tests were two-sided. The risk of adverse outcomes was modeled using multivariate logistic regression [11]. First order interactions were assessed using the likelihood ratio test and significance assumed at $p < 0.05$ after correction for the number of comparisons using the Bonferroni method. The goodness of fit of logistic regression models was assessed using the Hosmer and Lemeshow test. Assessment of linearity of age

and height in logistic models was performed using fractional polynomials. Cases with extreme values of age or height (≤0.1 percentile and ≥99.9 percentile) were excluded. Out-of-sample validation of the model was performed by dividing the cohort into model development and model validation groups. Models were constructed for the development group and the predicted numbers of cesarean sections were related to the observed number of events in the validation group when categorized into deciles of predicted probability. Selection of model development and validation groups was initially random and the process was then repeated selecting the groups on specific characteristics (hospital throughput, deprivation category and year of delivery). Random allocation into two groups was performed using a pseudo-random number. The predictive ability of models was assessed by the area under the receiver operating characteristic (ROC) curve, and curves were compared using the algorithm described by De Long et al [12]. The final logistic regression model fitted to the entire cohort was expressed as adjusted log likelihood ratios (ALLRs) using a modification of our recently described method [13] (see Supporting Information for details). Logistic regression analysis of the risk of perinatal death was performed using exact logistic regression due to the rarity of the event. All statistical analyses were performed using the Stata software package version 8.2 (Stata Corporation, College Station, Texas, United States), except exact logistic regression which was performed using LogExact version 5.0.1 (Cytel Software Corporation, Cambridge, Massachusetts, United States).

Results

Between 1985 and 2001, 68,380 women delivered who had one prior cesarean delivery. We excluded 150 (0.2%) births outside the range 24 to 43 wk, 4,700 (6.9%) preterm births, 366 (0.5%) antepartum stillbirths, 21,677 (31.7%) women delivered by planned cesarean section, 124 (0.2%) women whose infant was a perinatal death attributed to a congenital abnormality, and 76 (0.1%) women documented as being primigravid. A total of 25,836 (37.8%) women had one or more of these exclusions, leaving 42,544 (62.2%) women. Among the 25,964 (61.0%) women who delivered at or after 40-wk gestation, 2,585 (10.0%) had a missing value for height, one (<0.1%) had a missing value for age, 51 (0.2%) had an extreme value of height, and 41 (0.2%) had an extreme value of maternal age, leaving 23,286 women eligible for study. These women were randomly allocated to a model development or model validation group, and the demographics and basic outcome data for the cohort were tabulated (Table 1). Women who had previously had a vaginal birth were older than those with no previous vaginal birth (median IQR: 30 [27–34] versus 29 [25–32], respectively, $p < 0.001$).

In univariate and multivariate analysis in the model development group, all factors were significantly associated with the risk of emergency cesarean section except induction of labor using a means other than prostaglandin (Table 2). The area under the ROC curve in the development group was 0.706, which was significantly greater than for any of the individual predictors (all $p < 0.001$). There were no statistically significant first order interactions between the predictors. When the model was applied to the validation group, the area under the ROC curve was 0.708 (Table 3). The observed proportion of emergency cesarean deliveries and the proportion predicted by the multivariate model derived from the model development group were similar (Figure 1A). In the validation group, 36% of the women had a low predicted risk of caesarean section (<20%) and 16.5% of women had a high predicted risk (>40%); 10.9% and 47.7% of these women, respectively, actually had deliveries by caesarean section.

Table 1. Characteristics of Population by Allocation to Development or Validation Group

Characteristic	Development ($n = 11,643$)	Validation ($n = 11,643$)
Age, y (median IQR)	29 (26–32)	29 (26–32)
Height, cm (median IQR)	161 (157–165)	161 (157–165)
Previous vaginal birth	3,923 (33.7)	3,847 (33.0)
Year of delivery ≥1992	5,765 (49.5)	5,850 (50.2)
Gestation at delivery, wk		
40	6,619 (56.8)	6,543 (56.2)
41	4,076 (35.0)	4,094 (35.2)
42	948 (8.1)	1,006 (8.6)
Method of induction		
None	8,262 (71.0)	8,260 (71.0)
Non-prostaglandin	1,577 (13.5)	1,576 (13.5)
Prostaglandin	1,804 (15.5)	1,807 (15.5)
Male sex of infant	5,810 (49.9)	5,882 (50.5)
Birth weight, kg (median IQR)	3.58 (3.27–3.88)	3.58 (3.26–3.90)
Emergency cesarean	3,067 (26.4)	2,986 (25.6)
Uterine rupture	58 (0.5)	43 (0.4)
Uterine rupture leading to perinatal death	5 (0.04)	3 (0.03)

All data *n* (%) unless stated otherwise.

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The process of model development and validation was then repeated with nonrandom selection of the development and validation samples. Three nonrandom procedures for selection were evaluated, namely, hospital throughput (<3,000 births per year and ≥3,000 births per year), deprivation category (Carstairs category <5 and Carstairs category ≥5), and year of birth (1985–1992 and 1993–2001). The area under the ROC curve was similar when the development and validation samples were compared, (Table 3) and when the data were plotted according to the predicted risk, the expected and observed number of cesarean deliveries were similar in the validation samples (Figure 1B–1D).

A logistic regression model was then fitted for the whole cohort. The area under the ROC curve was 0.707 and the global goodness-of-fit test showed no evidence of poor fit ($p = 0.95$). The output was converted to ALLRs (Table 4) using a modification of our previously described method [13]. The calculation of a summary ALLR for a series of maternal characteristics is illustrated in the box. The summary ALLR could also be used in combination with a published nomogram to generate a predicted probability [14]. Assuming a prior probability of emergency cesarean delivery of 26%, a summary ALLR of 0.71 or less was associated with a less than 20% chance of emergency cesarean section, and a summary ALLR of 1.91 or more was associated with a greater than 40% chance of emergency cesarean section.

The probability of cesarean section was calculated for each woman in the cohort using the multivariate model. We then analyzed the risk of uterine rupture in relation to the

Table 2. Univariate and Multivariate Analysis of Predictors of Emergency Cesarean Section in the Model Development Group ($n = 11,643$)

Maternal Characteristic	Category	Univariate Analysis			Multivariate Analysis	
		OR (95% CI)	*p*-Value	Area under ROC Curve	OR (95% CI)	*p*-Value
Maternal age	Per 5-y increase	1.05 (1.01–1.10)	0.03	0.52	1.22 (1.16–1.28)	<0.001
Maternal height	Per 5-cm increase	0.79 (0.77–0.82)	<0.001	0.58	0.75 (0.73–0.78)	<0.001
Sex of infant	Female[a]	(1.0)	—		(1.0)	—
	Male	1.18 (1.08–1.28)	<0.001	0.52	1.18 (1.08–1.29)	<0.001
Previous vaginal birth	Yes[a]	(1.0)	—		(1.0)	—
	No	4.58 (4.08–5.13)	<0.001	0.64	5.08 (4.52–5.72)	<0.001
Method of induction of labor	None[a]	(1.0)	—		(1.0)	—
	Non-prostaglandin	1.01 (0.89–1.14)	0.87		1.00 (0.88–1.15)	0.95
	Prostaglandin	1.49 (1.34–1.67)	<0.001	0.54	1.42 (1.26–1.60)	<0.001
Gestational age (wk)	40[a]	(1.0)	—		(1.0)	—
	41	1.33 (1.21–1.45)	<0.001		1.30 (1.18–1.42)	<0.001
	42	1.46 (1.26–1.69)	<0.001	0.54	1.38 (1.17–1.62)	<0.001

Age and height were linear in both univariate and multivariate analysis (assessed by fractional polynomials).
Global goodness-of-fit test for multivariate model: $p = 0.79$.
[a]Referent category.
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predicted risk of emergency cesarean section. The predicted probability of cesarean section was also associated with the risk of all uterine rupture (Figure 2; odds ratio for a 5% increase in predicted risk = 1.22, 95% confidence interval [CI]: 1.14 to 1.31) and uterine rupture associated with perinatal death (odds ratio for a 5% increase in predicted risk = 1.32, 95% CI: 1.02 to 1.73). Among women with a predicted cesarean section risk of less than 20%, the incidence of uterine rupture was 2.0 (95% CI: 1.1 to 3.2) per 1,000, and among women with a cesarean section risk of greater than 40%, the incidence of uterine rupture was 9.1 (95% CI: 6.4 to 12.6) per 1,000, relative risk 4.5, (95% CI: 2.6 to 8.1).

The population studied had excluded women who delivered at 37- to 39-wk gestation. A model (excluding week of gestation) was fitted for women delivering between 40- and 42-wk and was evaluated among women delivered at 37- to 39-wk gestation in whom the documented duration of labor was greater than or equal to 4 h but otherwise applying the same inclusion and exclusion criteria as the main study cohort. The area under the ROC curve was 0.692. Among the 10,147 eligible women who delivered at 37 to 39 wk, there were 1,826 cesarean deliveries (18.0% compared with 26.0% in the rest of the population), giving a pretest odds of 0.22. When the probability of cesarean section was estimated using a prior odds of 0.22 and the ALLRs listed in Table 4 (excluding week of gestation), the observed and expected number of cesarean deliveries were similar (Figure 3).

Discussion

Women who have had a prior cesarean delivery need to choose whether to have a planned repeat cesarean section or to attempt vaginal birth in subsequent pregnancies. The risk of maternal morbidity depends on whether the attempt at vaginal birth is successful [1,4]. An informed discussion of this decision requires an assessment of the risk of emergency cesarean section. However, there is, at present, no validated method that allows antepartum assessment of the risks of emergency cesarean section [5], and counseling of women is, at best, semiquantitative. In the present study we provide a

Table 3. Assessment of the Modeling Approach in Development and Validation Samples

Characteristic	Development Sample			Validation Sample		
	Group	*n*	Area under ROC Curve (95% CI)	Group	*n*	Area under ROC Curve (95% CI)
Random allocation[a]	1 (arbitrary)	11,643	0.706 (0.695–0.716)	2 (arbitrary)	11,643	0.708 (0.698–0.718)
Hospital throughput[a]	<3,000 births/year	11,807	0.705 (0.694–0.715	≥3,000 births/year	11,479	0.709 (0.699–0.719)
Socio-economic deprivation[a]	Carstairs score <5	14,868	0.702 (0.693–0.711)	Carstairs score ≥5	8,418	0.715 (0.703–0.727)
Year of delivery[a]	1985–1992	11,615	0.710 (0.700–0.720)	1993–2001	11,671	0.701 (0.691–0.711)
Week of gestation[b]	≥40 wk	23,286	0.704 (0.697–0.711)	<40 wk	10,149	0.692 (0.679–0.705)

All models used the same covariates listed in Table 2 except the model used where comparison was on the basis of week of gestation: gestational age was not included as a covariate in that model.
[a]In the first four models, comparisons are within the group who delivered at ≥40 wk.
[b]The whole population who delivered at ≥40 wk was used to develop the model which was validated among women delivering between 37–39 wk who had a documented duration of labor ≥4 h.
The number of events in each of the development samples was 3,067, 2,999, 3,870, 2,768, and 6,053 (from the top to the bottom row, respectively). The number of events in each of the validation samples was 2,986, 3,054, 2,183, 3,285, and 1,826 (from the top to the bottom row, respectively).
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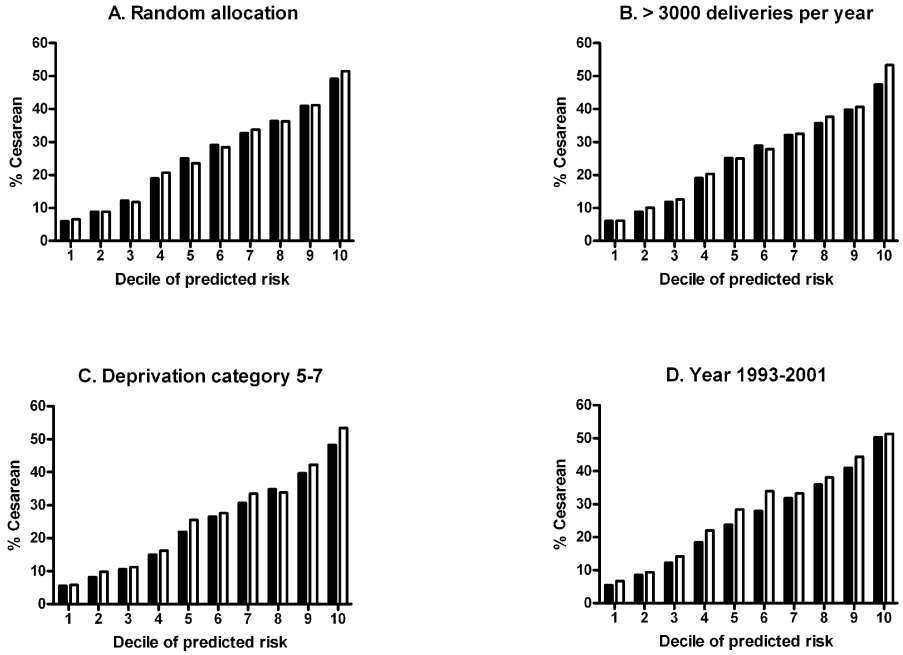

Figure 1. Observed and Expected Proportion of Cesarean Deliveries in the Model Validation Group by Decile of Predicted Probability

The white bars indicate the observed proportion and the black bars indicate the expected proportion of cesarean deliveries, based on estimates derived from logistic regression model fitted to the development group. Different graphs represent different procedures for selecting development and validation groups: (A) random selection, (B) selected on hospital throughput, (C) selected on deprivation category (Carstairs score), and (D) selected on year of delivery. Area under the ROC curve for each model is listed in Table 3.

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validated model that classifies over half this population as being at low or high risk of emergency cesarean section, on the basis of thresholds suggested by a previous systematic review [5]. When the model was validated, 36% of women had a predicted risk of cesarean section of less than 20%, and their overall cesarean section rate was 10.9%. Conversely, 16.5% of women had a predicted risk of cesarean section of greater than 40%, and their overall cesarean section rate was 47.7%.

One of the other principal concerns among women who have had a prior cesarean section is the risk of intrapartum uterine rupture. Uterine rupture is associated with an increased risk of severe maternal complications, such as hysterectomy and hemorrhage [1,4] and with an increased risk of severe effects on the infant, including hypoxic ischemic encephalopathy[4] and perinatal death [9]. Even if a woman had a low risk of emergency cesarean section, she may choose to have a planned repeat cesarean section due to concerns about the possibility of uterine rupture. However, we found that women who were at low risk of emergency cesarean section were also at low risk of uterine rupture, including catastrophic rupture leading to perinatal death. Among women with a predicted cesarean section risk of less than 20%, the incidence of uterine rupture was 2.0 per 1,000, whereas among women with a cesarean section risk of greater than 40%, the incidence of uterine rupture was 9.1 per 1,000. This is the first study, to our knowledge, to demonstrate a direct association between the risk of a failed attempt at vaginal birth and the risk of uterine rupture. This cannot be explained by ascertainment bias because the association was still apparent when the analysis was confined to catastrophic uterine rupture leading to death of the infant, which would be ascertained irrespective of the mode of delivery.

In order for this model to be clinically useful, it needs to be presented in a way that practicing clinicians can understand and apply. To this end, we have employed a method for converting the logistic regression model into ALLRs. These can be used like conventional likelihood ratios and an example is given in the box. The prior odds are multiplied by the appropriate ALLRs to give the posterior odds from which the probability of cesarean section can be derived. Because this method is very similar to that used for Down syndrome screening, we feel that it is likely to be generally understood by practicing clinicians. A previous method has been described in detail to convert logistic regression models into a Bayesian format [15]. This method provides identical results to our method for simple models. However, for models with categorical variables containing three or more groups or in which the scaling of a continuous variable changes between the univariate and multivariate analysis, the previously described method does not generate identical estimates of probability. Our method always generates estimates of probability that are identical to the logistic regression model. It can be thought of, therefore, as a simple format for the presentation of logistic regression models.

The present study has a number of strengths over previous studies. First, we had a population of over 23,000 women. The largest previous study included approximately 5,000 women [6]. Second, we were able to ascertain uterine rupture in our population, including uterine rupture leading to perinatal death. Studies using registry-based data have the profound weakness that uterine rupture may be inconsistently defined

Table 4. ALLRs for Maternal Characteristics and Fetal Sex Derived from Logistic Regression Model Fitted for the Whole Population

Category	Value	ALLR	Category	Value	ALLR
Height (cm)	143	2.68	Age (y)	18	0.62
	144	2.54		19	0.65
	145	2.40		20	0.68
	146	2.27		21	0.71
	147	2.15		22	0.74
	148	2.04		23	0.77
	149	1.93		24	0.81
	150	1.82		25	0.84
	151	1.72		26	0.88
	152	1.63		27	0.92
	153	1.54		28	0.96
	154	1.46		29	1.00
	155	1.38		30	1.04
	156	1.31		31	1.09
	157	1.24		32	1.13
	158	1.17		33	1.18
	159	1.11		34	1.23
	160	1.05		35	1.29
	161	0.99		36	1.34
	162	0.94		37	1.40
	163	0.89		38	1.46
	164	0.84		39	1.53
	165	0.80		40	1.59
	166	0.75		41	1.66
	167	0.71		42	1.74
	168	0.67		43	1.81
	169	0.64	Previous vaginal birth	Yes	0.30
	170	0.60		No	1.51
	171	0.57	Gestation (wk)	40	0.88
	172	0.54		41	1.13
	173	0.51		42	1.26
	174	0.48	Method of induction	None	0.93
	175	0.46		Non-prostaglandin	0.99
	176	0.43		Prostaglandin	1.37
	177	0.41	Sex of infant	Female	0.91
	178	0.39		Male	1.10
	179	0.37			
	180	0.35			
	181	0.33			
	182	0.31			

Derived from the following logistic regression model: log odds (cesarean) = 5.091 + (0.043 × age) + (−0.055 × height) + (0.193 × male) + (1.633 × no previous vaginal birth) + (0.067 × non-prostaglandin induction) + (0.393 × prostaglandin induction) + (0.248 × delivered at 41 wk) + (0.355 × delivered at 42 wk), where age is expressed in years and height is expressed in centimeters and all other variables are yes = 1 and no = 0.

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and include cases of avascular wound dehiscence detected at the time of cesarean delivery [2]. This study design could lead to ascertainment bias because women having cesarean delivery would be more likely to have avascular wound dehiscence identified. However, our data sources allowed us

Box 1.

Sample Calculation. Background risk of cesarean section = 26%. Convert into odds if prior odds of cesarean section = 26/74 = 0.35.

Example. A 37-y-old woman, 160 cm tall, with no previous vaginal birth, and with a male infant wishes to know probability of cesarean section if she requires induction of labor at 41 wk gestation using prostaglandin.

Summary. ALLR = 1.40 × 1.05 × 1.51 × 1.10 × 1.13 × 1.37 = 3.78. Posterior odds = 0.35 × 3.78 = 1.32. Chance of cesarean delivery = 1.32/(1 + 1.32) = 0.57 or 57%. (This is identical to the estimated risk using the logistic regression equation in the footnote of Table 4).

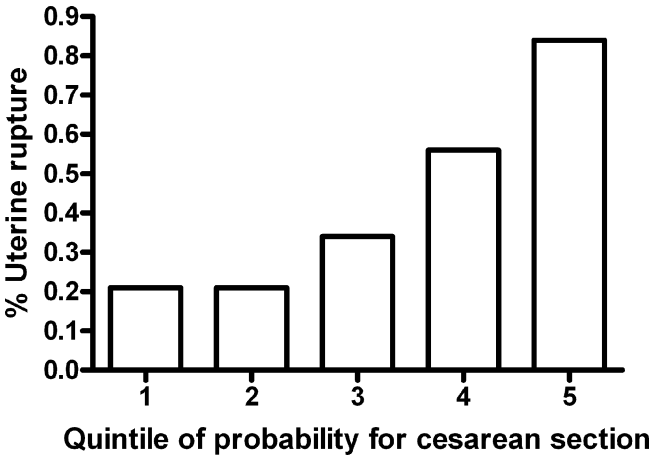

Figure 2. Proportion of Uterine Ruptures in Relation to the Quintile of Predicted Probability of Emergency Cesarean Delivery for the Whole Population

$n = 23,286$; $p < 0.001$ (Chi square test for trend).

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to identify uterine ruptures that led to death of the infant. Third, because of the large numbers, we could confine the analysis to women delivered at or after 40-wk gestation. Large-scale registries lack details such as whether an attempt at vaginal birth was planned. Planned cesarean sections are typically performed at 38–39 wk in the United Kingdom [16]. By confining the analysis to births at or after 40 wk, we could exclude women who were not truly attempting vaginal birth. Fourth, the risk of cesarean section could be estimated using information available in the antepartum period. Counseling of women regarding vaginal birth frequently involves the distinction between attempting vaginal birth if the onset of labor is spontaneous but not attempting it if labor needs to be induced, particularly if prostaglandins are used to ripen the cervix [17]. For this reason, we included week of delivery and method of induction of labor in the model, and, therefore, the current model can inform such decisions. Excluding gestation and mode of induction had very little practical effect on the predictive ability of the model (data not shown). Fifth, we analyzed continuous variables continuously rather than categorizing them, which increases statistical power. This analysis may explain why we observed a positive association between maternal age and risk of cesarean section, whereas some other studies have not [7]. Interestingly, the association with age became much stronger in multivariate analysis. This result may reflect negative confounding by previous vaginal birth. This factor was strongly protective against cesarean delivery, and these women were significantly older than other women.

The present study has some weaknesses. First, the data were obtained from Scotland and there may be concerns in applying this model to other populations. However, we assessed the robustness of the predictors employed by selecting records for the development and validation groups on the basis of factors that might reflect variation in other populations. We found the model was similarly predictive in and out of sample when these categorizations were performed by hospital throughput, socio-economic deprivation category, and year of birth. This finding suggests that the

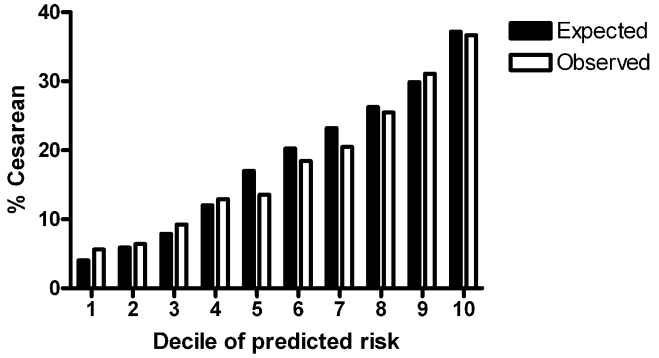

Figure 3. Use of ALLRs to Predict Probability of Cesarean Section among Women Delivered 37 to 39 wk with a Documented Duration of Labor of Greater than or Equal to 4 h

Probability estimated using likelihood ratios in Table 4 (excluding gestational age) and the prior odds of 0.22 (equivalent to background risk of cesarean section in this group).

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maternal and obstetric characteristics used in the model are likely to be robust even when applied to populations with different obstetric practices. Second, we lacked data on other factors that might be predictive of the risk of emergency cesarean delivery, such as body mass index, the indication for the previous cesarean section, and whether a previous vaginal birth preceded or followed the previous cesarean section. Nevertheless, we report the first validated model to give useful discrimination of risk to greater than 50% of the population [5].

A further potential weakness with the model is that it was derived from women delivering at or after 40-wk gestation. As discussed above, we confined the primary analysis to this group in order to identify women who were truly attempting vaginal birth. Some women who were scheduled for planned cesarean section will have attended prior to this date in labor. Such women would be documented as an intrapartum emergency cesarean section but did not truly attempt vaginal delivery. However, we needed to assess the validity of the model for women who deliver at earlier week of gestation at term. Another means to identify women who were truly attempting vaginal birth is to confine analysis to those with a documented duration of labor of at least 4 h. We evaluated the model in women who were delivered between 37 and 39 wk who had labor for 4 h or longer. The discriminative power of the model was comparable, with an area under the ROC curve of 0.692. These women had a lower prior risk of cesarean section (18%) than women at or after 40-wk gestation (26%). When ALLRs were employed and the lower overall rate of cesarean delivery was accounted for by using the prior odds of 0.22, the observed and expected numbers of cesarean deliveries were similar (Figure 3). We conclude that the ALLR-based model is appropriate for births between 37–39 wk if lower prior odds of cesarean delivery are employed. Moreover, this analysis highlights one advantage of an ALLR-based approach, namely, that it is simple to adjust the estimate of probability for a lower or higher prior odds of the outcome.

In conclusion, we present a simple, validated model for clinical estimation of the risk of emergency cesarean section among women with a prior cesarean delivery attempting vaginal birth. Women at high risk of cesarean delivery are also at increased risk of uterine rupture, including catastrophic rupture leading to perinatal death.

Supporting Information

The full logistic regression model for calculating ALLRs is

$$\log(odds|x_1, x_2, \ldots x_n) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n \quad (1)$$

where x_1, x_2,. . ., x_n are the predictor variables, β_1, β_2,. . ., β_n are their regression coefficients, and α is the constant. Let the fitted values of α, β_1, β_2,. . ., β_n be $\hat{\alpha}, \hat{\beta}_1, \hat{\beta}_2, \ldots \hat{\beta}_n$.

The log likelihood ratio for x_1, for example, may be defined as the log odds of the outcome conditional on x_1, x_2,. . ., x_n minus the log odds of the outcome conditional on x_2,. . ., x_n. The latter odds cannot in general be derived from equation 1 because the effects of the omitted x_1 are partly picked up by x_2,. . ., x_n: the true likelihood ratio for x_1 therefore depends on the values of x_2,. . ., x_n. We have created ALLRs that do not depend on the values of x_2,. . ., x_n.

To create the ALLRs, we force the coefficients in the second model to be the same as those estimated in the first model, but allowing a different intercept:

$$\log(odds|x_2, \ldots x_n) = \alpha_1^* + \hat{\beta}_2 x_2 + \ldots + \hat{\beta}_n x_n \quad (2)$$

In this model, only the parameter α_1^* is to be estimated; the other parameters take their fitted values from equation 1. We can then calculate the ALLR for x_1 as

$$ALLR_1 = \hat{\alpha} + \hat{\beta}_1 x_1 - \hat{\alpha}_1^*. \quad (3)$$

This procedure is repeated for each variable $x_2, \ldots, x_n$ to calculate $ALLR_2, \ldots, ALLR_n$

A small correction factor must be added to the ALLRs in order to ensure that the sum of the overall log odds and all the ALLRs is exactly equal to the log odds computed from equation 1. The appropriate correction factor is $c_i d$, where $d = \hat{\alpha} - \hat{\alpha}_0 + \sum_i (\hat{\alpha}_i^* - \hat{\alpha})$, $\hat{\alpha}_0$ is the overall log odds, and $\sum_i c_i = 1$. In this paper, $d = -0.021$ and all correction factors were smaller than 0.01 in magnitude. To ensure that values of each $ALLR_i$ straddle 1, c_i is calculated as $m_i/(m_1 + \ldots + m_n)$ where m_i is the sample minimum or maximum (depending on whether d is positive or negative) of $ALLR_i$.

At the end of this procedure, the sum of the overall log odds and all the ALLRs exactly equals the log odds computed from equation 1. Our procedure is therefore nothing more than a restatement of the results of the logistic regression in an easily interpretable format.

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Papers

Birth order, gestational age, and risk of delivery related perinatal death in twins: retrospective cohort study

Gordon C S Smith, Jill P Pell, Richard Dobbie

Abstract

Objective To determine whether twins born second are at increased risk of perinatal death because of complications during labour and delivery.
Design Retrospective cohort study.
Setting Scotland, 1992 and 1997.
Participants All twin births at or after 24 weeks' gestation, excluding twin pairs in which either twin died before labour or delivery or died during or after labour and delivery because of congenital abnormality, non-immune hydrops, or twin to twin transfusion syndrome.
Main outcome measure Delivery related perinatal deaths (deaths during labour or the neonatal period).
Results Overall, delivery related perinatal deaths were recorded for 23 first twins only and 23 second twins only of 1438 twin pairs born before 36 weeks (preterm) by means other than planned caesarean section ($P > 0.99$). No deaths of first twins and nine deaths of second twins (P=0.004) were recorded among the 2436 twin pairs born at or after 36 weeks (term). Discordance between first and second twins differed significantly in preterm and term births (P=0.007). Seven of nine deaths of second twins at term were due to anoxia during the birth (2.9 (95% confidence interval 1.2 to 5.9) per 1000); five of these deaths were associated with mechanical problems with the second delivery following vaginal delivery of the first twin. No deaths were recorded among 454 second twins delivered at term by planned caesarean section.
Conclusions Second twins born at term are at higher risk than first twins of death due to complications of delivery. Previous studies may not have shown an increased risk because of inadequate categorisation of deaths, lack of statistical power, inappropriate analyses, and pooling of data about preterm births and term births.

Introduction

Obstetricians recognise that second twins are vulnerable to complications during labour and delivery.[1] It is not clear, however, whether this is reflected in increased rates of perinatal mortality. Analysis of observational studies in the 1960s seemed to show that second twins were at higher risk of perinatal death than first twins.[2] These findings were subsequently refuted by a number of large scale studies that failed to show a higher risk[3–6] or that showed only a very slightly higher risk.[7] Previous large scale studies have generally lacked detailed information on the cause and timing of perinatal death. Consequently, differences in outcomes related to complications during delivery of the second twin may have been masked by other causes of death, such as prematurity, congenital abnormality, and antepartum events. We conducted a large scale, retrospective cohort study of delivery related perinatal deaths in twin pregnancies by linking a national register of data on discharges after childbirth to a national register of perinatal deaths.

Methods

Population

The Scottish morbidity record collects information on clinical and demographic characteristics and outcomes for all patients admitted to Scottish maternity hospitals. The register is subject to regular quality assurance checks, and data are available for more than 99% of registered births.[8] We used the register to identify all births between 1992 and 1997 and linked these records to records from the Scottish Stillbirth and Infant Death Enquiry, which has routinely classified all perinatal deaths in Scotland since 1983. It is virtually 100% complete and has been described in detail elsewhere.[9 10] The study used publicly collected data collected by NHS Scotland without identifiers and its use, therefore, did not require ethical approval.

Classification of perinatal deaths

Stillbirths were defined as babies born at or after 24 weeks' gestation who showed no signs of life after delivery. Stillbirths were subdivided into antepartum deaths (before the onset of labour) and intrapartum deaths (during labour). Neonatal death was defined as death during the first four weeks of life in a liveborn baby. The Scottish Stillbirth and Infant Death Enquiry's register documents the cause of death in two fields. Firstly, all deaths are classified according to a modified version of the Wigglesworth hierarchical system, which lists obstetric and paediatric causes[11]; the specific categories are described in detail elsewhere.[10] Secondly, each record has up to three obstetric and three paediatric ICD-9 (International Classification of Diseases, ninth revision) codes.

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We excluded all deaths that were due to congenital abnormality (Scottish Stillbirth and Infant Death Enquiry classifications 1-7), non-immune hydrops (ICD-9 code 778.0), and twin to twin transfusion syndrome (ICD-9 code 762.3). We defined delivery related perinatal death as intrapartum stillbirth or neonatal death not caused by congenital anomaly, hydrops, or twin to twin transfusion syndrome. The cause of death was subdivided into three paediatric categories: intrapartum anoxia, pulmonary causes, and all other paediatric causes. Within the category of intrapartum anoxia, we used the obstetric classification to identify deaths for which there was a direct obstetric mechanical cause, such as uterine rupture, malpresentation, cord compression (including prolapse), birth trauma, or anoxia associated with disproportion.

Definitions

Socioeconomic deprivation, smoking, parity, maternal age, and gestational age were defined as described previously.[12] Term was defined as ⩾36 weeks' gestation for twin pregnancies.[6]

Statistical analyses

Continuous variables were summarised by the median and the interquartile range. Paired continuous data were compared by using the Wilcoxon signed rank test, and unpaired continuous data were compared by using the Mann-Whitney U test. Discordance in birth weight was described by the absolute difference, expressed as a percentage of the weight of the larger twin. Univariate comparisons of unpaired dichotomous data were performed using Fisher's exact test, χ^2 test, and χ^2 test for trend, as appropriate, and multivariate comparison was made using logistic regression. Univariate comparison of dichotomous outcomes in first and second twins was performed using the McNemar test, and multivariate comparison was performed by using conditional logistic regression. Socioeconomic deprivation, smoking, parity, height, and maternal age were categorised as in table 1 and were entered into the logistic regression model as a series of dummy variables. In each case the referent category is identified in the table. The P values for all hypothesis tests were two sided. The 95% confidence intervals for risk of death were calculated using the binomial distribution. All statistical analyses were performed using version 7.0 of the Stata software package.

Results

Between 1992 and 1997, 4707 women delivered twins in Scotland. Gestational age was missing in the records for two of these women (<0.1%). Of the remaining women, 4690 (99.7%) gave birth at or after 24 weeks' gestation. Records were excluded when one or both twins died from antepartum stillbirth (n=117), congenital abnormality (n=26), twin to twin transfusion syndrome (n=19), or non-immune hydrops (n=6). As some overlap existed between these groups, a total of 145 (3.1%) pregnancies were excluded. Among the

Table 1 Maternal characteristics in relation to preterm birth among 3874 women with twin pregnancies delivered by a means other than planned caesarean section. Values are numbers (percentages) unless otherwise specified

	Gestational age at delivery		Odds ratio (95% CI) for delivery at <36 weeks			
Characteristics	<36 weeks (n=1438)	⩾36 weeks (n=2436)	Unadjusted	P value*	Adjusted	P value†
Age:						
<20	63 (4.4)	70 (2.9)	1.0		1.0	
20-24	234 (16.3)	328 (13.5)	0.8 (0.5 to 1.2)		1.2 (0.8 to 1.9)	
25-29	487 (33.9)	814 (33.4)	0.7 (0.5 to 1.0)	0.0008	1.1 (0.7 to 1.8)	0.74
30-34	449 (31.2)	858 (35.2)	0.6 (0.4 to 0.8)		1.2 (0.7 to 1.8)	
>34	205 (14.3)	366 (15.0)	0.6 (0.4 to 0.9)		1.3 (0.8 to 2.1)	
Parity:						
0	754 (52.4)	904 (37.1)	1.0		1.0	
1	387 (26.9)	904 (37.1)	0.5 (0.4 to 0.6)	<0.0001	0.5 (0.4 to 0.6)	<0.0001
>1	297 (20.6)	628 (25.8)	0.6 (0.5 to 0.7)		0.5 (0.4 to 0.7)	
Smoking status:						
Non-smoker	686 (57.1)	1304 (60.3)	1.0		1.0	
Ex-smoker	114 (9.5)	198 (9.1)	1.1 (0.9 to 1.4)	0.07	1.0 (0.8 to 1.3)	0.09
Smoker	402 (33.4)	662 (30.6)	1.2 (1.0 to 1.3)		1.2 (1.0 to 1.4)	
Missing	236	272				
Deprivation category:						
1 (least deprived)	272 (19.3)	527 (22.0)	1.0		1.0	
2	250 (17.7)	495 (20.7)	1.0 (0.8 to 1.2)		1.0 (0.8 to 1.3)	
3	272 (19.3)	452 (18.9)	1.2 (1.0 to 1.4)	0.0005	1.1 (0.9 to 1.4)	0.26
4	309 (21.9)	478 (20.0)	1.3 (1.0 to 1.5)		1.2 (0.9 to 1.5)	
5 (most deprived)	305 (21.6)	443 (18.5)	1.3 (1.1 to 1.6)		1.3 (1.0 to 1.6)	
Missing	28	41				
Height (cm):						
<155	121 (10.1)	195 (8.8)	1.0		1.0	
155-159	264 (22.0)	399 (18.0)	1.1 (0.8 to 1.4)		1.1 (0.8 to 1.5)	
160-164	374 (31.2)	686 (31.0)	0.9 (0.7 to 1.1)	0.0005	0.9 (0.7 to 1.2)	0.002
165-169	277 (23.1)	564 (25.5)	0.8 (0.6 to 1.0)		0.8 (0.6 to 1.0)	
>170	164 (13.7)	367 (16.6)	0.7 (0.5 to 1.0)		0.7 (0.5 to 1.0)	
Missing	238	225				

*χ^2 test for trend.
†Likelihood ratio test.

Table 2 Delivery related perinatal deaths of first and second twins delivered by a means other than planned caesarean section in relation to gestational age and cause of death

	Preterm births (n=1438)*					Term births (n=2436)				P value for preterm *v* term§
Cause of death	First twin	Second twin	Both twins	P value†	Odds ratio (95% CI) for second twin	First twin	Second twin‡	Both twins	P value†	
All	23	23	42	>0.99	1.0 (0.6 to 1.8)	0	9	0	0.004	0.007
Intrapartum anoxia	5	5	2	>0.99	1.0 (0.3 to 3.5)	0	7	0	0.02	0.04
Pulmonary causes	18	19	25	>0.99	1.1 (0.6 to 2.0)	0	0	0		
All other paediatric causes	11	10	4	>0.99	0.9 (0.4 to 2.1)	0	2	0	0.5	0.48

*In 11 of the preterm births, both twins died but because of different causes.
†McNemar's exact test for discordance between first twins and second twins.
‡Odds ratio for death of the second twin could not be calculated because the odds of death among first twins at term were zero in all categories.
§Fisher's exact test of discordant twin pairs, preterm versus term.

remaining 4545 pregnancies, 671 (14.8%) were delivered by planned caesarean section and 3874 (85.2%) by other means. On univariate analysis, age, socioeconomic status, height, and parity varied according to gestational age at the time of delivery in the group that excluded planned caesarean deliveries, but only parity and maternal height were independent predictors of preterm birth (table 1).

The numbers of deaths of first and second twins born before 36 weeks' gestation did not differ significantly (table 2). Among births at or after 36 weeks' gestation, no deaths were recorded among first twins and nine deaths among second twins (3.7 (95% confidence interval 1.7 to 7.0) per 1000 deliveries; P=0.004 for excess of deaths of second twins). Discordance between first and second twins was significantly different in preterm and term births (P=0.007; table 2).

Of the nine deaths of second twins at term, five were intrapartum stillbirths and four were neonatal deaths. Seven of the nine deaths were attributed to intrapartum anoxia (2.9 (1.2 to 5.9) per 1000 deliveries). Analysis of deaths due to intrapartum anoxia showed no difference between first and second twins born preterm (P>0.99), a significant difference between first and second twins born at term (P=0.02), and a significant difference in the discordance between first and second twins for preterm and term births (P=0.04). The cause of death was classified as mechanical in five of the seven anoxic deaths at term; this equated to 2.1 (0.7 to 4.8) per 1000 deliveries. Both twins were delivered vaginally in six out of the seven deliveries at term in which the second twin died from anoxia and in all five of the deliveries at term in which anoxia had an obstetric mechanical cause. Both twins were delivered by emergency caesarean section in one case in which the second twin died from intrapartum anoxia. Among the 2427 term pregnancies for which both twins were delivered by a means other than planned caesarean section and for which neither twin died, 581 (23.9%) emergency caesarean sections were done for one or both twins.

No differences in any maternal characteristics for twins delivered at term by a means other than planned caesarean section were seen according to whether the second twin died (table 3). When twins' characteristics were compared, no difference was seen in the proportion that were discordant for sex, but the percentage discrepancy in birth weight was significantly higher for pairs of twins in which the second twin died than for pairs in which both twins survived (15.1% *v* 9.5%; P=0.02). When the actual weights for the nine pregnancies in which the second twin died during delivery at term were analysed, four of the second twins were larger than the first twins and five were smaller; the median birth weight did not differ between the first and second twins (2590 (interquartile range 2410-3060) g *v* (2400 (2268-2840) g; P=0.55).

When the risk of death for deliveries from 24 weeks onwards by a means other than planned caesarean section was analysed with conditional logistic regression, a significant interaction between birth order and gestational age was confirmed: the odds ratio for the interaction term between gestational age, expressed as a continuous variable in weeks, and the second twin was 1.16 (1.01 to 1.35; P=0.04). No significant interactions were seen between second twin and maternal age, parity, height, smoking, or deprivation category (all P>0.05). In a model that included all of these interaction terms, the interaction between second twin and gestational age was significant (odds ratio 1.36, 1.01 to 1.85; P=0.04).

When outcomes for the 454 twin pairs delivered at term by planned caesarean section were analysed, no delivery related perinatal deaths of either first or

Table 3 Maternal and obstetric characteristics of pregnancies at term according to death of second twin among women not delivered by planned caesarean section. Values are numbers (%) unless otherwise specified

Characteristics	Both twins survived (n=2427)	Second twin died (n=9)	P value*
Mother			
Median (interquartile range) maternal age (years)	30 (26-33)	29 (26-32)	0.99
Median (interquartile range) height (cm)	163 (159-167)	162 (158-165)	0.72
Nulliparous	900 (37.1)†	4 (44.4)	0.73
Smoker	660 (30.6)†	2 (22.2)	>0.99
In upper two fifths of deprivation category	1000 (41.9)†	5 (55.6)	0.50
Twin			
Discordant for sex	808 (34.0)	2 (22.2)	0.73
Median (interquartile range) % discrepancy in birth weight	9.5 (4.5-15.9)	15.1 (12.1-21.0)	0.02

*Percentage estimated after records with missing values were excluded.
†Fisher's exact test or Mann Whitney U test, as appropriate.

second twins were seen. Among women who gave birth at term, deaths of second twins delivered by planned caesarean section and those delivered by other means did not differ significantly (P=0.22, Fisher's exact test).

Discussion

We observed an excess of delivery related perinatal deaths of second twins born at term compared with their cotwins. No difference in outcome was seen between first and second twins born preterm. The absolute risk of perinatal death for second twins born at term was approximately 1 in 270 for all causes, 1 in 350 for death due to intrapartum anoxia, and 1 in 500 for anoxic death due to a mechanical cause. These absolute risks are high in comparison with singleton births in Scotland over the same period: for singleton pregnancies at term delivered by a means other than planned caesarean section, delivery related perinatal death occurred in about 1 in 1000 births among nulliparous women and 1 in 2000 births among multiparous women; death due to a mechanical obstetric cause occurred in only 1 in 20 000 births.[13]

Methodological issues

Many studies have examined the issue of delivery related mortality in second twins. These studies have compared the outcome of second twins born vaginally either with vaginally delivered cotwins[2 3 5–7] or with second twins delivered by caesarean section.[4 14–16] They failed to show a significant association between birth order and the risk of delivery related perinatal death. We were able to make both comparisons in our study and also addressed several limitations in methods that were apparent in previous studies.

Firstly, this study examined the outcomes of over 4500 twin pairs. Many previous studies that examined perinatal mortality in relation to birth order had fewer than 1000 twin pairs and many had fewer than 500 twin pairs (see Boggess [17] for review). Given the relative rarity of delivery related perinatal death caused by intrapartum anoxia,[13] such studies are clearly underpowered and would inevitably yield negative findings.

Secondly, to our knowledge, this study is the only large scale analysis to include data on both intrapartum stillbirths and neonatal deaths but to exclude antepartum deaths. Given that most delivery related perinatal deaths in second twins at term were intrapartum stillbirths, previous large scale studies that excluded stillbirths probably underestimated the risk to the second twin.[3–5 7] The only large scale study that included stillbirths was unable to distinguish between antepartum and intrapartum stillbirths.[6]

Thirdly, most studies have compared first and second twins across the whole range of gestational ages rather than stratified by gestational age.[3 5 7] The former method is legitimate only if the relative risk is homogeneous across the range of gestational ages. A statistical interaction between birth order and gestational age, however, is predictable. Eighty per cent of twins delivered at 24 weeks die compared with less than 1% at term.[6] The principal determinant of the risk of death is prematurity, which clearly is the same for both twins. The potential for birth order to increase the baseline risk due to complications during labour and delivery, therefore, would be expected to increase with advancing gestational age. Our study confirmed a positive interaction between being a second twin and gestational age and thus confirms that the assumption of homogeneity implicit in previous analyses was invalid. Other maternal factors were also associated with preterm birth (table 1). Multivariate conditional logistic regression showed that the interaction between gestational age and birth order was not explained by an interaction between birth order and any of the other factors.

Finally, our statistical analysis took into account the paired nature of the data. Many previous studies, including previous large scale analyses,[3–7] compared data on first and second twins by using statistical techniques that assume independence of observations. The use of unpaired tests for paired data is inappropriate and results in loss of statistical power. We overcame this using McNemar's test and conditional logistic regression. If we had used the same analytical approach as some previous studies (failed to stratify by gestational age and used a statistical test for unpaired data), we would have observed, overall, 67 deaths among all first twins and 75 among second twins; this would have failed to reach significance (χ^2 test, P=0.49).

The excess of deaths due to intrapartum anoxia was significant only for twins born at term (table 2). Although no significant difference was seen between the risks of death for first and second twins born preterm, the confidence intervals for the odds ratio of death of the preterm second twin (relative to the first twin) due to intrapartum anoxia were 0.3 to 3.5. Our data cannot exclude an excess risk of anoxic death for preterm second twins; further larger analyses are required.

Discordance

No maternal characteristics were associated with an increased risk of delivery related perinatal death for second twins delivered at term (table 3). The absolute discrepancy in weight between twins was greater, however, in pregnancies complicated by death of the second twin at term. Interestingly, the discrepancies were equally distributed between pregnancies in which the second twin was larger than the first and those in which the first twin was larger. The actual number of events was too small to establish the relation between the direction of the weight difference and the cause of death. The registers we used lacked information on the presentation of the second twin before delivery of the first. However, the presentation of the second twin changes after delivery of the first twin in 20% of cases,[1] so it may not be possible to predict, before the first twin is delivered, which cases will be complicated by malpresentation of the second twin.

Caesarean deliveries

Since the excess of deaths of second twins at term seems to be attributable to labour, current data suggest that planned caesarean delivery may be protective against perinatal death among twins. Though no deaths occurred among 454 second twins delivered by planned caesarean section at term, the numbers were too small to confirm a protective effect of planned caesarean section. Previous studies on the association between caesarean section and the risk of perinatal death among second twins included fewer cases than reported in this study[14–16] or lacked information on

What is already known on this topic

It is difficult to assess the wellbeing of second twins during labour

Deliveries of second twins are at increased risk of mechanical problems, such as cord prolapse and malpresentation, after vaginal delivery of first twins

Increased risks of perinatal death in second twins have not been shown, but the methods of these studies were flawed

What this study adds

Second twins delivered at term are at increased risk of delivery related perinatal deaths

Intrapartum anoxia caused 75% of these deaths in second twins, and most of these resulted from mechanical problems after vaginal delivery of first twins

Planned caesarean section of twins at term may prevent perinatal deaths

whether the procedure was planned or an emergency procedure.[4] Sample size calculations show that it will be difficult to obtain randomised controlled trial data to test the hypothesis that planned caesarean section would be protective against perinatal death in twin pregnancies. With a rate of three deaths of second twins due to intrapartum anoxia per 1000 deliveries, allowing 80% power for a one sided test, and assuming that the rate of perinatal death in the planned caesarean group is zero, a randomised controlled trial would need to recruit about 6500 women with twin pregnancies. We propose that women with twins should be counselled about the risk to the second twin and the theoretical possibility of a protective effect of planned caesarean section when considering mode of delivery at term.

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Mode of delivery and the risk of delivery-related perinatal death among twins at term: a retrospective cohort study of 8073 births

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Objective To determine the risk of perinatal death among twins born at term in relation to mode of delivery.

Design Retrospective cohort study.

Setting Scotland 1985–2001.

Population All twin births at or after 36 weeks of gestation, excluding antepartum stillbirths and perinatal deaths due to congenital abnormality ($n = 8073$).

Methods The outcome of first and second twins was compared using McNemar's test and the outcome of twin pairs in relation to mode of delivery was compared using exact logistic regression.

Main outcome measures Intrapartum stillbirth or neonatal death of either twin.

Results Overall, there were six deaths of first twins and 30 deaths of second twins (OR for second twin 5.00, 95% CI 2.00–14.70). The odds ratio for death of the second twin due to intrapartum anoxia was 21 (95% CI 3.4–868.5). The associations were similar for twins delivered following induction of labour and for sex discordant twins. However, there was no association between birth order and the risk of death among 1472 deliveries by planned caesarean section. There was death of either twin among 2 of 1472 (0.14%) deliveries by planned caesarean section and 34 of 6601 (0.52%) deliveries by other means ($P = 0.05$, odds ratio for planned caesarean section 0.26 [95% CI 0.03–1.03]). The association was similar when adjusted for potential confounders. Assuming causality, we estimate that 264 caesarean deliveries (95% CI 158–808) would be required to prevent each death.

Conclusion Planned caesarean section may reduce the risk of perinatal death of twins at term by approximately 75% compared with attempting vaginal birth. This is principally due to reducing the risk of death of the second twin due to intrapartum anoxia.

INTRODUCTION

The effect of birth order on the risk of perinatal death among twins has been the subject of study for some years. Clinically, it is well recognised that the second twin is at increased risk of complications during labour due to difficulties in fetal monitoring and the possibility of traumatic delivery following vaginal birth of the first twin.[1] However, large scale epidemiological studies have generally failed to confirm increased perinatal mortality in relation to birth order.[2–4] We recently re-examined this and found a marked excess of delivery-related perinatal deaths among second twins compared with first twins.[5] The failure of previous studies to show this was due to lack of details regarding the timing and cause of perinatal death, failure to stratify by gestational age and the use of unpaired statistical tests to compare the outcome of first and second twins. Our findings suggested that delivery of all twins by planned caesarean section might reduce the risk of perinatal death. However, our own and other analyses lacked sufficient numbers to make this comparison. In the present study, we analysed data from over 8000 twin pairs born at or after 36 weeks of gestation and sought to determine the association between mode of delivery and the risk of perinatal death.

METHODS

The Scottish Morbidity Record (SMR2) collects information on clinical and demographic characteristics and outcomes for all patients admitted to Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been greater than 99% complete since the late 1970s.[6] A quality assurance exercise in 1996/97 demonstrated that mode of delivery was free of major or minor errors for 99.2% of cases in singletons or first twins and 95.2% of second twins [Dr Jim Chalmers MB ChB,

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Information and Statistics Division, National Health Service (NHS), Scotland, personal e-mail communication]. The SMR2 register was used to identify all births between 1985 and 2001. These were linked to records from the Scottish Stillbirth and Infant Death Enquiry (SSBIDE), which has routinely classified all perinatal deaths in Scotland since 1983. It is virtually 100% complete and has been described in detail elsewhere.[7,8] Record linkage employs a probability based matching approach which has approximately a 1% error rate overall and the method is described in detail elsewhere.[9] The SMR2 does not have an indicator of birth order whereas the SSBIDE does have such an indicator. It was possible, therefore, to establish the mode of delivery and presentation of the first twin in cases where one twin died.

Perinatal deaths were classified by the information in the SSBIDE where coding of the cause of death is performed by a single medically qualified individual[7] using a modification of the Wigglesworth classification.[10] Stillbirths were subdivided into antepartum (deaths before the onset of labour) and intrapartum (deaths during labour). There can be ambiguity in this regard, but the definition by its nature lacks a gold standard and depends on the judgement of the coordinator on the basis of clinical and autopsy data. Neonatal death was defined as death during the first four weeks of life in a liveborn baby. Death due to congenital abnormality is classified under the hierarchical system and was defined as any structural or genetic defect incompatible with life or potentially treatable but causing death and these were excluded. Having excluded deaths due to congenital abnormality and rhesus isoimmunisation, deaths are then classed according to direct obstetric causes (in order): toxaemia, haemorrhage (including abruption), mechanical, maternal and then cases with none of these obstetric causes. Mechanical is defined as death from a direct physical obstetric cause such as cord compression (including prolapse), birth trauma or asphyxia associated with disproportion. In the absence of any of the listed direct obstetric causes, the deaths were classified by the paediatric diagnoses and these were grouped into intrapartum anoxia and all others. The cause of deaths was subdivided into deaths due to intrapartum anoxia and all other causes. Within the category of intrapartum anoxia we used the obstetric classification to identify those where there was a direct obstetric mechanical causes.

We defined delivery-related perinatal death as intrapartum stillbirth or neonatal death not caused by congenital anomaly. Term was defined as $\geq$36 weeks of gestation for twin pregnancies.[11] Small for gestational age (SGA) was defined as $\leq$5th centile for sex and gestational age, using centiles generated within the study cohort. Hospital throughput was defined as the total number of births recorded in the SMR2 database for the given hospital over the given year. Other maternal characteristics were defined as previously described.[12] Information on maternal weight and body mass index were not available.

Continuous variables were summarised by the median and inter-quartile range (IQR). Paired continuous data were compared using the Wilcoxon signed rank test and unpaired continuous data were compared using the Mann–Whitney *U* test. Discordance in birthweight was described by the absolute difference expressed as a percentage of the weight

Table 1. Maternal, obstetric and demographic factors in relation to death of either twin.

Characteristics	Both twins survived (n = 8037)	Death of either twin (n = 36)	P*
Age (years)			
<25	1497 (18.6)	2 (5.6)	0.3
25–29	2708 (33.7)	15 (41.7)	
30–34	2650 (33.0)	14 (38.9)	
>34	1182 (14.7)	5 (13.9)	
Parity			
0	3081 (38.3)	16 (44.4)	0.6
1	2975 (37.0)	12 (33.3)	
>1	1981 (24.7)	8 (22.2)	
Deprivation category†			
1 (least deprived)	1712 (21.6)	6 (17.1)	0.9
2	1513 (19.1)	8 (22.9)	
3	1530 (19.3)	8 (22.9)	
4	1537 (19.4)	5 (14.3)	
5 (most deprived)	1632 (20.6)	8 (22.9)	
Height (cm)†			
<155	693 (9.8)	4 (11.8)	0.5
155–159	1343 (19.0)	6 (17.7)	
160–164	2205 (31.1)	13 (38.2)	
165–169	1675 (23.6)	7 (20.6)	
>170	1172 (16.5)	4 (11.8)	
Mode of delivery			
Planned caesarean	1470 (18.3)	2 (5.6)	0.05
SGA†			
None	7241 (90.5)	28 (80.0)	0.04
Either twin	764 (9.5)	7 (20.0)	
Birthweight discrepancy†			
Median percent birthweight (IQR)	9.6 (4.5–16.3)	14.7 (6.3–24.0)	0.001
Sex discordance of twin pairs†			
Concordant	5406 (67.4)	28 (77.8)	0.2
Discordant	2615 (32.6)	8 (22.2)	
Year of birth			
Median year of birth (IQR)	1993 (1989–1997)	1991 (1987–1995)	0.01

Values are presented as n (%) unless otherwise stated; SGA denotes small for gestational age.

* Fisher's Exact Test, χ^2 test, Mann–Whitney *U* test or trend test as appropriate.

† Cases with missing data excluded (n = 951 for height and n = 114 for deprivation category and 33 cases had missing data for sex or birthweight).

of the larger twin. Univariate comparisons of unpaired dichotomous data were performed using Fisher's Exact Test. Due to the small number of events among women delivered by planned caesarean section, multivariate comparison was made using exact logistic regression. Univariate comparison of dichotomous outcomes in first and second twins was performed using McNemar's test. The *P* values for all hypothesis tests were two sided. The 95% confidence intervals for risk of death were calculated using the binomial distribution. All statistical analyses were performed using the Stata software package (Stata, TX, USA), version 8.2 or LogExact version 5.0 (Cytel Software, MA, USA).

RESULTS

There were 8213 records of twin pairs born at or after 36 weeks of gestation in the linked database. We excluded 95 (1.2%) cases where one or both twins were antepartum stillbirths, 34 (0.4%) where one or both twins were an intrapartum stillbirth or neonatal death due to congenital abnormality, 17 records where one twin was documented as being delivered by planned caesarean section but the other was not and six pregnancies where induction of labour was recorded but the mode of delivery was documented as planned caesarean section for both twins. Some of the records had multiple exclusions and the remaining 8073 records formed the study group which was 98.3% of all documented twin births at term. There were 36 delivery-related perinatal deaths among this group, which equated to 22.9% of all perinatal deaths documented in the 8213 twin pairs delivered at term. There was no cases among the 8073 records where both twins of a pair died.

The demographic, maternal and obstetric characteristics of the study group are tabulated by whether there was a delivery-related perinatal death. Death of either twin was associated with delivery by a means other than planned caesarean section, with increased discordance in birthweight and with delivery at earlier years within the study period, but was not significantly associated with other maternal, demographic or obstetric factors (Table 1). The risk of death of either twin did not increase with advancing week of gestation from 36 weeks ($P = 0.12$) or hospital throughput, expressed as number of births per annum ($P = 0.93$). Of the 8073 deliveries, 1472 (18.2%) were planned caesarean sections and 1759 (21.8%) were emergency caesarean sections, giving an overall caesarean section rate of 40.0%. The proportion of women delivered by planned caesarean section increased over the period of study (odds ratio of planned section per one year, 1.05, 95% CI 1.04–1.07, $P < 0.001$). Among the hospitals that delivered more than 100 twins over the study period, the median proportion of planned caesarean deliveries was 18.6%, the IQR 16.9–20.8% and the range was 10.6–30.0%.

Overall, there was a fivefold excess of death among second twins compared with first twins (Table 2). This was due to a 21-fold excess risk of death of the second twin due to intrapartum anoxia. The associations between birth order

Table 2. Univariate associations between delivery related perinatal death and birth order.

Cause of death	First twin *n* (%)	Second twin, *n* (%)	OR (95% CI) for second twin	*P**
All twin births (*n* = 8073)				
All cause	6 (0.07)	30 (0.37)	5.0 (2.0–14.7)	0.0001
Intrapartum anoxia	1 (0.01)	21 (0.26)	21.0 (3.4–868.5)	<0.0001
Other causes	5 (0.06)	9 (0.11)	1.8 (0.5–6.8)	0.4
Deliveries by planned caesarean section (*n* = 1472)				
All cause†	0	2 (0.14)	∞ (0.2–∞)	0.5
Intrapartum anoxia†	0	0	∞ (0.2–∞)	–
Other causes†	0	2 (0.14)	∞ (0.2–∞)	0.5
Deliveries by means other than planned caesarean section (*n* = 6601)				
All cause	6 (0.09)	28 (0.42)	4.7 (1.9–13.8)	0.0002
Intrapartum anoxia	1 (0.02)	21 (0.32)	21.0 (3.4–868.5)	<0.0001
Other causes	5 (0.08)	7 (0.11)	1.4 (0.4–5.6)	0.8
Induced deliveries (*n* = 3087)				
All cause	2 (0.06)	11 (0.36)	5.5 (1.2–51.1)	0.02
Intrapartum anoxia†	0	7 (0.23)	∞ (1.4–∞)	0.02
Other causes	2 (0.06)	4 (0.13)	2.0 (0.3–22.1)	0.7
Sex discordant twins only (*n* = 2623)				
All cause	1	7	7.0 (0.9–315.5)	0.07
Intrapartum anoxia†	0	7	∞ (1.4–∞)	0.02
Other causes	1	0	0.0 (0.0–39.0)	>0.99

* McNemar's exact test for discordance between first and second twins.

† Odds ratio (OR) for death of the second twin could not be calculated because the odds of death among first twins were zero.

Table 3. Crude and adjusted odds ratios for the risk of death of either twin associated with planned caesarean section.*

	Odds ratio (95% CI)	$P^{\dagger}$
Unadjusted (all cases)	0.26 (0.03–1.03)	0.06†
Unadjusted (excluding missing data)‡	0.27 (0.03–1.06)	0.07
Adjusted for year of birth	0.30 (0.03–1.16)	0.10
Adjusted for SGA‡	0.26 (0.03–1.03)	0.06
Adjusted for birthweight discrepancy‡	0.26 (0.03–1.02)	0.05

* Factors included in the model were those with statistically significant univariate associations.

† *P* value from exact logistic regression (two sided). The two-sided *P* value from Fisher's exact test was 0.05. One-sided *P* value = 0.028 both tests.

‡ 33 cases were excluded from all these analyses because they have a missing record for sex and/or a missing birthweight measurement for either twin.

and perinatal death were similar when confined to twins delivered by a means other than planned caesarean section, those where labour was induced and those where both twins were sex discordant. When the analysis was confined to twin pairs delivered by planned caesarean section, there was no overall excess risk of death of the second twin, although the number of events was too small to exclude a significant effect of birth order.

When women delivered by planned caesarean section ($n = 1472$) were compared with women delivered by other means ($n = 6601$) they were older (median [IQR] in years: 30 [27–34] *vs* 29 [25–32], $P < 0.0001$) and smaller stature (median [IQR] in cm: 162 [157–167] *vs* 163 [159–167], $P = 0.0005$) than other women. Twin pairs delivered by planned caesarean section had greater birthweight discordance (median [IQR] percentage discrepancy: 10.3 [5.1–17.0] *vs* 9.4 [4.5–16.2], $P = 0.0008$) and were more likely to be sex discordant (35.3% *vs* 32.0%, $P = 0.01$) and one or both twins were more likely to be SGA (11.2% *vs* 9.2%, $P = 0.02$).

The risk of perinatal death was approximately 75% lower among women delivered by planned caesarean section (Table 3). The odds ratio for planned caesarean section was essentially unaffected by adjusting for birthweight discrepancy, SGA or year of birth. Among those twins delivered by a means other than planned caesarean section, the all-cause risk of death of the first twin was 0.9 per 1000 deliveries (95% CI 0.3–2.0), the all-cause risk of death in the second twin was 4.2 per 1000 deliveries (95% CI 2.8–6.1), the risk of death of the second twin due to intrapartum anoxia was 3.2 per 1000 deliveries (95% CI 2.0–4.9) and the risk of death of the second twin due to intrapartum anoxia secondary to an obstetric mechanical cause was 1.5 per 1000 (95% CI 0.7–2.8). The risk difference (95% CI) associated with planned caesarean section compared with other modes of delivery was 3.79 (1.24–6.34) per 1000 for death of either twin indicating that the number of caesarean sections required to prevent each death, assuming causality, was 264 (95% CI 158–808).

There were 34 deaths of either twin among the 6601 women delivered by a means other than planned caesarean section. In none of these cases was the first twin a vaginal breech birth. Of the 34 deaths, there were 24 cephalic vaginal births of the first twin. In the remaining 10 cases, both twins were delivered by emergency caesarean section. Among these the presentation of the first twin was cephalic in 6 out of 10, undocumented in 2 and breech in 2. Therefore, the first twin presented cephalically in 30 (88%) of the 34 cases, which resulted in death of either twin.

DISCUSSION

We have recently demonstrated that among twin pairs born at term, there is a marked excess of delivery-related perinatal deaths among second twins.[5] Three quarters of these deaths were due to intrapartum anoxia and over half were related to a direct obstetric mechanical cause. This was consistent with a Swedish study of over a million term births, which demonstrated a fourfold risk of a depressed 5-minute Apgar score among second but not first twins.[13] We hypothesised that planned caesarean delivery of twins would reduce the risk of perinatal death, primarily by reducing the risk of anoxic death of the second twin. In the present study, we show that delivery by planned caesarean section was associated with a 75% lower risk of perinatal death of either twin when compared with those delivered by other means. This reduction in risk was not significantly changed by adjusting for potential confounders. Residual confounding and bias are unlikely to explain our results since planned caesarean section would typically be employed in the presence of risk factors for adverse outcome. Consistent with this, women delivered by planned caesarean section were older and shorter than other mothers and their offspring had greater birthweight discrepancies and increased rates of SGA.

These findings suggest that delivering all twins by planned caesarean section may reduce the number of perinatal deaths. Currently, planned caesarean delivery is usually offered to women with twins where the first twin is presenting by the breech.[1] However, in the present study, approximately 90% of the deaths occurred among twin pairs where the first was in a cephalic presentation. Assuming causality, we estimate that 264 caesarean deliveries would need to be performed to prevent each death. Many women may chose to accept the small risk of perinatal death in order to achieve vaginal birth and facilities should be provided to allow this choice. However, we suggest that all women with twins should be informed of the likely reduction in risk of perinatal death associated with planned caesarean delivery and that this option should be made available to those who chose not to accept the risk. Women and clinicians who remain uncertain should consider participating in the randomised controlled trial of planned caesarean section for twins that is currently under way.[14]

This information must be placed in the context of short and long term maternal morbidity associated with caesarean delivery.[15] However, attempting vaginal birth of twins carries its own maternal risks. For example, approximately 4% of twin deliveries result in caesarean delivery of the second twin following vaginal birth of the first.[16,17] This scenario carries a 20-fold risk of general anaesthesia.[17] Given the high rates of caesarean delivery among twins,[16] the greater risks of emergency compared with planned caesarean section[18] and the specific intrapartum complications associated with twins,[17] it is not clear that the risk of severe maternal morbidity would be increased by a decision for planned caesarean section. For example, maternal mortality is 70% higher when caesarean delivery is performed intrapartum rather than as a planned procedure.[18] In our study, 27% of women not delivered by planned caesarean section were delivered by emergency section. The increased use of general anaesthesia for twin sections may result in an even higher relative risk of mortality comparing emergency caesarean delivery in twins with planned procedures. Thus, it may be that maternal morbidity may be neutral or could even favour planned caesarean section. The question may be answered by a randomised controlled trial. Such trials will inevitably be under-powered for severe maternal morbidity and for maternal mortality.

Many previous studies have addressed the issue of mode of delivery and the risk of perinatal death among twins. However, meta-analysis of these studies did not clearly indicate whether planned caesarean section was likely to reduce the risk of death.[19] Analysis of this question requires detailed information about the cause of death. Many types of death could not be prevented by planned caesarean section at term, such as antepartum stillbirths and deaths due to lethal congenital abnormality. Collectively, these accounted for more than three quarters of all perinatal deaths among twins at term in the present study. Failure to exclude these outcomes from analyses of perinatal mortality would obscure the potential protective effect of planned caesarean section on truly delivery-related perinatal deaths. Moreover, since delivery-related perinatal death among twins is relatively rare, the question can only be addressed by a database that combines large number of women with detailed information on the cause of perinatal death. Finally, obstetric details are also required in order to differentiate between key factors, such as planned *versus* emergency caesarean section. This is the first adequately powered analysis, to our knowledge, that combines detailed information on obstetric characteristics and the cause of perinatal death in a sufficient number of term twin births.

The observation of reduced risk of perinatal death following planned caesarean section is biologically plausible. Of the 34 deaths among infants delivered by other means, approximately two-thirds were due to intrapartum anoxia. Planned caesarean section eliminates the risk of death due to intrapartum anoxia. It is clearly plausible, therefore, that planned caesarean section would reduce the risk of death among twin births. The absolute risk of death of the second twin due to this event was approximately 3.2 per 1000. This is approximately 10 times higher than among singleton births at term.[12] Caesarean section is associated with an increased risk of future antepartum stillbirth. However, the absolute risk is in the region of 0.9 per 1000[20] and would not mitigate against the benefit of planned caesarean section on the basis of the current analysis. The two-sided P value for planned caesarean delivery was at the borderline level of statistical significance ($P = 0.05$ using Fisher's Exact Test and $P = 0.06$ using univariate exact logistic regression). We reported the two-sided value to be conservative. Given the prior hypothesis that caesarean section might be protective, a one-sided test may have been appropriate, which yielded P values of 0.028 using both exact methods.

We lacked data to estimate reliably whether the second twin was in a cephalic or non-cephalic presentation. However, presentation of the second twin changes in up to 20% of cases following delivery of the first.[1] Further studies, possibly using a case–control design, will be required to address this issue. We also lacked data on chorionicity. However, the effect of birth order was virtually identical in sex discordant as sex concordant twins. Sex discordant twins pairs are, necessarily, both dizygous and dichorionic and the effect of birth order cannot therefore be explained by complications arising from monochorionic twinning. The excess risk of death among second twins was also observed among women having labour induced indicating that the lower risk of death among twins delivered by planned caesarean section did not indicate a general lower risk of adverse events among twin pairs delivered electively.

Conflict of interest

None.

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RESEARCH

Birth order of twins and risk of perinatal death related to delivery in England, Northern Ireland, and Wales, 1994-2003: retrospective cohort study

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ABSTRACT

Objective To determine the effect of birth order on the risk of perinatal death in twin pregnancies.

Design Retrospective cohort study.

Setting England, Northern Ireland, and Wales, 1994-2003.

Participants 1377 twin pregnancies with one intrapartum stillbirth or neonatal death from causes other than congenital abnormality and one surviving infant.

Main outcome measures The risk of perinatal death in the first and second twin estimated with conditional logistic regression.

Results There was no association between birth order and the risk of death overall (odds ratio 1.0, 95% confidence interval 0.9 to 1.1). However, there was a highly significant interaction with gestational age (P<0.001). There was no association between birth order and the risk of death among infants born before 36 weeks' gestation but there was an increased risk of death among second twins born at term (2.3, 1.7 to 3.2, P<0.001), which was stronger for deaths caused by intrapartum anoxia or trauma (3.4, 2.2 to 5.3). Among term births, there was a trend (P=0.1) towards a greater risk of the second twin dying from anoxia among those delivered vaginally (4.1, 1.8 to 9.5) compared with those delivered by caesarean section (1.8, 0.9 to 3.6).

Conclusions In this cohort, compared with first twins, second twins born at term were at increased risk of perinatal death related to delivery. Vaginally delivered second twins had a fourfold risk of death caused by intrapartum anoxia.

INTRODUCTION

Though vaginal delivery of a second twin is recognised as a time of obstetric risk, we do not know whether second twins are at increased risk of perinatal death. Many studies on the association between birth order and the risk of death have methodological flaws, specifically, the failure to identify deaths truly related to delivery, the failure to use paired statistical tests to compare the outcome of first and second twins, and the failure to stratify analyses by gestational age.[1] An analysis of nationally collected data on pregnancy and perinatal death from Scotland in 1992 and 1997 showed a significantly increased risk of intrapartum stillbirth or neonatal death among second twins born at term, but included only nine such deaths.[2] A follow-up study of the same data source over a more prolonged period (1985 to 2001) showed a similar association but included only 36 deaths at term.[3] A subsequent analysis of US data found no variation in the risk of neonatal death related to birth order among twins and concluded that the increased perinatal mortality among second twins was "merely an artefact of mortality comparisons."[4] Data from multiple sources, however, indicate an increased risk of morbidity for the second twin at term: a large scale study from Sweden found that second twins had a fourfold risk of an Apgar score <7 at five minutes,[5] and a recent analysis of data from Nova Scotia found a threefold risk of morbidity for the second twin delivered vaginally but no excess risk for those delivered by planned caesarean section.[6] It remains unclear, therefore, whether attempted vaginal delivery of the second twin at term is associated with an increased risk of perinatal death. We studied the association between birth order and the risk of perinatal death among twin pregnancies in England, Northern Ireland, and Wales, 1994-2003.

METHODS

Data on perinatal death in England, Northern Ireland, and Wales have been collected nationally since 1994. This is currently coordinated by the Confidential Enquiry into Maternal and Child Health (CEMACH) and had previously been done by the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI). A network of local clinicians and health professionals at hospital level notify regional offices of perinatal deaths. Coroners' officers, child health systems, and congenital anomaly registers also report deaths. Regional managers then code the death according to the information provided, which includes autopsy results (if performed). From 1995, data from England and Wales were linked to the Office for National Statistics' registry of death certifications, ensuring 100% ascertainment of all registered stillbirths and neonatal deaths. In 1994, the dataset was about 95% complete when compared with national

death registrations. The death registry was compiled nationally at the inquiry's central office in London, and the CEMACH database includes all records obtained by CESDI. We used the registry of deaths for 1994-2003 for our analyses.

The data source included only information on deaths. We obtained the total number of twin births over the period of time from the Office of National Statistics and the Northern Ireland Statistics and Research Agency. However, these lack any detailed obstetric data. Hence, we had no information from cases where both twins survived and, in cases where only one twin died, we had no information on the characteristics of the survivor. We could still study the association between birth order and the risk of death, however, as statistical methods for comparison of a dichotomous outcome (such as death) in pairs uses only those instances that are discordant for the outcome of interest (see below and elsewhere for review[1]). Our analyses with this study design, however, were limited to the relative risk of death for the second twin referent to the first and determination of whether the relative risk of death for the second twin varies in relation to any characteristic common to both, such as gestational age and maternal characteristics.

We classified events using a series of fields in the available database. Firstly, we classified deaths as stillbirth, early neonatal death, and late neonatal death. A further field documented whether death of the infant took place before or after the onset of labour or whether the time of death was unknown. Intrapartum stillbirth was defined as a birth when the infant was born showing no signs of life and the death was documented as occurring during labour. Neonatal death was defined as death of a liveborn infant within the first four weeks of life. We classified cause of death according to a modified version of the Wigglesworth system into one of nine categories: congenital defect/malformation; unexplained antepartum fetal death; death from intrapartum "asphyxia," "anoxia," or "trauma"; immaturity; infection; other specific causes; injury or non-intrapartum trauma; sudden infant death; and unclassifiable.[7] We excluded those deaths where the cause was stated to be a lethal or severe congenital abnormality and classified all other intrapartum stillbirths and neonatal deaths as perinatal deaths related to delivery. We also analysed anoxic deaths as a subgroup of these events, which we defined as those where the cause was classified as "death from intrapartum asphyxia, anoxia, or trauma." As the study used wholly anonymised data and data collection was part of a national clinical audit, we did not require individual consent.

Statistics

We used conditional logistic regression to estimate the odds ratio of death for the second twin referent to the first. The method ignores concordant pairs (that is, where both twins survived or both twins died) and is therefore appropriate in a dataset containing data on deaths only. We tested for interactions between birth order and both maternal and obstetric characteristics with interaction terms and assumed significance at $P<0.05$. The characteristics tested for interaction were gestational age, maternal age (expressed as a continuous variable), maternal ethnicity (white versus all others), and method of delivery. Interactions were expressed as odds ratios with 95% confidence intervals. The latter illustrates the power of the study to exclude a given degree of effect modification and is preferable to post hoc power calculations.[8] All statistical analysis was performed with Stata version 8.2 (StataCorp, College Station, TX).

RESULTS

The database had records for 5758 twin pregnancies in 1994-2003 where death of one or both infants was recorded. In 4221 of these, one infant died and the other survived. From these, we excluded eight records (0.2%) that did not document birth order, 55 (1.3%) where the gestational age at birth was missing, 450 (10.7%) where delivery was before 24 weeks, 178 (4.7%) where a therapeutic abortion was performed, 1975 (46.8%) where death was classed as stillbirth and the timing of fetal death was before labour or unknown, and 752 (17.8%) where the infant had a lethal or severe congenital abnormality. A total of 2844 records (67.4%) had one or more of these exclusions, leaving a study group of 1377 in which there was one intrapartum stillbirth or neonatal death but the other twin survived. The table shows the characteristics of this group (table). Over the same period of time, the Office for National Statistics documented a total of 96 116 certified twin pregnancies in England and Wales and the Northern Ireland Statistics and Research Agency recorded 3482, giving a total of 99 598 twin pregnancies as our denominator. Further details of the denominator, such as gestational age at birth and method of delivery, were not available.

Birth order was not associated with the overall risk of perinatal death related to delivery: the odds ratio for the second twin was 1.0 (95% confidence interval 0.9 to 1.1). There were no significant interactions between birth order and maternal age (odds ratio for interaction 0.9, 0.7 to 1.1, P=0.2) or white ethnicity (1.2, 0.9 to 1.5, P=0.2). There was, however, a highly significant interaction with gestational age ($P<0.001$). There was no association between birth order and the risk of death among infants born before 36 weeks' gestation (fig 1), but there was an increased risk of death among second twins born at term (2.3, 1.7 to 3.2, $P<0.001$). When we confined the analysis to deaths caused by anoxia, there was a weak association with being a second twin for all births (1.4, 1.1 to 1.8, P=0.02). Again, there was a highly significant interaction with gestational age ($P<0.001$). When we stratified by gestational age, we found no association between birth order and the risk of death caused by anoxia before 36 weeks (fig 1) but a strong association for births at and beyond 36 weeks (3.4, 2.2 to 5.3).

We then assessed the risk of perinatal death related to delivery among second twins born at term in

Characteristics of the study cohort. Figures are numbers (percentage) unless stated otherwise

	Data
Maternal age (years):	
Median (IQR)	29 (25-33)
Missing	55 (4.0)
Ethnicity:	
White	1118 (81.2)
Black	88 (6.4)
Other	124 (9.0)
Missing	47 (3.4)
Gestational age (weeks):	
24-27	703 (51.0)
28-31	367 (26.7)
32-35	130 (9.4)
≥36	177 (12.9)
Presentation†:	
Cephalic	471 (34.2)
Breech	327 (23.8)
Other	77 (5.6)
Missing*	502 (36.5)
Mode of delivery†:	
Spontaneous vaginal	343 (24.9)
Assisted vaginal	114 (8.3)
Elective caesarean	74 (5.4)
Emergency caesarean	442 (32.1)
Other/missing*	404 (29.3)
Sex of infant†:	
Male	786 (57.1)
Female	587 (42.6)
Missing	4 (0.3)
Birth weight (g)†:	
Median (IQR)	970 (730-1440)
Missing	14 (1.0)
Cause of death:	
Asphyxia, anoxia, or trauma	242 (17.6)
Immaturity	735 (53.5)
Infection	164 (11.9)
Other specific	187 (13.6)
Injury	4 (0.3)
Unexplained‡	39 (2.8)
Missing or unclassifiable	6 (0.4)

IQR=interquartile range.
*Recorded only from 1996 onwards; 93.8% of missing records for mode of delivery and 74.7% of missing records for presentation were for births before 1996.
†For infant who died; data were not available for the survivor.
‡Includes in utero and neonatal deaths.

relation to method of delivery in the 121 twin pairs for whom we had this information. When we looked at all causes of perinatal death related to delivery we found no significant difference in those delivered by caesarean section (odds ratio for interaction term 0.9, 0.4 to 1.8, P=0.7). When we confined the analysis to deaths caused by intrapartum anoxia we found an interaction of borderline significance between birth order and caesarean section (0.4, 0.1 to 1.3, P=0.1). The odds ratio for the second twin was 1.8 (0.9 to 3.6) among those delivered by caesarean section and 4.1 (1.8 to 9.5) among

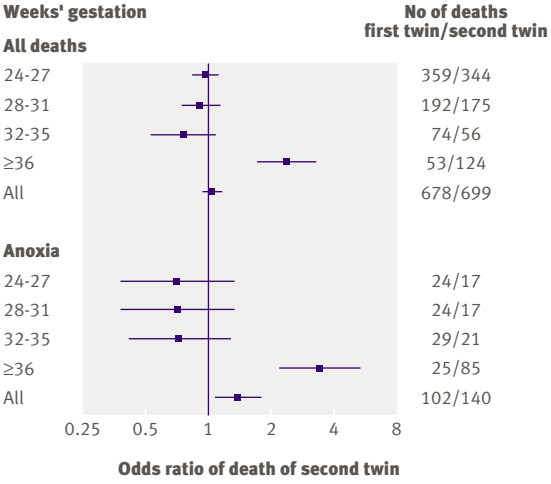

Fig 1 | Odds ratio for perinatal death related to delivery of second twin for all causes and deaths caused by anoxia, stratified by gestational age. Numbers of deaths are actual numbers of losses of first and second twins, confined to births where other twin survived

those delivered vaginally (fig 2). There were only 19 twin pairs delivered by planned caesarean section at term where one died and the other survived. Among this group, the odds ratio for any perinatal death of the second twin related to delivery was 1.4 (0.6 to 3.4) and 1.0 (0.1 to 7.1) for death caused by anoxia.

Sensitivity analyses

We performed two sensitivity analyses. Firstly, we repeated the analysis excluding eligible births from 1994 (n=178), when the dataset was less complete. The results were similar to the main analysis, with a significant interaction between birth order and gestational age (P<0.001) and no significant association between birth order and the risk of death at preterm gestations but a significantly increased risk of all cause death for the second twin at term (2.4, 1.7 to 3.5) and for death caused by anoxia (3.3, 2.0 to 5.4). Secondly, we repeated the analysis including cases

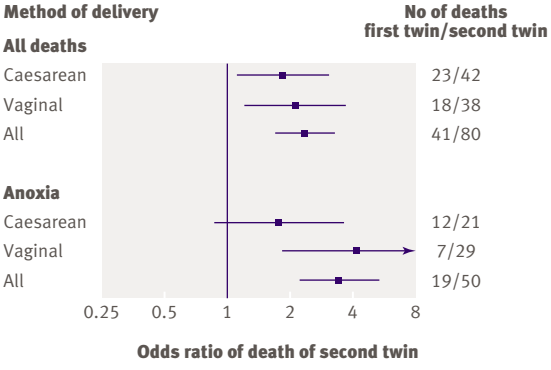

Fig 2 | Odds ratio for perinatal death related to delivery of second twin at term gestation for all deaths and deaths caused by anoxia, stratified by method of delivery. Numbers of deaths are actual numbers of losses of first and second twins, confined to births where the other twin survived (excludes cases with missing record of method of delivery)

where the baby was stillborn but the timing of death in relation to the onset of labour was documented as "unknown" (n=179). The results were similar to the main dataset, with a significant interaction between birth order and gestational age (P<0.001) and no significant association between birth order and the risk of death at preterm gestations but a significantly increased risk of all cause death for the second twin at term (2.3, 1.8 to 3.0) and for death caused by anoxia (3.3, 2.1 to 5.0).

DISCUSSION

In this retrospective cohort study we found an increased risk of death of second twins compared with first twins born at term in England, Northern Ireland, and Wales, 1994-2003. There was an interaction between the effect of birth order and gestational age. There was no association between birth order and the risk of death among infants born at preterm gestations, but we found a strong association between birth order and the risk of death at term. The interaction between birth order and gestational age is unlikely to be a chance finding. Firstly, it was highly significant (P<0.001). Secondly, we had previously observed such an interaction in another population,[2] and the presence of an interaction was a prior hypothesis. Thirdly, it is biologically plausible. The risk of death at term is low and a small absolute risk of complications for the second twin will result in a much greater relative risk of death (when compared with the first twin) than at preterm gestations, where the background risk of death is high for both.[2] The association between birth order and the risk of perinatal death at term was stronger for deaths attributed to intrapartum anoxia. These findings clearly show an increased risk for death of the second twin delivered at term, principally because of complications of labour and delivery.

Comparison with other research

A previous observational study found a lower risk of death of either twin with planned caesarean delivery.[3] Consistent with this, the risk of anoxic death of the second twin was lower among those delivered by caesarean section than those delivered vaginally, although not significantly so. The data source we used was confined to infants who died so we did not know how the surviving twin had been delivered. In some cases where the second twin died after a caesarean delivery, the first twin may have been delivered vaginally. This delivery combination is known to increase the risk of death for the second twin.[9 10] It is likely, therefore, that the protective effect of caesarean delivery would be greater than our results suggest. The number of planned caesarean sections in the present analysis was too small to confirm or exclude a significant association between birth order and the risk of perinatal death with this method of delivery.

A large scale study of US birth and death certifications (1995-7) published in 2004 found no significant difference in the risk of neonatal death among second twins.[4] The analysis, however, had several weaknesses —namely, the failure to use paired statistical comparison of first and second twins, the known shortcomings of the US birth and death certification databases,[11 12] and stratification by birth weight rather than gestational age. Moreover, other analyses of the same data source suggested an increased risk of death of the second twin related to delivery: the risk of neonatal death of the second twin was lower when both babies were delivered by caesarean section compared with those delivered vaginally.[9 10] The US data also lack information on whether death of the infant occurred before or during labour and cannot, therefore, address the effect of birth order on the risk of intrapartum stillbirth. The strengths of our study are the use of more appropriate statistical methods and that data were available for a large number of losses, including detailed information on both the timing and cause of perinatal death.

Our results are consistent with those of several previous studies of birth order and perinatal morbidity. These have shown an increased risk of a depressed five minute Apgar score in the second twin.[5 13] We found no association between birth order and the risk of perinatal death at preterm gestations, whereas other studies have shown an increased risk of fetal distress or morbidity for second twins born preterm.[13] Our interpretation of these findings is that labour and delivery are associated with risks to the second twin at all gestations. The major determinant of perinatal death at preterm gestations, however, is the degree of prematurity. Hence, a small additional risk to the second twin during vaginal birth has no significant effect on the relative risk of death, except at term. Other studies with data on both twins have identified risk factors for death of the second twin, including discordant birth weights,[2] delivery by a means other than planned caesarean section,[3] operative vaginal delivery of the first twin (when compared with spontaneous vaginal delivery of the first twin),[14] and a prolonged interval between delivery of the first twin and delivery of the second.[13]

The findings of this and other studies suggest that planned caesarean section may be beneficial for all twins. Direct evidence for a protective effect of caesarean section would require a randomised controlled trial, although statistical power might be a problem.[2] This and previous studies have important lessons for any randomised controlled trial of planned caesarean

WHAT IS ALREADY KNOWN ON THIS TOPIC

Vaginal delivery of the second twin is recognised as a time of high risk

Recent studies of the effect of birth order on the risk of perinatal death have produced inconsistent results

WHAT THIS STUDY ADDS

There was no association between birth order and the relative risk of perinatal death related to delivery among preterm twins

At term, the second twin had a greater than twofold risk of perinatal death related to delivery and a greater than threefold risk of death caused by intrapartum anoxia

section for all twin pregnancies. Inclusion of preterm births may mask a protective effect of caesarean section on perinatal mortality if the principal effect of caesarean section is to reduce the risk of complications for the second twin. Moreover, this and previous studies showed that it is a minority of all perinatal deaths of twins that are related to complications during labour and delivery. Failure to exclude losses that are largely independent of method of delivery, including antepartum stillbirth and deaths caused by congenital abnormality or prematurity, may mask a protective effect of caesarean delivery.

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Ethical approval: The directors of CEMACH approved the study.

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Section 3. Ultrasonic predictors of pregnancy outcome

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The relation between fetal abdominal circumference and birthweight: findings in 3512 pregnancies

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Objectives To establish the relation between fetal abdominal circumference and birthweight in a large population of fetuses; to identify whether the error in estimating birthweight by abdominal circumference varied with the magnitude of abdominal circumference; and to establish whether adding femur length to abdominal circumference caused a clinically important reduction of error in predicting birthweight.

Design A retrospective study.

Setting The ultrasound department of a teaching maternity hospital offering a tertiary referral service.

Sample From 3512 nondiabetic women with a normally formed singleton fetus, an abdominal circumference measurement of the infant was made within seven days of delivery; of these, 1213 had a femur length measurement performed at the same time.

Results There was a linear relation between abdominal circumference and birthweight. There was a strong inverse correlation between the proportional error in predicting birthweight from the abdominal circumference and the magnitude of the abdominal circumference. Both the Campbell and Wilkin equation (abdominal circumference alone) and the Hadlock equation (abdominal circumference and femur length) were associated with systematic errors, especially with larger birthweight infants. The median absolute errors for the two equations were not significantly different overall (6·98% and 6·86% respectively), although the Hadlock equation was significantly more accurate in predicting birthweight in infants weighing greater than 4500 g. However, no threshold value of abdominal circumference or of estimated fetal weight using the Hadlock equation had a positive predictive value in estimating infants of > 4500 g of greater than 35%.

Conclusions Prediction of birthweight should be by abdominal circumference alone. Table 1 presents robust estimates of the error of predicting birthweight using fetal abdominal circumference.

INTRODUCTION

Prediction of birthweight using ultrasonic examination of the fetus was first described by Campbell and Wilkin in 1975[1]. The single measurement which correlates most strongly with birthweight is fetal abdominal circumference (AC), and this is widely used as a single parameter of fetal size[2]. The definitive description relating fetal AC to birthweight is the original study of 140 fetuses which only included 11 infants < 2000 g birthweight[1,2]. These authors hypothesised that the proportional error in predicting birthweight was the same across the range of AC. However, there were insufficient numbers of infants at the extremes of birthweight to test that hypothesis.

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Some studies have used additional parameters of fetal biometry in an attempt to improve the accuracy of estimates[3]. However, given the error inherent in all techniques of predicting birthweight[2], we decided to focus on quantifying the error of the prediction rather than on obtaining small improvements in accuracy. To this end we sought to quantify the variation in birthweight in infants with a given magnitude of AC in a large population with reasonable numbers of infants at the extremes of birthweight. We also sought to test the hypothesis that the proportional error in predicting birthweight from AC is unaffected by the magnitude of the AC.

Furthermore, we sought to determine whether using additional fetal measurements did indeed cause a clinically important reduction in the error of the estimate over using AC alone. The main parameters used in other equations in addition to AC are femur length, biparietal diameter and head circumference.

Table 1. The relation between fetal abdominal circumference (AC) and birthweight (BW).

AC (mm)	*n*	Median BW (g)	10th–90th centile BW (g)	Range BW (g)
200–209	13	900	750–1030	740–1040
210–219	20	1040	830–1370	780–1400
220–229	20	1060	750–1410	650–1460
230–239	28	1255	980–1470	900–1860
240–249	36	1435	1200–1790	1080–1950
250–259	37	1580	1290–1925	1180–2260
260–269	56	1835	1490–2190	1340–2400
270–279	89	2000	1640–2320	1390–2620
280–289	134	2265	1920–2660	1530–2910
290–299	219	2530	2130–2900	1820–3100
300–309	350	2685	2340–3080	2010–3420
310–319	387	2850	2470–3290	2110–3650
320–329	484	3060	2700–3470	2350–3770
330–339	439	3260	2880–3700	2570–3980
340–349	423	3380	3040–3860	2670–4240
350–359	314	3615	3240–4040	2890–4460
360–369	245	3750	3330–4190	3020–4610
370–379	117	3840	3480–4360	3180–4790
380–389	66	4140	3660–4640	3470–4820
390–399	35	4290	3665–4675	3640–5000

We chose femur length as the additional parameter because it can usually be easily measured (unlike head circumference and biparietal diameter which can only be measured in about 35% of fetuses at term or during labour[4]) and the error of the prediction from AC and femur length is only minimally greater than using all four parameters together[3]. Of the myriad of equations available, we chose to compare the Campbell and Wilkin equation[1] (AC alone) and the Hadlock equation[5] (AC plus femur length) as these are the two recommended for use by the British Medical Ultrasound Society[2].

METHODS

Over a 10 year period the results of all ultrasound scans performed in the main department during working hours were collected in a computer database, along with comprehensive details of the given patient's medical and obstetric history and of the current pregnancy. Following delivery the database was updated with details of the labour and mode of delivery, and significant parameters of the neonate.

Measurements of AC and femur length were made on a range of ultrasound machines by trained staff in the ultrasound department using standard techniques[2]. The AC was measured directly rather than by calculation from the abdominal diameter. The femur length was measured if requested by the clinician. A measurement of AC was obtained within seven days of delivery from the infants of 3512 nondiabetic women who had had a normally formed singleton fetus. In 1213 of these infants, a measurement of femur length was also made.

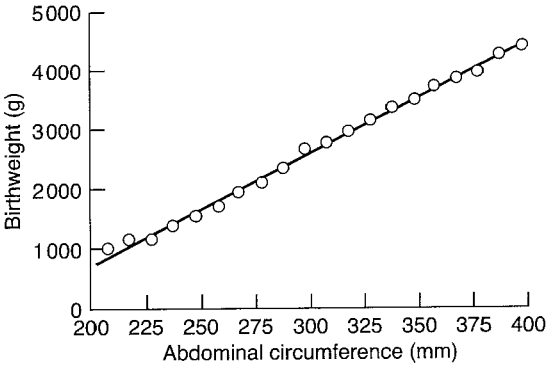

Fig. 1. Correlation between birthweight (BW) and abdominal circumference (AC). The median BW (g) for each of the groups from Table 1 is plotted against AC (mm).
Equation of line: $BW = 18{\cdot}7 \times AC - 3069$; $r^2 = 0{\cdot}996$, $P < 0{\cdot}0001$.

Statistics

The two equations compared were the Campbell and Wilkin equation using AC alone[1] and the Hadlock equation, using AC and femur length[5]. The systematic error was calculated by the signed percentage error (the difference between the birthweight and estimated birthweight expressed as a percent of birthweight). A systematic error was assumed to exist where the 95% confidence intervals of the mean percentage difference excluded zero. The absolute error (i.e. nonsigned) was summarised by the median and the interquartile range as it is, necessarily, skewed. Comparison of the absolute error was made by obtaining the difference in absolute error between the two equations for each individual patient. This was then compared with zero using a one-sample Wilcoxon signed rank test and 95% CI were obtained. Statistical analysis was performed using Minitab release 8.2 on an Apple Macintosh.

RESULTS

1. Relation between AC and birthweight

The median, 10th and 90th centiles and range of birthweight for groups of infants within a given range of AC, arranged in 10 mm increments from 200 mm, are given in Table 1. There was a very strong positive correlation between the median birthweight of each group and the AC ($r^2 = 0{\cdot}996$) (Fig. 1). The r^2 value was the same for a second order polynomial, and only very slightly greater for a third order polynomial curve (0·998). There was a strong inverse correlation

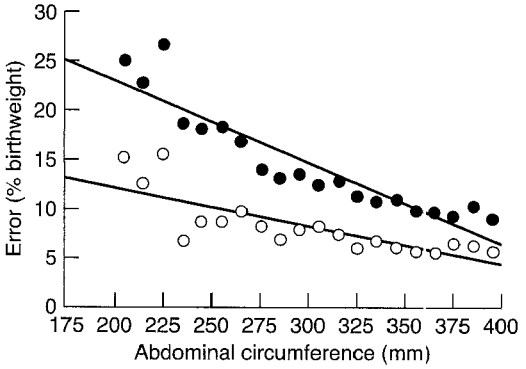

Fig. 2. The median and 75th centile of the error in predicting birthweight from abdominal circumference (AC) *versus* magnitude of AC. The population of 3512 fetuses was grouped according to AC (as in Table 1) and the difference between the predicted birthweight (from the regression line in Fig. 1) and the actual birthweight was expressed as a % of birthweight and corrected for sign (i.e. the absolute error). For each group within a given range of AC, the median absolute error (open circles) and 75th centile (filled circles) of the absolute error were calculated and plotted against AC. There was a strong inverse correlation between the magnitude of AC (mm) and both the median error and the 75th centile of the error (expressed as % of birthweight) in the groups.
Equations of lines:
Median % error = 19·96 – 0·039 × AC; $r^2 = 0{\cdot}612$, $P < 0{\cdot}0001$.
75th centile % error = 39·36 – 0·082 × AC; $r^2 = 0{\cdot}848$, $P < 0{\cdot}0001$.

between the proportional error in predicting birthweight using the simple regression equation and the magnitude of the AC (Fig. 2).

2. Comparison of Campbell and Wilkin and Hadlock equations

Standard existing equations for predicting birthweight were compared using the data from the 1213 fetuses that had both an AC and femur length measurement performed within one week of delivery. The Campbell and Wilkin equation (AC alone) was associated with a significant overestimation of birthweight between 500 and 999 g and 1500 and 2999 g and a significant underestimate of birthweight between 3500 and 4999 g (Fig. 3a). The Hadlock equation (AC and femur length) resulted in a significant underestimate of birthweight between 1000 and 1499 g and 4000 and 4999 g (Fig. 3b).

The median absolute error (i.e. nonsigned) was 6·98% (interquartile range 3·46 to 12·03) for the Campbell and Wilkin equation and 6·86% (interquartile range 3·48 to 11·66) for the Hadlock equation. The median difference in absolute error between the two equations was 0·18% of birthweight (95% CI –0·12 to 0·56, $P = 0{\cdot}314$ one-sample Wilcoxon signed rank). The median error was significantly less for the Hadlock equation between 500 and 1499 g, 2000 and 2499 g, and 4000 and 4999 g; significantly less for

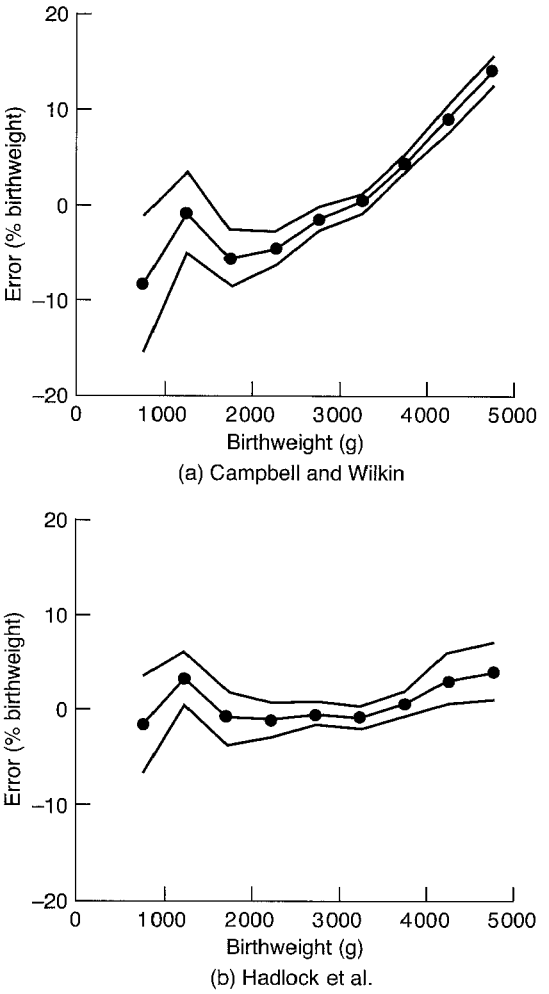

Fig. 3. The mean and 95% confidence intervals of the signed proportional error in predicting birthweight (BW) from abdominal circumference *versus* $BW^{1.5}$. The difference between the actual and predicted BW was obtained for a given equation and expressed as a percent of BW (signed error). The data are analysed according to the eventual BW, being grouped by 499 g increments from 500 g. The mean and 95% confidence intervals of the signed error for each group have been plotted. A positive value indicates underestimation and a negative value overestimation of BW. Where the confidence intervals exclude zero, a statistically significant error is assumed. $n = 1213$. The middle line is the mean and the lines above and below are the 95% the confidence intervals.
(a) Campbell and Wilkin equation[1]:
$\log_e(BW) = -4{\cdot}564 + 0{\cdot}0282(AC) - 0{\cdot}0000331(AC)^2 + \log_e 1000$.
(b) Hadlock *et al.* equation[5]:
$\log_{10}(BW) = 1{\cdot}304 + 0{\cdot}05281(AC) + 0{\cdot}1938(FL) - 0{\cdot}004(AC \times FL)$.

the Campbell and Wilkin equation between 3000 and 3999 g; and not significantly different between the two equations between 1500 and 1999 g and 2500 and 2999 g (Fig. 4). The only weight range where the median difference in error between the two equations exceeded 5% of birthweight was in the range 4500 and 4999 g, where the Hadlock equation was associated with a median reduction in error of 9·00% of

Table 2. Diagnostic efficacy of threshold abdominal circumference and Hadlock-estimated fetal weights in predicting macrosomia (birthweight > 4500 g). Values are % (*n*). EFW = estimated fetal weight predicted by Hadlock equation[5]; PPV = positive predictive value; NPV = negative predictive value.

AC (mm)	EFW (g)	Sensitivity	Specificity	PPV	NPV
≥360	—	100 (16/16)	88 (1055/1197)	10 (16/158)	100 (1055/1055)
≥370	—	94 (15/16)	94 (1130/1197)	18 (15/82)	>99 (1130/1131)
≥380	—	69 (11/16)	98 (1170/1197)	29 (11/38)	>99 (1170/1175)
≥390	—	31 (5/16)	99 (1187/1197)	33 (5/15)	99 (1187/1198)
	≥3750	100 (16/16)	86 (1033/1197)	9* (16/180)	100 (1033/1033)
	≥4000	94 (15/16)	93 (1113/1197)	15* (15/99)	>99 (1113/1114)
	≥4250	88 (14/16)	97 (1161/1197)	28 (14/50)	>99 (1161/1163)
	≥4500	44 (7/16)	99 (1181/1197)	30 (7/23)	99 (1181/1190)
	≥4750	6 (1/16)	>99 (1194/1197)	25 (1/4)	99 (1194/1209)

*When confined to infants with an AC ≥ 360 mm, the PPV for an EFW ≥ 3750 was 12% (16/139) and for ≥ 4000 was 15% (16/97). The PPV for the other thresholds were unchanged.

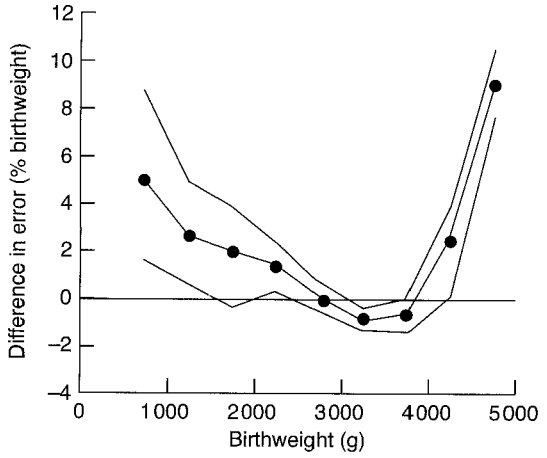

Fig. 4. The median and 95% confidence intervals of the difference in absolute error between the Campbell and Wilkin and Hadlock equations in predicting birthweight. For a given fetus the difference between the estimated and actual birthweight was calculated, changed to a positive sign if negative, and expressed as a percentage of birthweight (absolute error). The % error of the Hadlock equation was subtracted from that of the Campbell and Wilkin equation. The data are summarised according to the same birthweight groups as Fig. 3. The median difference was calculated and the 95% confidence interval of the difference obtained from a one sample Wilcoxon signed rank test. A positive value indicates a greater error with the Campbell and Wilkin equation and a negative value a greater error with the Hadlock equation. Where the confidence intervals exclude zero, a statistically significant difference is assumed. $n = 1213$. The middle line is the median and the lines above and below are the 95% confidence intervals.

birthweight compared with the Campbell and Wilkin equation (95% CI 7·66 to 10·44, $P < 0·0001$, one-sample Wilcoxon signed rank).

3. Prediction of macrosomia

The sensitivity, specificity, and positive and negative predictive values in predicting a birthweight > 4500 g for threshold levels of AC or estimated fetal weight (Hadlock equation) are given in Table 2.

DISCUSSION

There are a number of areas of obstetric practice where prediction of birthweight is deemed important, such as contemplating vaginal breech delivery[6] and in predicting the outcome of preterm delivery[7]. Some would argue that the potential for large individual errors renders such estimates of little value. Clearly, where used, the error attached to the estimate is of critical importance.

It had previously been hypothesised that the proportional error in estimating birthweight from fetal AC alone was the same across the range of abdominal circumference[1]. Our data (Fig. 2) indicate that the proportional error increases significantly with decreasing fetal AC. The underestimate of the variation in birthweight within a range of AC in smaller infants using existing data[1] may lead to clinically important errors. It has been stated that fetuses with an AC between 210 and 219 mm would be almost 95% certain to be < 1000 g[1], whereas our 10th and 90th centiles for this range of AC were much wider (830 and 1370 g) and, indeed, 55% of infants within this range of fetal AC had a birthweight > 1000 g (Table 1). We propose that the data in Table 1 should replace the currently recommended tabular data relating fetal AC to birthweight[2]. We also propose that estimates of birthweight should be accompanied by the 10th and 90th centiles of the estimate to aid the clinician in interpreting the information.

Regarding the mathematical relation between AC and birthweight, the original study[1] proposed that it was best modelled using a third order polynomial equation of $\log_e$ (birthweight) *versus* AC. Our data (Fig. 1) illustrates that the relation between fetal AC and birthweight in the range studied is linear. The original study[1] plotted a line through a scatter of their raw data. As most of their infants' birthweight was > 2000 g, the equation will have been modelled to minimise error in this group. Use of the medians of

each group means that our mathematical model is determined equally across the range of AC. This may account for the different relation observed.

A number of small studies have demonstrated that adding femur length to AC in equations to predict birthweight reduces the error by about 5%[2]. However, in our group of 1213 fetuses who had both an AC and femur length measurement within seven days of delivery, we found no significant difference in the median error of the prediction between the currently recommended equations[2] comparing AC alone[1] with AC plus femur length[5].

When analysed according to eventual birthweight, there was only one group where one equation was associated with a median improvement in accuracy of > 5% of birthweight, namely, using the Hadlock equation in infants with an eventual birthweight > 4500 g. No fetus with an AC < 360 mm had a birthweight > 4500 g (Table 1). It could be argued, therefore, that any fetus with an AC > 360 mm should also have a femur length measured to improve the prediction of macrosomia. To test how useful this might be clinically, we calculated the sensitivity, specificity, and positive and negative predictive values of threshold levels of AC and estimated fetal weight in predicting a birthweight > 4500 g (Table 2). No level of AC alone or Hadlock estimated fetal weight had a positive predictive value of > 35%. The decreased error in this range of birthweight with the Hadlock equation is reflected by the slightly better sensitivities for a given positive predictive value compared with AC alone, but we would conclude from these data that neither technique adequately indicates the strong likelihood of macrosomia or detects a sufficient proportion of macrosomic infants to be clinically useful in this context.

We conclude that when attempting to predict birthweight from a single scan, it should be done by AC alone and that the prediction should be accompanied by the 10th and 90th centile of the estimate. The currently recommended tabular data relating AC to birthweight[2] may lead to an underestimate in the error of the prediction in low birthweight infants. We present a revised table for routine clinical use which provides robust estimates of the error in predicting birthweight from a single measurement of AC (see Table 1).

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SHORT COMMUNICATION

Estimating human fetal blood volume on the basis of gestational age and fetal abdominal circumference

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Introduction

Intravascular transfusion of the human fetus is now a standard procedure for the management of fetal anaemia both due to allo-immunisation and parvovirus infection. The volume of blood required to correct a given degree of anaemia depends on the fetal blood volume as well as the severity of the anaemia. While the latter can be measured directly at the time of cordocentesis, the fetal blood volume is estimated on the basis of an empirically derived equation using the relationship between the volume of blood per kilogram of weight at each week of gestation and assuming that the fetus is on the 50th percentile of weight for the given gestational age[1]. In the present study, we sought to test the hypothesis that combining gestational age with an ultrasonic estimate of fetal weight might improve the ability to predict fetal blood volume and thus the post-transfusion haematocrit (Hct).

Methods

Inclusion criteria

Over the period 1992–2000, we obtained case records of pregnancies where fetal intrauterine transfusion had been performed in our unit in the management of fetal anaemia secondary to allo-immunisation. From these records, transfusion details were obtained where an ultrasound scan performed within seven days of the transfusion had recorded an abdominal circumference (measured using standard techniques[2]) and the baby was not affected by hydrops. We identified a total of 280 transfusions in 91 pregnancies where these criteria were met and where the donor, pre- and post-transfusion Hct, and volume of donor blood transfused had been recorded. The criteria were met and complete data were available for approximately 80% of the procedures.

Clinical procedure

Fetal blood transfusions were only included where the blood was administered through an intravascular route (usually the umbilical vein). The Hct prior and following transfusion was estimated from a 2-mL sample using a Coulter counter.

Analysis

The estimated blood volume (EBV) in millilitres (mL) was calculated from the following equation[1]:

$$\mathrm{EBV} = (\mathrm{DonVol} * (\mathrm{DonHct} - \mathrm{PostHct}) + 2 * (\mathrm{PostHct} - \mathrm{PreHct}))/(\mathrm{PostHct} - \mathrm{PreHct}) \quad (1)$$

where: DonVol = volume of donor blood transfused; DonHct = Hct of donor blood; PreHct = Hct preceding transfusion; PostHct = Hct following transfusion.

Regression equations were then constructed to estimate the blood volume from the gestational age and/or the abdominal circumference in a randomly selected subset of 154 transfusions. The ability of these equations to predict post-transfusion Hct was then compared with the Nicolaides *et al.*'s equation[1] in the remaining 126 cases. Statistical analysis was performed using Stata version 6.0 for the PC.

Results

In a sample of 154 cases, regression analysis was performed to derive equations which would predict the fetal blood volume on the basis of (1) gestational age, (2) abdominal circumference, and (3) gestational age and the

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abdominal circumference. Preliminary analysis demonstrated that the relationship between both gestational age and abdominal circumference was linear. On the basis of these equations, the post-transfusion Hct on a further 126 cases was predicted. The difference (unsigned) between the actual post-transfusion Hct in the 126 cases and the value predicted from regression equations derived from the other 154 cases was compared. The magnitude of the difference was virtually identical when the equation was based on gestational age alone (median difference = 1.60 [interquartile range 0.78–3.07]), abdominal circumference alone (1.76 [0.90–3.31]), both gestational age and abdominal circumference (1.62 [0.75–3.24]), or when the post-transfusion Hct was estimated using the Nicolaides *et al.* equation[1] (1.74 [0.72–3.26]). The differences were virtually identical when gestational age and abdominal circumference were modelled as second-order polynomials (data not shown).

Equations were then derived from the whole population to predict fetal blood volume from the gestational age (Fig. 1A) or from the fetal abdominal circumference (Fig. 1B).

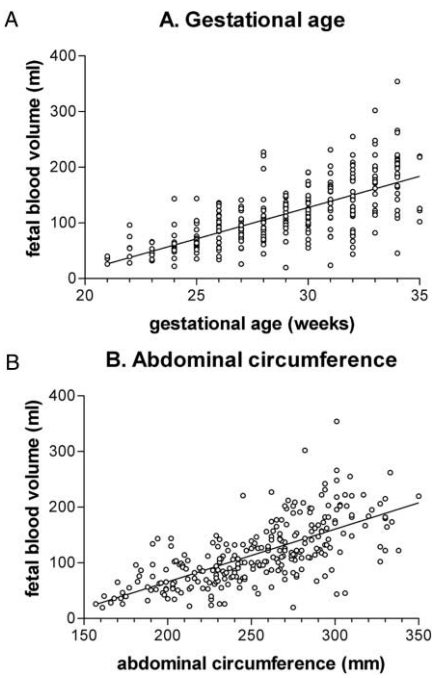

Fig. 1. Linear regression analysis of relationship between estimated fetal blood volume (EFBV) at the time of intrauterine transfusion and (A) gestational age in weeks and (B) fetal abdominal circumference. Equations: (a) EFBV = (11.2***GA***) − 209.4; (b) EFBV = (0.95***AC***) − 123.4, where EFBV is measured in millilitres, gestational age is measured in completed weeks, and abdominal circumference is measured in millimetres.

Discussion

The principle aim of the present study was to determine whether incorporation of an ultrasonic index of fetal size improved the empirical prediction of fetal blood volume. We found that a model combining abdominal circumference and gestational age did not result in a better prediction of the post-transfusion Hct than using either parameter on its own. In practice, most cases with Rhesus allo-immunisation in the UK will have an accurate estimate of gestational age based on early ultrasound. However, in the event that a women books late for antenatal care and requires fetal blood transfusion, we suggest that the equation described in Fig. 1B should provide a similar level of accuracy to current methods for estimating post-transfusion Hct. Finally, current methods for estimating the amount of blood to transfuse require the use of standard curves. We propose the following simple spreadsheet equations to estimate the volume of blood required using gestational age alone:

$$((E - A)/(B - E)) * (F - D) \quad (2)$$

In cases where the gestational age is not known with certainty, the following equation allows the volume of blood required for transfusion on the basis of the abdominal circumference alone:

$$((E - A)/(B - E)) * (H - D) \quad (3)$$

where: A = pre-transfusion Hct (%); B = Hct of donor blood (%); C = gestational age (weeks); D = sample volume (mL); E = target Hct (typically 40%—allows for overtransfusion); F = estimated fetal blood volume (mL) on the basis of gestational age = $(11.2C) - 209.4$; G = abdominal circumference (mm); H = estimated fetal blood volume (mL) on the basis of abdominal circumference = $(0.95G) - 123.4$.

These equations should only be used when the gestational age is between 21 and 35 weeks (Equation 2) or where the abdominal circumference is between 160 and 340 mm (Equation 3) and there is no hydrops.

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FIRST-TRIMESTER GROWTH AND THE RISK OF LOW BIRTH WEIGHT

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ABSTRACT

Background Previous studies have demonstrated a correlation between first-trimester size and birth weight. It is not known, however, whether low birth weight is related to first-trimester growth. We sought to determine whether the risk of low birth weight and birth weight that was low for gestational age is related to the size of the embryo or the fetus in the first trimester.

Methods From a data base of ultrasound records of more than 30,000 pregnancies, we identified women who had no important medical problems, a normal menstrual history, and a first-trimester ultrasound scan in which the crown–rump length of the embryo or fetus had been measured. We examined the relation between the outcome of 4229 pregnancies and the difference between the measured and the expected crown–rump length in the first trimester, expressed as equivalent days of growth.

Results A first-trimester crown–rump length that was two to six days smaller than expected was associated with an increased risk (as compared with a normal or slightly larger than expected crown–rump length) of a birth weight below 2500 g (relative risk, 1.8; 95 percent confidence interval, 1.3 to 2.4), a birth weight below 2500 g at term (relative risk, 2.3; 95 percent confidence interval, 1.4 to 3.8), a birth weight below the fifth percentile for gestational age (relative risk, 3.0; 95 percent confidence interval, 2.0 to 4.4), and delivery between 24 and 32 weeks of gestation (relative risk, 2.1; 95 percent confidence interval, 1.1 to 4.0), but not with delivery between 33 and 36 weeks (relative risk, 1.0; 95 percent confidence interval, 0.7 to 1.5).

Conclusions Suboptimal first-trimester growth may be associated with low birth weight, low birthweight percentile, and premature delivery. (N Engl J Med 1998;339:1817-22.)

LOW birth weight (less than 2500 g) and birth weight that is low for gestational age are associated with increased perinatal morbidity and mortality,[1] short- and long-term childhood morbidity and mortality,[2,3] and a range of cardiovascular and metabolic diseases in later life.[4] Consequently, the factors determining birth weight (other than gestational age) have been the focus of intense study for many years, and the risk factors for low birth weight at term have been reviewed in detail.[5]

It has previously been suggested that variations in fetal size are largely determined in the second half of pregnancy.[6] However, a 1993 study demonstrated a correlation between first-trimester crown–rump length and birth weight.[7] We tested the hypothesis that a smaller-than-expected crown–rump length in the first trimester is associated with low birth weight and birth weight that is low for gestational age.

METHODS

Source of Data

The results of all ultrasound scans obtained between 1985 and 1995 at the Queen Mother's Hospital, Glasgow, United Kingdom, were entered into a computer data base along with details of the women's medical, gynecologic, and obstetrical history, antenatal complications, and pregnancy outcome. The data base included all pregnant women referred for antenatal care, because all underwent ultrasonography at their first antenatal visit.

Over the 10-year period, 31,269 embryos or fetuses with a known date of delivery were scanned at least once. The gestational age at delivery was recorded for 31,259, and birth weight was recorded for 30,789. Of the 480 infants for whom birth weight was missing, 460 were delivered at less than 24 weeks.

We excluded pregnancies in which any of the following was present or had occurred: a history of rhesus isoimmunization (279 cases), essential hypertension (324 cases), cardiac disease (128 cases), type 1 diabetes mellitus (115 cases), other medical problems (992 cases), nonviable embryo or fetus at first scanning (115 cases), amniocentesis (1259 cases), chorionic-villus sampling (929 cases), multiple pregnancy (364 cases), antenatal detection of fetal abnormality (515 cases), therapeutic termination of pregnancy (224 cases), postnatal detection of fetal abnormality (560 cases), intrauterine contraceptive device seen on ultrasonography (42 cases), and second sac seen on ultrasonography (85 cases). There were a total of 4568 exclusions (some cases had multiple reasons for exclusion).

The crown–rump length was measured by the sonographer using electronic calipers on a frozen image on a monitor.[8] The crown–rump length was converted to the equivalent number of days of gestational age on the basis of the following equation:

$$\text{gestational age in days} = 8.052\sqrt{\text{crown–rump length in millimeters}} + 23.73.$$

The equation had been previously derived at the Queen Mother's Hospital with static ultrasonography[9] and subsequently validated with real-time scanners (both transabdominal[10] and transvaginal[11,12]). It is currently recommended by the British Medical Ultrasound Society for first-trimester estimation of gestational age.[8] The scans analyzed in the present study were obtained by real-time ultrasonography with several machines; the majority were transabdominal scans through a full urinary bladder.

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The inclusion criteria based on the ultrasonographic record were a single viable embryo or fetus present when the first ultrasound scan was obtained and a crown–rump length at the time of this scan that was less than the expected size in women who had had amenorrhea for 13 weeks. These criteria were fulfilled by 11,314 of the 26,701 nonexcluded cases.

The inclusion criteria from the menstrual history were that there was a date recorded for the first day of the last menstrual period and that it was recorded as certain, that the woman had not taken an oral contraceptive in the preceding 3 months, and that she had a regular 28-day menstrual cycle. Of the 11,314 women with no exclusion criteria who had an early ultrasound scan, 4229 fulfilled the menstrual inclusion criteria and had had their infants' birth weights recorded.

Analysis of the Data

The aim of the analysis was to relate first-trimester growth to the outcome of the pregnancy. The difference between the actual and predicted crown–rump length was expressed in days of gestation — that is, the estimated age in postmenstrual days according to crown–rump length minus the number of days of amenorrhea (i.e., the number of days since the beginning of the last menstrual period). A negative difference indicated an embryo (up to eight weeks of postconception age) or a fetus (after eight weeks of postconception age) that was smaller than expected. In pregnancies with a known date of conception through in vitro fertilization, the crown–rump length expressed in this way has 95 percent confidence intervals of approximately five to six days of postconception age in the first trimester.[13] Therefore, our analysis focused on the 3397 embryos and fetuses in which the difference was between −6 and +6 days, because larger differences were unlikely to be due to variations in growth. Similarly, in the management of these pregnancies, the estimated gestational age was only altered on the basis of the crown–rump length when the difference was outside this range. Variation outside this range is presumably due to deviation of the time of ovulation from the assumed day 14 or to incorrect recollection of the menstrual history. A normal crown–rump length was defined as a value one day or less above or below the expected value (−1 to +1), because this is approximately equivalent to the standard deviation of repeated measurements in the first trimester.[9]

Low birth weight was defined as birth weight below 2500 g, and low birth weight at term was defined as birth weight below 2500 g at 37 or more weeks of gestation. Birth weight was also classified as above or below the fifth percentile for gestational age. Term was defined as at least 37 weeks of gestation, and preterm deliveries were subdivided into two groups — those at 24 to 32 weeks of gestation and those at 33 to 36 weeks of gestation.

Measurement of Maternal Serum Alpha-Fetoprotein

Maternal serum alpha-fetoprotein was measured between 15 and 20 weeks of gestation and quantified as multiples of the median for a given gestational age.[14] These values were not corrected for maternal stature, since the data base contained only the analyte values.

Birth-Weight Percentiles

The birth-weight percentiles we used were derived from 120,250 live births in Scotland before 1985. A description of the collection and analysis of data on 55,387 live births between 1975 and 1979 has been published.[15]

Statistical Analysis

Numerical data were summarized as medians and interquartile ranges, and groups were compared with the Mann–Whitney U test. Proportions were compared with use of Fisher's exact test (two-tailed) and relative risks and 95 percent confidence intervals. The effect of multiple variables on dichotomous outcomes was analyzed by logistic-regression analysis. Statistical analysis was performed with the Stata software package (release 5.0 for Windows NT, Stata, College Station, Tex.).

RESULTS

The distribution of the differences between the values for observed and expected crown–rump length was skewed toward negative values: the mode was 0 days, the median was −1 day, and the interquartile range was −4 to 0 days. When the comparison was made between embryos or fetuses that were smaller than expected, approximately as large as expected, and larger than expected, there were significant differences in the proportions of infants with low birth weight (<2500 g), low birth weight at term (<2500 g at 37 or more weeks), birth weight below the fifth percentile for gestational age, delivery between 24 and 32 weeks, and birth weight greater than 4000 g (Table 1). The association between smaller-than-expected crown–rump length and low birth weight was significant in pregnancies with values of −7 to −2 for the number of days of difference between observed and expected length (Fig. 1).

The proportions with these outcomes in the groups with larger-than-expected (+2 to +6 days) and normal (−1 to +1 day) crown–rump lengths were similar (Table 1). These two groups were therefore pooled to form the reference group. As compared with this group, embryos or fetuses with a smaller-than-expected crown–rump length (−6 to −2 days) had an increased risk of low birth weight, low birth weight at term, birth weight below the fifth percentile for gestational age, and delivery between 24 and 32 weeks, but not delivery between 33 and 36 weeks (Table 2). The associations were still significant when gestational age at delivery was calculated from the crown–rump length rather than from the last menstrual period (Table 2). The relative risks were of similar magnitude and statistical significance when the normal group (−1 to +1 day) was used as the reference group.

A smaller-than-expected crown–rump length was associated with an increase of borderline significance in the risk of an elevated maternal serum alpha-fetoprotein concentration in the second trimester ($P=0.09$) (Table 2). An elevated maternal serum alpha-fetoprotein concentration was significantly associated with low birth weight, low birth weight at term, and premature delivery among embryos or fetuses with smaller-than-expected crown–rump lengths (Table 3).

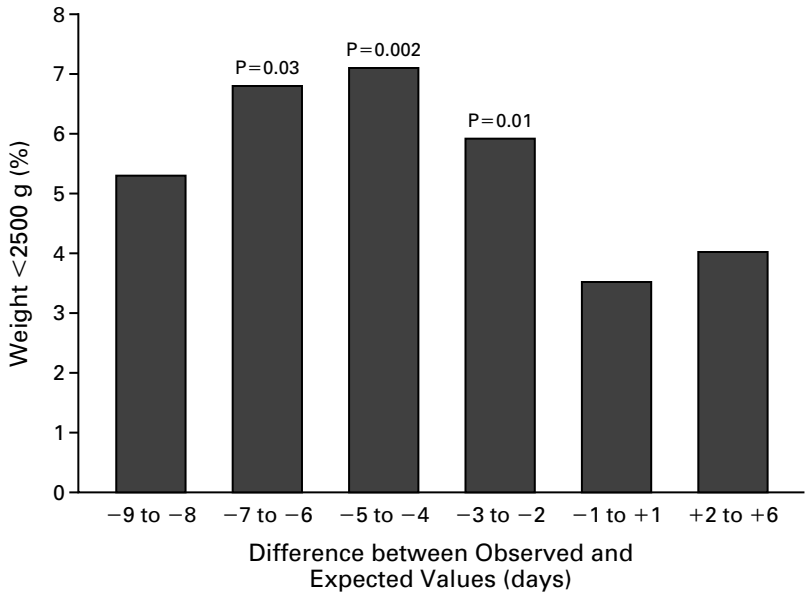
A smaller-than-expected crown–rump length was associated with several other potential risk factors for low birth weight (Table 4). Furthermore, the proportion of embryos or fetuses with smaller-than-expected crown–rump lengths was slightly higher

TABLE 1. ADVERSE OUTCOMES ACCORDING TO THE DIFFERENCE BETWEEN OBSERVED AND EXPECTED FIRST-TRIMESTER CROWN–RUMP LENGTHS.

OUTCOME	CROWN–RUMP LENGTH*			P VALUE†
	SMALLER THAN EXPECTED	NORMAL	LARGER THAN EXPECTED	
	% (no. with outcome/no. without outcome)			
Birth weight <2500 g	6.4 (83/1206)	3.5 (53/1461)	4.0 (24/570)	0.001
Birth weight <2500 g at ≥37 wk	2.9 (38/1251)	1.3 (20/1494)	1.2 (7/587)	0.004
Birth weight <5th percentile	5.0 (65/1224)	1.6 (24/1490)	2.0 (12/582)	<0.001
Birth weight >4000 g	9.2 (119/1170)	11.5 (174/1340)	12.8 (76/518)	0.04
Delivery at 24–32 wk	1.7 (22/1267)	0.7 (11/1503)	1.0 (6/587)	0.05
Delivery at 33–36 wk	3.9 (50/1239)	3.6 (55/1459)	3.9 (23/570)	0.93

*Crown–rump length was expressed as equivalent days of growth. Smaller than expected was −6 to −2 days, normal −1 to +1 day, and larger than expected +2 to +6 days.

†P values are for the comparison of proportions in the three groups by Fisher's exact test. Gestational age at delivery was calculated from the last menstrual period.



NO. OF INFANTS						
Weight <2500 g	8	14	33	44	53	24
Weight ≥2500 g	142	191	429	705	1461	570

Figure 1. Proportion of Infants with Birth Weights of Less Than 2500 g According to the Difference between Observed and Expected First-Trimester Crown–Rump Lengths.

P values are for the comparison with the group with normal crown–rump length (−1 to +1 day) by Fisher's exact test (two-tailed). The proportion of infants with low birth weight in the pooled group for whom the difference was −9 to +6 days was not significantly different from the proportion of infants for whom the difference was less than −9 days (32 of 492; P=0.12) or greater than +6 days (2 of 63; P=0.77). The crown–rump length was expressed as equivalent days of growth.

TABLE 2. RELATIVE RISKS ASSOCIATED WITH A SMALLER-THAN-EXPECTED FIRST-TRIMESTER CROWN–RUMP LENGTH.

OUTCOME	CROWN–RUMP LENGTH*		RELATIVE RISK (95% CI)†	P VALUE‡
	SMALLER THAN EXPECTED	NORMAL OR LARGER THAN EXPECTED		
	no. with outcome/ no. without outcome			
Birth weight <2500 g	83/1206	77/2031	1.8 (1.3–2.4)	<0.001
Birth weight <2500 g at ≥37 wk according to last menstrual period	38/1251	27/2081	2.3 (1.4–3.8)	<0.001
Birth weight <2500 g at ≥37 wk according to crown–rump length	33/1256	26/2081	2.1 (1.2–3.5)	0.006
Birth weight <5th percentile according to last menstrual period	65/1224	36/2072	3.0 (2.0–4.4)	<0.001
Birth weight <5th percentile according to crown–rump length	45/1244	42/2066	1.8 (1.2–2.7)	0.01
Alpha-fetoprotein >2× median§	41/1050	44/1657	1.5 (1.0–2.2)	0.09
Emergency cesarean section	120/1169	204/1904	1.0 (0.8–1.2)	0.76
Perinatal death	3/1286	6/2102	0.8 (0.2–3.3)	1.0
Delivery at 24–32 wk according to last menstrual period	22/1267	17/2090	2.1 (1.1–4.0)	0.02
Delivery at 24–32 wk according to crown–rump length	23/1266	17/2091	2.2 (1.2–4.1)	0.01
Delivery at 33–36 wk according to last menstrual period	50/1239	78/2029	1.0 (0.7–1.5)	0.78

*Crown–rump length was expressed as equivalent days of growth. Smaller than expected was −6 to −2 days, and normal or larger than expected −1 to +6 days.

†CI denotes confidence interval.

‡P values are for the comparison between groups by a two-tailed Fisher's exact test.

§Testing of alpha-fetoprotein was optional; 82 percent of the patients elected to have the test performed.

TABLE 3. OCCURRENCE OF ADVERSE OUTCOMES ACCORDING TO MATERNAL SERUM ALPHA-FETOPROTEIN LEVEL AND THE DIFFERENCE BETWEEN OBSERVED AND EXPECTED CROWN–RUMP LENGTHS.*

OUTCOME	SMALLER-THAN-EXPECTED LENGTH				NORMAL OR LARGER-THAN-EXPECTED LENGTH			
	ELEVATED AFP	NORMAL AFP	RR (95% CI)	P VALUE†	ELEVATED AFP	NORMAL AFP	RR (95% CI)	P VALUE†
	no. with outcome/ no. without outcome				no. with outcome/ no. without outcome			
Birth weight <2500 g	8/33	58/992	3.5 (1.8–6.9)	0.002	2/42	64/1593	1.2 (0.3–4.7)	0.69
Birth weight <2500 g at ≥37 wk	4/37	24/1026	4.3 (1.6–11.7)	0.02	1/43	25/1632	1.5 (0.2–10.9)	0.50
Delivery at 24–32 wk	3/38	15/1035	5.1 (1.5–17.0)	0.03	1/43	13/1644	2.9 (0.4–21.7)	0.31

*AFP denotes maternal serum alpha-fetoprotein, RR relative risk, and CI confidence interval. Crown–rump length was expressed as equivalent days of growth. Smaller than expected was −6 to −2 days, and normal or larger than expected −1 to +6 days. An elevated alpha-fetoprotein level was defined as a level more than two times the median.

†P values are for the comparison between groups by a two-tailed Fisher's exact test.

for scans performed before the 10th week of amenorrhea than for scans performed later: 42 percent (261 of 622) as compared with 37 percent (1028 of 2775) (P=0.02). However, the relations between first-trimester growth and these outcomes were still significant in multivariate logistic-regression analyses that included a number of other risk factors and early ultrasound studies as covariates (Table 5).

DISCUSSION

The central findings of our study are that there is a significant relation between smaller-than-expected size in the first trimester and low birth weight (<2500 g), birth weight that is low for gestational age, and extremely premature delivery (24 to 32 weeks) among otherwise normal babies. Restricted growth of the embryo or fetus in very early preg-

TABLE 4. FREQUENCY OF POSSIBLE RISK FACTORS FOR LOW BIRTH WEIGHT AND LOW WEIGHT FOR GESTATIONAL AGE ACCORDING TO THE DIFFERENCE BETWEEN OBSERVED AND EXPECTED FIRST-TRIMESTER CROWN–RUMP LENGTHS.

RISK FACTOR	CROWN–RUMP LENGTH*		P VALUE†
	SMALLER THAN EXPECTED (N=1289)	NORMAL OR LARGER THAN EXPECTED (N=2108)	
	median (interquartile range)		
Mother's age (yr)	28 (25–31)	27 (24–30)	<0.001
Gestational age at time of ultrasound scan (days)			
According to last menstrual period	83 (72–89)	81 (73–86)	<0.001
According to crown–rump length	79 (74–87)	82 (74–87)	<0.001
Parity	1 (0–1)	1 (0–1)	0.17
No. of previous spontaneous abortions	0 (0–0)	0 (0–0)	0.77
No. of previous therapeutic abortions	0 (0–0)	0 (0–0)	0.74
	% (no.)		
Mother's age, <20 yr	5.2 (67)	3.3 (69)	0.007
Mother's age, >40 yr	0.0 (0)	0.2 (5)	0.16
Mother nulliparous	48.3 (622)	45.2 (952)	0.08
Parity >3	1.8 (23)	1.7 (36)	0.89
Bleeding			
1st trimester	10.9 (141)	9.0 (189)	0.06
2nd trimester	3.2 (41)	2.6 (55)	0.34
3rd trimester	5.2 (67)	4.6 (98)	0.51
Pregnancy-induced hypertension	10.9 (141)	11.1 (235)	0.87
Elective delivery	28.7 (370)	23.3 (491)	<0.001
Male infant	49.4 (637)	52.2 (1101)	0.11

*Crown–rump length was expressed as equivalent days of growth. Smaller than expected was −6 to −2 days, and normal or larger than expected −1 to +6 days.

†Medians were compared by the Mann–Whitney U test, and proportions by Fisher's exact test (two-tailed).

TABLE 5. ADJUSTED ODDS RATIOS FOR ADVERSE OUTCOMES ASSOCIATED WITH A SMALLER-THAN-EXPECTED CROWN–RUMP LENGTH.*

OUTCOME	ADJUSTED ODDS RATIO (95% CI)	P VALUE
Birth weight <2500 g	1.7 (1.2–2.3)	0.002
Birth weight <2500 g at ≥37 wk	2.1 (1.3–3.5)	0.004
Birth weight <5th percentile	2.8 (1.9–4.3)	<0.001
Delivery at 24–32 wk	2.0 (1.1–4.0)	0.03

*The logistic-regression models included age; parity; previous spontaneous abortions; previous therapeutic abortions; bleeding in the first, second, and third trimesters; pregnancy-induced hypertension; elective delivery; fetal sex; and ultrasound scanning before 10 weeks. The adjusted odds ratio associated with a smaller-than-expected crown–rump length (difference from expected, −6 to −2 days) is with reference to the pooled group with either normal crown–rump length (−1 to +1 day) or a larger-than-expected crown–rump length (+2 to +6 days). CI denotes confidence interval.

nancy may be causally related to these outcomes. However, given the highly selected nature of the pregnancies in which these measurements can be made, the proportion of these outcomes that might be attributed to first-trimester growth in the general population is not known.

In our study, unlike studies of conceptions by means of in vitro fertilization, the exact postconception age at the time of ultrasonography was unknown. The size of the embryo or fetus in the first trimester may also differ from the expected size because of variation in the timing of ovulation. If ovulation occurred on day 17 and was followed by normal conception, implantation, and growth, the fetus would be the equivalent of 3 days smaller than would be expected if ovulation had taken place on day 14. If this fetus was then born 41 weeks after the last menstrual period, gestational age would be the postconception equivalent of 40 weeks and 4 days, but the infant's birth weight would be judged by the 41-week percentile. However, the relations of a smaller-than-expected crown–rump length with low birth weight at term and birth weight below the fifth percentile were still significant when gestational age at delivery was calculated from the crown–rump length.

We found that the risk of low birth weight was lowest among embryos or fetuses with a normal or larger-than-expected crown–rump length (difference from expected of −1 to +6 days). The risk of low birth weight was increased when the difference between the observed and expected crown–rump length was −7 to −2 days. Outside this range, the risk of low birth weight was similar to the average for the whole group. We interpret this pattern to mean that when the differences between observed and expected crown–rump length are large, the measurement gives little information about the growth of the embryo or fetus, because large differences are most likely due to an incorrectly estimated postconception age that largely obscures the variation related to growth.[7,13] Therefore, the risk of low birth weight is similar to the average. In groups with moderately negative values (−7 to −2 days), there is a greater proportion of cases in which the embryo or fetus is smaller than expected because of below-average growth, and therefore the risk of low birth weight is higher. However, as the difference between the observed and expected sizes nears zero and then becomes positive, the proportion of cases in which the growth of the embryo or fetus is suboptimal is smaller, and therefore the risk of low birth weight is lower.

The distribution of the difference between observed and expected crown–rump length was skewed toward negative values. This is unlikely to be due to an error in the equation used, since the mode of the difference was zero, and 36 percent of measurements were within ±1 day of the estimated value. The skewing is more likely to be due to a skewing

in the timing of ovulation toward the second half of the cycle.[16] It may also be related to skewing in the distribution of embryonic or fetal size toward small stature.

The prediction of adverse outcome by a smaller-than-expected crown–rump length was additive with the predictive power of a high maternal serum alpha-fetoprotein concentration in the second trimester (Table 3). The apparent lack of a significant relation between maternal serum alpha-fetoprotein concentrations and adverse outcomes in cases involving normal or larger-than-expected crown–rump lengths may be due to the small number of adverse outcomes in this group.

If there is a causal relation between poor first-trimester growth and low birth weight, it may be that a suboptimal environment in the first trimester limits fetal growth for the remainder of pregnancy. Alternatively, poor growth in the first trimester may be secondary to a disorder of placentation that is manifested throughout pregnancy by suboptimal transfer of nutrients to the fetus. It also seems likely that some fetuses may be physiologically small throughout pregnancy.

The association between a smaller-than-expected crown–rump length and delivery between 24 and 32 weeks, but not between 33 and 36 weeks, is consistent with the hypothesis that the pathophysiology of extremely premature delivery may be different from that of moderately premature delivery.[17] Furthermore, it suggests that in at least a proportion of cases, extremely premature delivery may be the result of a chronically suboptimal intrauterine environment, a possibility that is consistent with the results of other studies of the causes of premature delivery.[18]

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ORIGINAL ARTICLE

Cervical Length at Mid-Pregnancy and the Risk of Primary Cesarean Delivery

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ABSTRACT

BACKGROUND

Physiological and biochemical studies suggest that normal parturition at term is dependent on programmed development of the uterus in early pregnancy. It is recognized that a short cervix in mid-pregnancy is associated with an increased risk of spontaneous preterm birth. We hypothesized that a long cervix in mid-pregnancy would be associated with an increased risk of cesarean delivery during labor at term.

METHODS

We studied 27,472 primiparous women who had a cervical length of 16 mm or more at a median of 23 weeks of gestation and who ultimately delivered a live infant in labor at term.

RESULTS

The rate of cesarean delivery at term was lowest (16.0%) among women with a mid-pregnancy cervical length in the lowest quartile (16 to 30 mm) and was significantly greater in the second quartile (18.4%, 31 to 35 mm), third quartile (21.7%, 36 to 39 mm), and fourth quartile (25.7%, 40 to 67 mm) (P<0.001 for trend). The odds ratio for cesarean delivery among women in the fourth quartile, as compared with the first quartile, was 1.81 (95% confidence interval [CI], 1.66 to 1.97), and the odds ratio adjusted for maternal age, body-mass index, smoking status, race or ethnic group, gestational age at birth, spontaneous or induced labor, birth-weight percentile, and hospital of delivery was 1.68 (95% CI, 1.53 to 1.84; P<0.001). The increased risk of cesarean delivery was attributable to procedures performed for poor progress in labor.

CONCLUSIONS

The cervical length at mid-pregnancy is an independent predictor of the risk of cesarean delivery at term in primiparous women.

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Rates of cesarean delivery have increased dramatically throughout the developed world in recent years.[1] This trend has recently increased because of declining rates of vaginal birth after cesarean delivery.[1] With the decrease in vaginal birth after cesarean delivery, the rate of primary cesarean delivery will become an even more important determinant of overall cesarean rates. The major cause of primary cesarean delivery is poor progress during labor (dystocia).[2] A number of risk factors for such poor progress have been identified, such as advanced maternal age,[3] obesity,[4] and delivery after 40 weeks of gestation.[5] However, the biologic mechanisms that lead to poor progress during labor are poorly understood.

Studies of parturition in animals suggest that preparation for labor is evident at relatively early stages of gestation.[6,7] In women, it is well recognized that the cervix undergoes preparative changes in the weeks before the onset of labor[8] and also that a short cervix in mid-pregnancy is associated with an increased risk of spontaneous preterm birth.[9] We conducted a study to determine whether the length of the cervix in mid-pregnancy was associated with the risk of intrapartum cesarean delivery at term among primiparous women.

METHODS

The data analyzed in our study were obtained as part of multicenter studies of screening and intervention during pregnancy, conducted between 1998 and 2006, at eight hospitals in and around London: Basildon Hospital, Basildon; Queen Elizabeth Hospital, Woolwich; Harold Wood Hospital, Romford; King George Hospital, Ilford; King's College Hospital, London; Queen Mary's Hospital, Sidcup; University Hospital, Lewisham, London; and Southend University Hospital, Essex. Women recruited to the studies underwent transvaginal ultrasonography, including assessment of cervical length and uterine-artery Doppler flow velocimetry, between 22 and 24 weeks of gestation. Women with a short cervix (15 mm or less in length) recruited between January 1998 and May 2002 were offered participation in a trial of cervical cerclage, and those recruited between September 2003 and May 2006 were offered participation in a trial of vaginal administration of progesterone. Between January 2001 and July 2002, women with a mean pulsatility index of 1.6 or more (representing approximately the top 5% of values in the general population, with increasing values indicating decreasing diastolic velocity, a measure of placental impedance to blood flow) were offered participation in a trial of low-dose aspirin as prophylaxis for preeclampsia. The details of these trials are reported elsewhere.[10-12]

Measurements of cervical length were performed with the use of transvaginal ultrasonographic images[13] by ultrasonographers trained in these methods. Quality control of the screening, handling of data, and verification of adherence to protocols at the various centers was performed on a regular basis by the trial coordinators. Clinical details and medical and obstetrical histories were obtained during face-to-face interviews with the mothers that were conducted by a research obstetrician using a structured questionnaire.

The inclusion criteria for the current analysis were that the women were primiparous, had a cervical-length measurement performed, and ultimately delivered at term. We excluded women who had a stillbirth or therapeutic abortion, women whose cervical length was 15 mm or less, and women whose infants were delivered by prelabor cesarean section. Hence, all women randomly assigned to either the control group or the interventional group of the cervical-cerclage trial or the progesterone trial were excluded from the present study.

The outcome of each pregnancy was obtained from the computerized delivery records in each participating hospital. This information included data on the mode of delivery, the gestational age at birth, whether the patient was in labor, whether the onset of labor was spontaneous or induced, and the indications for operative delivery. Outcome data for the infant were also recorded, including whether the birth was a live birth or stillbirth, the birth weight, and the sex. The data were entered into the computer soon after delivery by the attending midwife or obstetrician. The primary outcome was cesarean delivery performed during labor at term. We performed subgroup analyses on the basis of whether the indication or indications for cesarean delivery recorded in the computerized medical records included a failure to progress in labor.

These studies were approved by the South

Thames Multicenter Research Ethics Committee, as well as the local ethics committees of the individual hospitals. Written informed consent was obtained from the women who agreed to participate.

STATISTICAL ANALYSIS

Continuous variables were summarized by calculating the median and interquartile range, and subgroups of patients were compared with the use of the Kruskal–Wallis test. Univariate comparisons of categorical data were performed with the chi-square test for trend. All reported P values are two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. Birth weight was analyzed as the percentile for sex and week of gestation. For the analysis of main effects, all variables were categorized. Adjusted odds ratios were obtained by means of multivariable logistic-regression analysis.[14] The independent variables included were cervical length, maternal age, body-mass index, smoking status, race or ethnic group, gestational age at birth, spontaneous or induced labor, birth-weight percentile, and hospital of delivery.

We planned to assess the interaction between cervical length and all other variables. We tested interaction terms between cervical length and other maternal variables using cervical length as a continuous variable and the other variables as categorical variables. The statistical significance of the interactions was assessed with the use of backward stepwise regression, in which statistical significance was estimated by means of the likelihood-ratio test to assess the effect of removing interaction terms for all strata of the given variable.[14] Given that eight tests of interaction were performed, the threshold for statistical significance for interaction terms was reduced to P values of less than 0.00625 (according to the Bonferroni method). Since cesarean delivery is a common outcome, adjusted odds ratios from multivariable logistic regression were converted into adjusted relative risks, according to the method of Zhang and Yu.[15] Adjusted relative risks were compared with adjusted incidence-rate ratios obtained from Poisson regression.[16] We estimated attributable fractions by using the method of Greenland and Drescher.[17] All statistical analyses were performed with the Stata software package, version 10.

RESULTS

Data were available from a total of 59,314 women. We excluded 682 records (1.1%) because the patient had a cervical length of 15 mm or less and 252 records (0.4%) because of a stillbirth or therapeutic abortion. A total of 58,405 women (98.5%) had neither outcome, and 30,452 of these women (52.1%) were primiparous. Of these 30,452 women, 1635 (5.4%) delivered preterm; of the remaining 28,817 women, 1345 (4.7%) delivered by prelabor cesarean section. This left a study group of 27,472 women, representing 90.2% of all eligible primiparous women screened. The median gestational age at the time of measurement of cervical length was 23 weeks (interquartile range, 22 weeks 5 days to 23 weeks 2 days).

Table 1 summarizes the characteristics of the cohort in relation to the quartile of cervical length. The cervical length at 23 weeks of gestation was positively associated with increasing maternal age, nonsmoking (vs. smoking), increasing body-mass index, white race, increasing gestational age at birth, induced (vs. spontaneous) labor, and increasing birth-weight percentile. A total of 5542 women underwent cesarean section. In 4615 of these procedures (83.3%), failure of labor to progress was included in the list of indications.

The rate of cesarean delivery was lowest among women with a cervical length at 23 weeks in the lowest quartile (16.0%) and was significantly greater in the second quartile (18.4%), third quartile (21.7%), and fourth quartile (25.7%) (P<0.001 for trend). The risk of cesarean delivery increased with increasing absolute values of midpregnancy cervical length. Rates of cesarean delivery started to rise at a cervical length of 25 mm and plateaued at a cervical length of 50 mm, approximately doubling across the range of observed values (Fig. 1). The association between cervical length and the rate of cesarean delivery was attributable to the procedure being performed in women for whom the indication included poor progress during labor.

Adjustment for a range of characteristics (maternal age, body-mass index, smoking status, race or ethnic group, gestational age at birth, spontaneous or induced labor, birth-weight percentile, and hospital of delivery) slightly attenuated but did not eliminate the significant association bet-

Table 1. Baseline Characteristics of the Cohort, According to the Quartile of Cervical Length at 23 Weeks of Gestation.*

Maternal Characteristic or Outcome	Quartile of Cervical Length				P Value
	1 (N=7061)	2 (N=8075)	3 (N=6065)	4 (N=6271)	
Cervical length — mm	16–30	31–35	36–39	40–67	<0.001
Age — yr					
Median	27.0	28.0	28.8	29.4	<0.001
IQR	22.0–31.5	23.0–31.7	24.2–32.0	25.3–32.9	
Body-mass index†					
Median	23.5	23.8	23.9	24.2	<0.001
IQR	21.3–26.5	21.5–26.7	21.6–27.0	22.0–27.3	
Current smoker — no. (%)	949 (13.4)	1027 (12.7)	685 (11.3)	586 (9.3)	<0.001
Race or ethnic group — no. (%)‡					
White	4384 (62.1)	5653 (70.0)	4483 (73.9)	4726 (75.4)	<0.001
Black	1963 (27.8)	1592 (19.7)	1054 (17.4)	1046 (16.7)	<0.001
Other	714 (10.1)	830 (10.3)	528 (8.7)	499 (8.0)	<0.001
Gestational age at birth — wk					
Median	40.0	40.0	40.0	40.3	<0.001
IQR	39.0–41.0	39.0–41.0	39.1–41.0	39.4–41.1	
Induced labor — no. (%)	1101 (15.6)	1444 (17.9)	1068 (17.6)	1402 (22.4)	<0.001
Birth-weight percentile					
Median	46	49	52	54	<0.001
IQR	21–72	25–74	28–76	28–78	
Cesarean delivery — no. (%)					
All	1133 (16.0)	1482 (18.4)	1315 (21.7)	1612 (25.7)	<0.001
Poor progress during labor§	884 (12.5)	1195 (14.8)	1101 (18.2)	1435 (22.9)	<0.001
Other	249 (3.5)	287 (3.6)	214 (3.5)	177 (2.8)	0.03

* Numbers among the quartiles are unequal owing to ties. P values were calculated with the use of the chi-square test for trend or the Kruskal–Wallis test, as appropriate. IQR denotes interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was self-reported.
§ Poor progress during labor was reported in computerized medical records listing this condition as an indication for cesarean delivery.

tween cervical length and the risk of cesarean delivery at term (Table 2). When the outcome was limited to cesarean delivery because of a failure of labor to progress, the association with cervical length was slightly stronger (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). There were no significant interactions between cervical length and any of the maternal characteristics in predicting the risk of intrapartum cesarean delivery (Fig. 2). The interaction between cervical length and birth-weight percentile had a P value of 0.01, but this value was greater than 0.00625, the threshold of significance used for the analysis of interaction, and the stratified analysis showed no clear pattern of interaction across the strata of birth-weight percentile (Fig. 2).

The attributable fraction for cesarean delivery associated with the upper three quartiles of cervical length was 20.5% (95% confidence interval [CI], 16.6 to 24.1). After adjustment for maternal characteristics, this fraction was 17.2% (95% CI, 13.4 to 20.9).

Since cesarean delivery was common, the output of logistic-regression models was also expressed as the adjusted relative risk.[15] The ad-

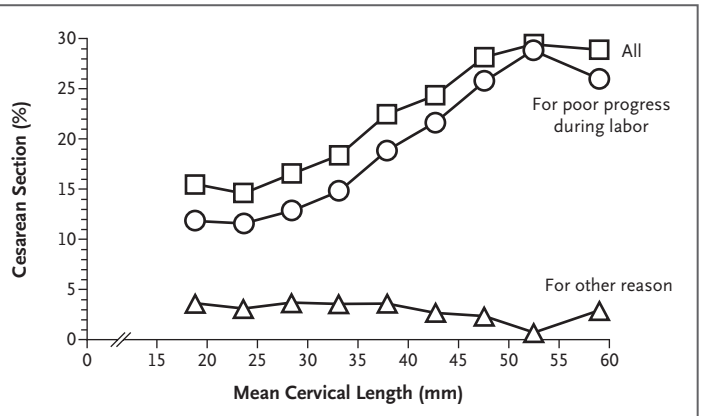

Figure 1. Proportion of Cesarean Deliveries in Relation to Absolute Values of Cervical Length Measured at 23 Weeks of Gestation.

justed relative risk of cesarean delivery for the highest quartile of cervical length was 1.49 (95% CI, 1.39 to 1.59). This value was very similar to the adjusted incidence-rate ratio (1.45; 95% CI, 1.34 to 1.57) estimated with the use of Poisson regression, an analysis that is also recommended for common outcomes.[16]

DISCUSSION

We found that the risk of intrapartum cesarean delivery at term among primiparous women was associated with the length of the cervix in mid-pregnancy. The risk of cesarean delivery began to increase when the cervical length at 23 weeks was greater than 25 mm and approximately doubled across the range of lengths. The relationship persisted after adjustment for several maternal characteristics. There was no strong evidence of an interaction between cervical length and other factors associated with the risk of cesarean delivery. These findings suggest that cervical length at mid-pregnancy is an important indicator of the risk of primary cesarean delivery at term.

We hypothesize that poor progress during labor at term is determined by the development of the uterus at much earlier stages of pregnancy. In the present study, we tested a prediction arising from that hypothesis — namely, that a long cervix in mid-pregnancy would be associated with an increased risk of emergency cesarean delivery during labor at term. The most common cause of intrapartum primary cesarean section is poor progress during labor. This is cited as the sole indication, or as a joint indication with fetal distress, in approximately 80% of intrapartum procedures at term among primiparous women,[18] and the proportion was very similar in the present study. Our analysis of cesarean delivery according to the indication for it was consistent with this finding, showing that the increased risk of this event among women who had a long cervix in mid-pregnancy was explained by the increased risk of poor progress during labor. It has previously been shown that cervical length at 37 weeks of gestation is strongly associated with the risk of cesarean section for poor progress during labor.[19] Our study did not involve serial measurement of cervical length throughout pregnancy. Hence, we could not determine whether the association between cervical length at mid-pregnancy and the risk of cesarean delivery at term was related to the cervical length at earlier or later gestational ages.

Our findings are consistent with those from studies of a range of animal species, which have shown that changes in preparation for labor and delivery occur through the second half of pregnancy,[8] and from longitudinal studies of pregnant rodents, which have showed a clear pattern of biochemical changes occurring in mid-pregnancy that are preparative for the ultimate process of labor.[7,20] The relation between such physiological and biochemical changes in mid-pregnancy in animals and variation in the cervical length at mid-pregnancy in women is currently unclear. Further study is needed to assess the possibility that a long cervix in mid-pregnancy may reflect dysfunctional development of the uterus, which is ultimately manifested in the need for cesarean delivery at term.

This study was a secondary analysis of data that were obtained for other purposes. Because the primary outcome of the original interventional trials was spontaneous preterm birth, the indication for cesarean delivery was ascertained only from the computerized delivery record, and we do not have data to validate the listed indications. Moreover, it is possible that the association between cervical length at mid-pregnancy and the risk of cesarean delivery was a chance finding. However, the association was signifi-

Table 2. Unadjusted and Adjusted Odds Ratios for Cesarean Delivery, According to Overall Outcome Characteristics.

Variable	Unadjusted Analysis		Adjusted Analysis	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)*	P Value
Quartile of cervical length				
1 (referent)	1.0		1.0	
2	1.18 (1.08–1.28)	<0.001	1.16 (1.06–1.27)	0.001
3	1.45 (1.33–1.58)	<0.001	1.43 (1.31–1.57)	<0.001
4	1.81 (1.66–1.97)	<0.001	1.68 (1.53–1.84)	<0.001
Age				
<20 yr	0.44 (0.39–0.51)	<0.001	0.49 (0.42–0.56)	<0.001
20–24 yr	0.67 (0.61–0.73)	<0.001	0.69 (0.62–0.76)	<0.001
25–29 yr (referent)	1.0		1.0	
30–34 yr	1.19 (1.11–1.29)	<0.001	1.23 (1.14–1.33)	<0.001
35–39 yr	1.57 (1.42–1.73)	<0.001	1.57 (1.41–1.74)	<0.001
≥40 yr	1.71 (1.37–2.15)	<0.001	1.59 (1.25–2.03)	<0.001
Body-mass index (before pregnancy)				
<20.0	0.72 (0.63–0.81)	<0.001	0.82 (0.73–0.93)	<0.001
20.0–24.9 (referent)	1.0		1.0	
25.0–29.9	1.57 (1.47–1.68)	<0.001	1.40 (1.30–1.50)	<0.001
30.0–34.9	2.02 (1.83–2.24)	<0.001	1.68 (1.51–1.87)	<0.001
≥35.0	2.60 (2.27–2.97)	<0.001	2.05 (1.77–2.37)	<0.001
Current smoker				
No (referent)	1.0		1.0	
Yes	0.73 (0.66–0.81)	<0.001	1.04 (0.94–1.16)	0.45
Race or ethnic group				
White (referent)	1.0		1.0	
Black	1.40 (1.30–1.50)	<0.001	1.81 (1.66–1.97)	<0.001
Other	0.96 (0.86–1.06)	0.40	1.41 (1.26–1.59)	<0.001
Gestational age at birth				
37 wk	1.20 (1.05–1.38)	0.009	1.01 (0.87–1.17)	0.87
38 wk	0.88 (0.79–0.98)	0.02	0.78 (0.70–0.88)	<0.001
39 wk	0.78 (0.71–0.85)	<0.001	0.75 (0.68–0.82)	<0.001
40 wk (referent)	1.0		1.0	
41 wk	1.47 (1.36–1.59)	<0.001	1.25 (1.15–1.36)	<0.001
≥42 wk	2.38 (2.13–2.67)	<0.001	1.44 (1.27–1.64)	<0.001
Onset of labor				
Spontaneous (referent)	1.0		1.0	
Induced	2.80 (2.61–2.99)	<0.001	2.37 (2.19–2.56)	<0.001
Birth-weight percentile				
1–3	1.51 (1.29–1.77)	<0.001	1.49 (1.26–1.77)	<0.001
4–10	0.92 (0.81–1.04)	0.16	0.91 (0.80–1.03)	0.15
11–20	0.83 (0.75–0.93)	0.001	0.85 (0.76–0.96)	0.007
21–80 (referent)	1.0		1.0	
81–90	1.40 (1.27–1.54)	<0.001	1.35 (1.22–1.49)	<0.001
91–97	1.85 (1.67–2.06)	<0.001	1.81 (1.62–2.03)	<0.001
98–100	3.15 (2.73–3.65)	<0.001	2.87 (2.46–3.36)	<0.001

* These odds ratios and 95% CIs were adjusted for maternal age, body-mass index, smoking status, race or ethnic group, gestational age at birth, spontaneous or induced labor, birth-weight percentile, and hospital of delivery.

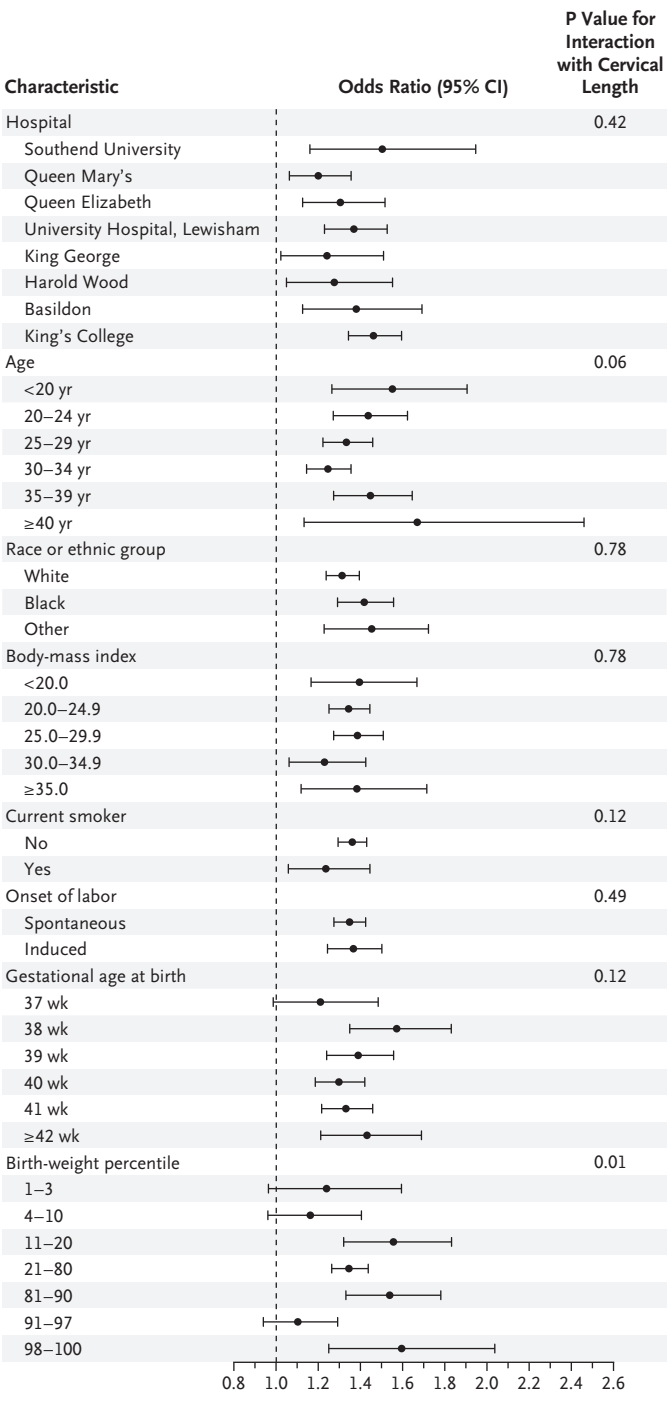

Figure 2. Odds Ratios for Cesarean Delivery per 10-mm Increase in Cervical Length, According to Overall Outcome Characteristics.

Odds ratios were stratified for each characteristic and adjusted for all other characteristics listed. P values were estimated with the use of the likelihood-ratio test. Given that eight comparisons were made, the threshold for statistical significance was P<0.00625.

cant at a P value of less than 0.001. Hence, the probability of this being a chance finding is very low. Although the association persisted in the multivariable analysis, it is also possible that it reflects residual confounding either due to a failure to measure important maternal variables directly or due to unmeasured confounders. For example, body-mass index is a proxy measure of adiposity, and residual confounding by this variable cannot be ruled out. If residual confounding by obesity explained the association found in the multivariable analysis, it is likely that an interaction between body-mass index and cervical length would have been observed. However, the association between cervical length and emergency cesarean delivery was similar among lean women, those of normal weight, and those who were overweight or obese (Fig. 2). Similarly, the relation between cervical length and cesarean delivery was consistent across strata of other maternal and outcome factors and across the eight hospitals studied.

Our study excluded women who delivered preterm. Women who deliver preterm are a heterogeneous group, consisting both of those with spontaneous preterm births and those with indicated preterm births. Moreover, intrapartum cesarean delivery for breech presentation is common before term, and the inclusion of preterm births would have complicated the interpretation of associations between cervical length and cesarean delivery for failure of labor to progress. Since the study group consisted of approximately 90% of all primiparous women screened, our findings are relevant to the general population of primiparous women.

Poor progress during labor at term is the most common indication for primary cesarean section and, hence, an important determinant of overall rates of cesarean section. Our finding that a long cervix in mid-pregnancy is predictive of cesarean section during labor at term suggests that poor progress during labor in women who deliver at term may be related to dysfunctional development of the uterus at much earlier stages of pregnancy.

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No potential conflict of interest relevant to this article was reported.

APPENDIX

The members of the Fetal Medicine Foundation Second Trimester Screening Group were as follows: *University Hospital Lewisham, London:* A. Delfino, M. Fokialaki, S. Flint; *Queen Elizabeth Hospital, Woolrich:* F. Molina, S. Turan, K. Gajewska, V. Palanappian; *King's College Hospital, London:* E. Karanastasi, A.M. Cacho, C. Skentou; *King George Hospital, Ilford:* L. Thompson, J. Webber, E. Osei; *Basildon Hospital, Basildon:* M.S. To, G. Fletcher, J. Parminter; *Harold Wood Hospital, Romford:* A. Moakes, C. Otigbah, R. Utidjian; *Queen Mary's Hospital, Sidcup:* S. Preston, A. Morgan, A. Abbas; *Southend University Hospital, Essex:* P. Hagan, M. Singh — all in the United Kingdom.

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Maternal Uterine Artery Doppler Flow Velocimetry and the Risk of Stillbirth

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OBJECTIVE: We sought to relate the risk of antepartum stillbirth to uterine artery Doppler flow velocimetry at 22–24 weeks.

METHODS: Data were available from 30,519 unselected women from seven units in the UK who had uterine artery Doppler performed between 22 and 24 weeks of gestation. The risk of stillbirth (n=109) was assessed using time to event and logistic regression analysis. Stillbirths were subdivided into placental (due to abruption, preeclampsia, or growth restriction) or unexplained.

RESULTS: The risk of placental stillbirth was increased among women with a mean pulsatility index in the top decile (adjusted hazard ratio [HR] 5.5, 95% confidence interval [CI] 2.8–10.6) and those with a bilateral notch (adjusted HR 3.9, 95% CI 2.0–7.8). The relationship between a mean pulsatility index in the top decile and the risk of unexplained stillbirth was weaker (adjusted HR 2.5, 95% CI 1.1–5.6) and there was no association with a bilateral notch. Placental stillbirths occurred at earlier gestations than unexplained stillbirths (median [interquartile range] 30 [26–36] compared with 38 [36–40], $P<.001$). Consequently, being in the top 5% of predicted risk of stillbirth on the basis of the combination of mean pulsatility index and notching was a good predictor (sensitivity, specificity, and positive likelihood ratio) of all cause stillbirth up to 32 weeks (58%, 95%, and 12.1, respectively) but a poor predictor of stillbirth at later gestations (7%, 95%, and 1.3, respectively).

CONCLUSION: Abnormal uterine artery Doppler was a better predictor of the risk of stillbirth due to placental causes than unexplained stillbirth. Consequently, abnormal uterine artery Doppler was a good predictor of stillbirth at extreme preterm gestations but a poor predictor of stillbirth at term.

(Obstet Gynecol 2007;109:144–51)

LEVEL OF EVIDENCE: II

Death of the fetus before the onset of labor (antepartum stillbirth) is the single most important cause of perinatal death.[1] Some of these deaths are clearly directly related to function of the placenta, such as those due to abruption. Approximately two thirds have no direct cause and are referred to as unexplained.[2] However, many of these are associated with growth restriction[3] and are also thought to be related to placental function.[4] Invasion of maternal vessels by the trophoblast is a key process in early placentation.[5] Consequently, vascular resistance in the uterine circulation normally decreases in the first half of pregnancy. This process can be quantified by Doppler flow velocimetry of the uterine arteries, and previous studies have shown associations between high resistance patterns of flow and a range of complications in pregnancy.[6,7] However, the nature of the association with stillbirth is unclear both in terms of different causes of stillbirth and the timing of losses. The aims of the present study were 1) to relate the risk of stillbirth to indices of Doppler flow velocimetry of the uterine arteries performed at 22–24 weeks of gestation in relation to presumed placental and nonplacental causes of stillbirth and the timing of stillbirth, and 2) to characterize the properties of uterine artery Doppler as a screening test for stillbirth in an unselected population.

MATERIALS AND METHODS

The data analyzed in the present study were obtained as part of a multicenter study of screening and intervention in pregnancy involving seven hospitals

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in and around London (Basildon Hospital; Greenwich Hospital; Harold Wood Hospital, Romford; King George Hospital, Ilford; King's College Hospital, London; Queen Mary's Hospital, Sidcup; University Hospital Lewisham, London). Women recruited to the study had a scan at 22–24 weeks of gestation, which included assessment of cervical length and uterine artery Doppler flow velocimetry. Those with a short cervix were offered participation in a trial of cervical cerclage, and those with a mean pulsatility index of 1.6 or above were offered participation in a trial of low-dose aspirin as prophylaxis for preeclampsia. These studies were approved by the South Thames Multicenter Research Ethics Committee, as well as the local ethics committees of individual hospitals. Written informed consent was obtained from the women agreeing to participate in the study. The details of these trials are reported elsewhere.[8,9]

The current analysis used this cohort but excluded women recruited to the trial of cervical cerclage. Maternal details and past medical and obstetric history were obtained using a questionnaire. Uterine artery Doppler studies were performed by using transvaginal ultrasonography[10] by ultrasonographers trained in this method. Each uterine artery was identified using color flow mapping, and three similar consecutive waveforms were obtained using pulsed wave Doppler. The pulsatility index was measured, and the mean pulsatility index of the two uterine arteries was calculated.[6] Quality control of screening, handling of data, and verification of adherence to protocols at the different centers was performed on a regular basis by the trial coordinators. The study period was October 1999 to August 2002. Women with a mean pulsatility index greater than 1.6, which in an earlier study represented the 95th centile,[10] were followed up with growth scans, blood pressure measurements, and urinalysis for protein at 28, 32, and 36 weeks. Women with normal uterine artery Doppler received routine antenatal care. Maternal history and Doppler findings were recorded in a computer database at the time of the Doppler studies in each participating center.

For the purposes of dichotomizing uterine mean pulsatility index, those women with values in the top 10% were considered to have elevated mean pulsatility index; this was 1.43 and above in the present analysis. Outcome was ascertained by computerized databases in each of the centers. In all cases of adverse outcome (abruption, preterm birth, preeclampsia, and stillbirth), the clinical case record (and stillbirth autopsy, where performed) was reviewed by a medically qualified individual, the diagnosis confirmed, and further details were obtained, as necessary. Stillbirths were defined as delivery of an infant which showed no signs of life. Losses due to congenital abnormality were excluded. Stillbirth was defined as all intrauterine fetal deaths subsequent to the measurement of uterine artery Doppler. The median gestational age of assessment of uterine artery Doppler was 23 weeks. Stillbirths were divided into those where the fetus was thought to have died before the onset of labor (antepartum) and those where the fetus was thought to have been alive at the start of labor. All analyses for the present study focused on antepartum stillbirths. The presumed cause of stillbirth was obtained from the case notes. Where the women suffered severe preeclampsia or had an abruption, these were assumed to have caused the stillbirth. Abruption was diagnosed on the basis of clinical presentation and the presence of a retroplacental clot. Preeclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy. This requires two recordings of diastolic blood pressure of more than 90 mm Hg at least 4 hours apart in previously normotensive women, and proteinuria of 300 mg or more in 24 hours, or two readings of at least two pluses on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available.

In the absence of a direct cause, stillbirths were regarded as unexplained. These were subdivided into those where the birth weight was less than the 10th percentile for sex and gestation (small for gestational age) and those where the birth weight percentile was above this threshold (appropriate for gestational age). Unexplained stillbirths where the fetus was small for gestational age were assumed to be due to intrauterine growth restriction. Stillbirths due to preeclampsia, abruption, or small for gestational age unexplained stillbirths were collectively considered to be placentally related stillbirths.

Body mass index was defined as the woman's prepregnancy weight in kilograms divided by her height in meters squared. Primigravid women were defined as those who had no previous births and any previous pregnancies had been spontaneous losses before 16 weeks or therapeutic abortions. Previous preterm birth was defined as a woman who had any previous live birth before 37 weeks of gestation. Previous loss was defined as any woman who had given birth to an infant showing no signs of life at or after 16 weeks of gestation and thus included prior intrauterine fetal deaths and stillbirths. Parous women with no previous complications were defined as those whose previous births had all been live births at term.

Continuous variables were summarized by the median and interquartile range (IQR) and comparisons between groups were made using the Mann-Whitney *U* test. Univariable comparisons of dichotomous data were made using the χ^2 test. The *P* values for all hypothesis

tests were two-tailed, and statistical significance was set at $P<.05$. The risk of stillbirth was compared between groups using time-to-event analyses (Kaplan-Meier and Cox proportional hazards model) in which gestational age was used as the time scale, antepartum stillbirth due to the specified cause was defined as the event, and all other births were treated as censored. This method uses ongoing pregnancies as the denominator, as previously suggested,[11] but accounts for censoring due to birth, allows multivariable analysis,[12] and can be used in situations where not all individuals would ultimately experience the event.[13] This analytic approach allows assessment of the relative risk accounting for variation in the duration of pregnancy. Survival data were plotted as cumulative percentage, with event as recommended for rare outcomes,[14] and univariable statistical comparisons were made using the log rank test. Crude and adjusted hazard ratios were estimated using the proportional hazards model.[15] The proportional hazards assumption was tested using the test of Grambsch and Therneau[16] as previously described for the analysis of stillbirth risk.[17,18] Logistic regression analysis was used to estimate adjusted odds ratios within given gestational windows. In these analyses, the number of antepartum stillbirths within the given range was the numerator and the number of all births at the given or later gestations was the denominator. Mean pulsatility index was treated as a continuous variable in the logistic regression analysis. Linearity in the log odds scale was assessed using fractional polynomials.[19] For predictive models, variables were selected using backward stepwise logistic regression,[20] with the threshold for removal being $P=.05$. Logistic regression models were converted to tables of likelihood ratios using a previously described method.[21] All statistical analyses were performed using the Stata 8 software package (Stata Corporation, College Station, TX).

RESULTS

Data were available from 30,755 women who had uterine artery Doppler performed between 22 and 24 weeks of gestation. Two hundred fifty-six women with a short cervix or who had cervical cerclage or both were excluded, leaving a study group of 30,519. There were 5 (2.0%) stillbirths among 255 women randomly assigned to aspirin and 4 (1.6%) stillbirths among 256 women assigned to placebo ($P=.8$). There were 109 antepartum stillbirths in the cohort. Women who had an antepartum stillbirth had higher body mass index, were more likely to be African American and were more likely to have had a complicated previous pregnancy (Table 1). Two of the stillbirths

Table 1. Maternal and Doppler Characteristics in Relation to Ultimate Outcome of Pregnancy

	No Stillbirth (n=30,410)	Stillbirth (n=109)	P*
Characteristics			
Maternal age (yr)	30 (26-34)	31 (26-34)	.4
Height	1.63 (1.58–1.68)	1.63 (1.58–1.68)	.4
Body mass index	25 (22-28)	26 (23–30)	.002
Smoker			
Nonsmoker or ex-smoker	25,897 (85.2)	88 (80.7)	
Current smoker	4,513 (14.8)	21 (19.3)	.2
Ethnic group			
Asian or other	2,885 (9.5)	6 (5.5)	
African American	5,502 (18.1)	43 (39.4)	<.001
White	22,023 (72.4)	60 (55.0)	
Past obstetric history			
Primigravid	15,462 (50.8)	52 (47.7)	.001
Parous (uncomplicated)	12,019 (39.5)	36 (33.0)	
Previous preterm birth	2,291 (7.5)	12 (11.0)	
Previous IUFD or stillbirth	638 (2.1)	9 (8.3)	
Doppler findings			
Uterine notch			
None	24,173 (79.5)	67 (61.5)	
Unilateral	3,207 (10.6)	6 (5.5)	<.001
Bilateral	3,030 (10.0)	36 (33.0)	
Mean PI	1.02 (0.87–1.21)	1.26 (0.95–1.64)	<.001
Mean PI in top decile	2,950 (9.7)	39 (35.8)	<.001

IUFD, intrauterine fetal death; PI, pulsatility index.
Data are n (%) or median (interquartile range), as appropriate.
*P value by Fisher exact test or Mann-Whitney U test, as appropriate.

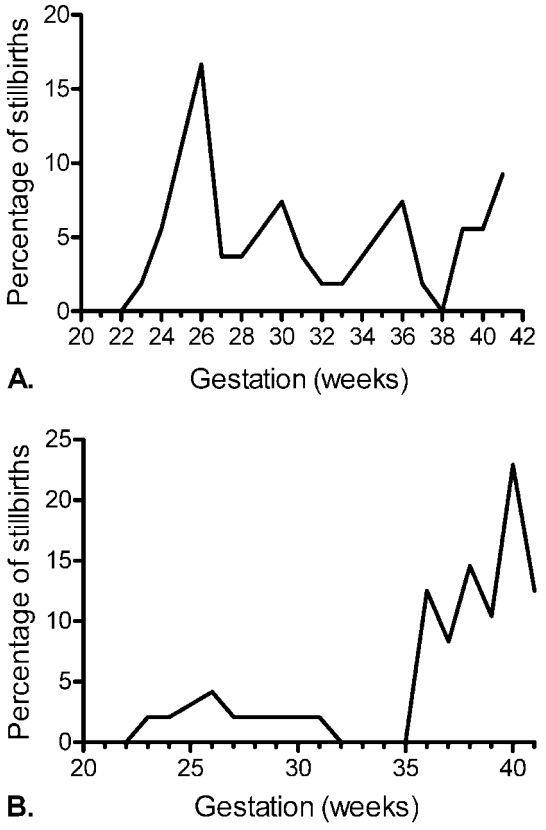

Fig. 1. Timing of stillbirths in relation to whether the cause was placental **(A)** or unexplained **(B)**. The median (interquartile range) of delivery in weeks was 30 (26–36) for placental stillbirths and 38 (36–40) for unexplained stillbirths (Mann Whitney *U* test, *P*<.001).

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were related to road traffic accidents, four to maternal diabetes, and one to second trimester rupture of the membranes. All further analyses focused on the remaining 102, of which 54 were attributed to a placental cause (abruption, preeclampsia, or intrauterine growth restriction, or any combination of these) and 48 that were unexplained, with a birth weight appropriate for gestational age. Stillbirths due to a placental cause occurred at earlier gestations than unexplained stillbirths (Fig. 1).

A uterine artery mean pulsatility index in the top decile and a bilateral notch were both associated with an increased risk of all-cause stillbirth and stillbirth due to a placental cause (Table 2). A uterine artery mean pulsatility index in the top decile was also associated with the risk of unexplained stillbirth. There were no associations between a unilateral notch and the risk of any type of stillbirth. The relationship between a composite index of abnormal Doppler (uterine mean pulsatility index in the top decile or bilateral notch or both) and the Kaplan-Meier cumulative risk of stillbirth is plotted in Figure 2. This illustrates that abnormal uterine artery Doppler was more strongly associated with all-cause stillbirth and stillbirth due to placental causes at extreme preterm gestations (Fig. 2). The relative risk of unexplained stillbirth among women with abnormal uterine artery Doppler was similar across the whole range of gestation. Overall, 4,769 (15.6%) of women had abnormal Doppler (either mean pulsatility index in the top decile or bilateral notches). Among these women, the absolute risks per 1,000 (95% confidence interval of stillbirth were 5.9 (3.9–8.5) up to 32 weeks and 3.1 (1.8–5.2) at or after 33 weeks of gestation. The risks of these events for the whole population were 1.3 (1.0–1.8) and 2.0 (1.5–2.6), respectively. The relative risk of stillbirth associated with abnormal Doppler did not significantly differ across the seven centers in relation

Table 2. Time-to-Event Analysis of Stillbirth Risk in Relation to Second Trimester Uterine Artery Doppler

Doppler Findings	All Stillbirth				Placental Stillbirth				Unexplained Stillbirth			
	HR 1*	*P*	HR 2†	*P*	HR 1*	*P*	HR 2†	*P*	HR 1*	*P*	HR 2†	*P*
Top decile PI	4.6 (2.9–7.5)	<.001	4.0 (2.4–6.5)	<.001	6.5 (3.4–12.6)‡	<.001	5.5 (2.8–10.6)	<.001	2.8 (1.2–6.3)	.01	2.5 (1.1–5.6)	.03
Unilateral notch	0.5 (0.2–1.2)	.1	0.5 (0.2–1.3)	.2	0.4 (0.1–1.6)	.2	0.4 (0.1–1.8)	.2	0.6 (0.3–1.9)	.4	0.7 (0.2–2.0)	.5
Bilateral notch	2.4§(1.4–3.9)	.001	2.5‡ (1.5–4.1)	.001	3.9 (2.0–7.6)	<.001	3.9 (2.0–7.8)	<.001	0.9‡ (0.4–2.5)	.9	1.0‡ (0.4–2.7)	>.9

HR, hazard ratio; PI, pulsatility index.
Data in parentheses are 95% confidence intervals.
* Adjusted for other Doppler parameters only.
† Adjusted for other Doppler parameters and maternal age, height, body mass index, smoking, ethnicity, and past obstetric history.
‡ P<.05, test of proportional hazards assumption.
§ P<.01, test of proportional hazards assumption.

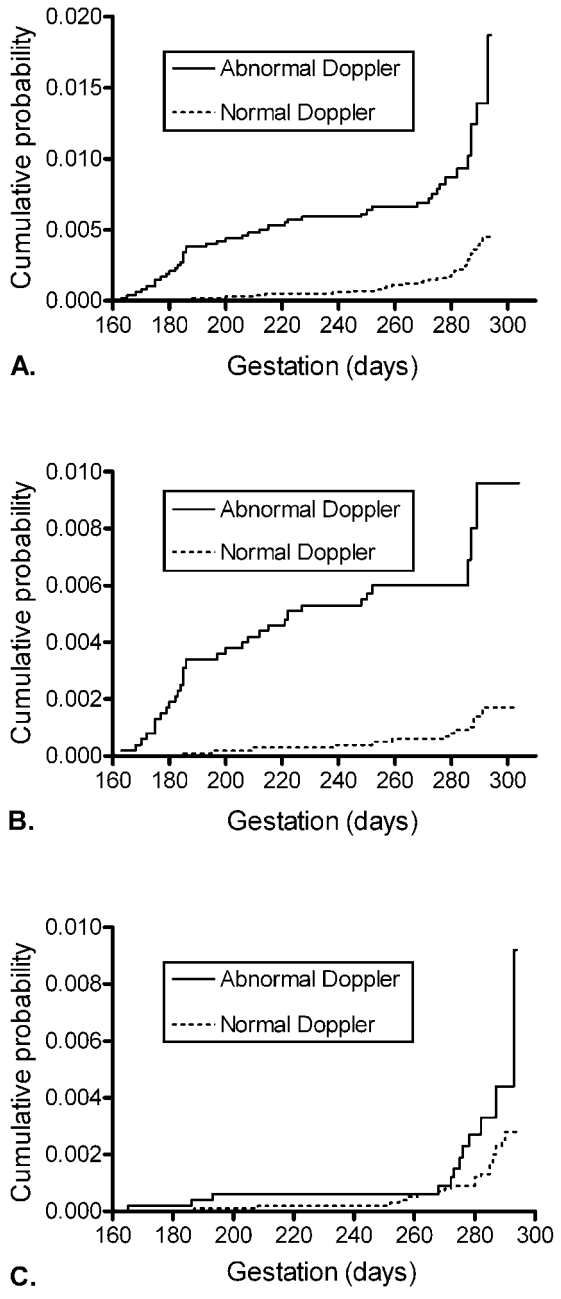

Fig. 2. Kaplan-Meier plots of cumulative probability of stillbirth expressed as cumulative risk of failure in relation to abnormal Doppler (*solid line*, uterine artery mean pulsatility index in top decile or bilateral notch or both) compared with normal Doppler (*broken line*, all other women). Hazard ratio (HR) for abnormal Doppler: **A.** All stillbirths: HR 4.4 (95% confidence interval [CI] 2.9–6.5), log rank test, $P<.001$, proportional hazard test $P<.001$; **B.** Stillbirths due to a placental cause: HR 7.8 (95% CI 4.5–13.4), log rank test, $P<.001$, proportional hazard test $P=.002$. **C.** Unexplained stillbirth: HR=2.1 (95% CI 1.1–4.0), log rank test, $P=.03$, proportional hazard test $P=.7$.

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either to all-cause stillbirth ($P=.2$) or stillbirth due to a placental cause ($P=.3$).

The ability of combinations of Doppler and maternal indices to predict stillbirth risk were then explored in relation to all-cause stillbirth, separately examining events before 33 weeks of gestation and those at 33 weeks and beyond (Table 3). Uterine artery Doppler was a better predictor of stillbirth before 33 weeks of gestation than maternal characteristics. Conversely, maternal characteristics performed better at later gestations. When the population in the top 5% of predicted risk were regarded as having screened positive, combined models of maternal and Doppler characteristics had a sensitivity of approximately 50% for early stillbirths but only 20% for late stillbirths. Logistic regression models for each event were generated using selection of significant variables and then converted to likelihood ratios (Tables 4 and 5). These provide a means to estimate stillbirth risk on the basis of uterine Doppler and maternal characteristics.

DISCUSSION

We show that an abnormal pattern of uterine artery Doppler flow velocimetry at 22–24 weeks is strongly associated with the subsequent risk of stillbirth. The strength of the association was much greater for stillbirths due to placental causes than for unexplained stillbirths where the fetus had a birth weight appropriate for gestational age. The former group of stillbirths tended to occur at much earlier weeks of gestation. Consequently, abnormal uterine artery Doppler performed much better as a screening test for stillbirth at extreme preterm gestations than those occurring at late gestation.

The approach of characterizing an arbitrary threshold of mean pulsatility index as being elevated results in loss of information. Moreover, some maternal characteristics were also significantly predictive of the risk of stillbirth. Prediction of the risk of stillbirth for an individual women would ideally take into account the precise level of the mean pulsatility index and combine this with her other characteristics to produce an estimate of her personal risk. We addressed these issues by developing multivariable logistic regression models that incorporated mean pulsatility index as a continuous variable along with the maternal characteristics. Although this addresses the two issues above, estimating a summary probability from such a model requires very sophisticated statistical knowledge. We addressed this by using a recently described method to convert logistic regression models into tables of likelihood ratios.[21] A summary

Table 3. Screening Characteristics of Combinations of Maternal and Doppler Indices in Predicting Early and Late Stillbirths

Outcome and Predictors	Top 5% Screen Positive*				
	Area Under ROC Curve*	Sensitivity	Specificity	Positive LR	Negative LR
All-cause stillbirth at 32 wk or less					
Doppler† alone	0.84 (0.77–0.91)	58.5 (42.1–73.7)	95.2 (94.9–95.4)	12.1	0.44
Doppler† and maternal‡	0.89 (0.84–0.95)	53.7 (37.4–69.3)	95.1 (94.8–95.3)	10.9	0.49
Maternal‡ alone	0.75 (0.66–0.83)	31.7 (18.1–48.1)	95.1 (94.8–95.3)	6.4	0.72
Selected Doppler and maternal§	0.87 (0.80–0.93)	61.0 (44.5–75.8)	95.1 (94.8–95.3)	12.4	0.41
All cause stillbirth at 33 wk or more					
Doppler† alone	0.62 (0.54–0.70)	6.6 (1.8–15.9)	95.1 (94.8–95.3)	1.3	0.98
Doppler† and maternal‡	0.70 (0.64–0.77)	21.3 (11.9–33.7)	95.0 (94.8–95.3)	4.3	0.83
Maternal‡ alone	0.68 (0.61–0.75)	18.0 (9.4–30.0)	95.1 (94.8–95.3)	3.7	0.86
Selected Doppler and maternal§	0.67 (0.60–0.75)	13.1 (5.8–24.2)	95.1 (94.8–95.3)	2.7	0.91

ROC, receiver operating characteristic; LR, likelihood ratio.
Data in parentheses are 95% confidence intervals.
*The area under the ROC curve was calculated using the estimated probability of stillbirth from the given logistic model. The sensitivity, specificity, and likelihood ratios were estimated when women in the top 5% of predicted risk were deemed to have screened positive.
† Doppler scores are mean pulsatility index (expressed as a continuous variable), unilateral notch and bilateral notch. In all models, mean pulsatility index was linear in the log odds scale on the basis of fractional polynomial analysis.
‡ Maternal characteristics in the model were age, height, body mass index, smoking, ethnicity, and past obstetric history.
§ Details of the selected models are provided in Tables 4 and 5.

likelihood ratio can be calculated by multiplying the combination of likelihood ratios which are associated with a given woman's characteristics. The background risk of stillbirth is then multiplied by the summary likelihood ratio and the woman's individual risk can be calculated. Before widespread application of these models, their accuracy should be evaluated in other populations. The fact that the association between abnormal uterine artery Doppler and the risk of stillbirth did not significantly vary across the seven centers suggests that these models are likely to be generalizable. Moreover, an advantage of the likelihood ratio approach is that it is relatively simple to account for variation in the background risk of stillbirth when applied to other populations.

The data from the present study are essential for the design of any interventional studies that aim to reduce the risk of stillbirth in an unselected population screened using uterine artery Doppler. A series of randomized controlled trials of uterine and umbilical artery Doppler have been conducted. Meta-analysis of these trials demonstrates no reduction in perinatal mortality.[22] However, these trials were conducted in the absence of detailed information about the screening properties of the test. The key properties which need to be known when designing a trial are the range of gestational age where the risk is increased and the absolute risk of stillbirth over that period. The timing of the risk is essential for planning the timing of any intervention. The absolute risk of a loss associated with an abnormal test result is essential for a power calculation. Previous trials were conducted in the absence of these data.[22] The current model could be used in a trial to identify women at increased risk of stillbirth. There are a number of possible interventions in the high-risk group. One example would be intensive fetal surveillance (computerized cardiotocography, biometry, uteroplacental and venous Doppler, and biophysical profile) with delivery of those deemed to be at imminent risk of intrauterine fetal death.

A relative weakness of the present analysis was that the Doppler results were revealed and clinical management was modified on the basis of the result. The effect of this on the present analysis is difficult to assess. The nature of the intervention was that women with an elevated uterine mean pulsatility index were scanned every 4 weeks. This is comparable to the protocol used in a randomized controlled trial of uterine artery Doppler that did not demonstrate a protective effect on perinatal mortality.[23] However, it is possible that some fetal deaths may have been prevented by this intervention or by the attending obstetrician being aware of the abnormal uterine artery Doppler. Further studies with a noninterventional design would be required to eliminate this potential source of error.

A further weakness in the present study relates to classification of stillbirths on the basis of birth weight. If the interval between death of the fetus and birth is

Table 4. Likelihood Ratios for Stillbirth Between 24 and 32 Weeks of Gestation

Characteristic	Likelihood Ratio
Uterine artery mean PI	
0.1	0.12
0.2	0.14
0.3	0.17
0.4	0.21
0.5	0.25
0.6	0.30
0.7	0.36
0.8	0.44
0.9	0.53
1.0	0.64
1.1	0.77
1.2	0.94
1.3	1.13
1.4	1.37
1.5	1.65
1.6	2.00
1.7	2.42
1.8	2.92
1.9	3.53
2.0	4.27
2.1	5.16
2.2	6.24
2.3	7.54
2.4	9.11
Bilateral notch	
Absent	0.55
Present	2.71
Ethnicity	
Non-African American	0.72
African American	2.09
Previous loss	
None	0.89
One or more	4.05

PI, pulsatility index.
Population risk of stillbirth over this interval was 1.3 per 1,000.
Logistic model was log odds = –9.996 + (1.896×mean PI) + (1.593×bilateral notch) + (1.066×African American ethnicity) + (1.517×previous loss), where categorical outcomes were expressed as yes=1 and no=0.

Table 5. Likelihood Ratios for Stillbirth Between 33-43 Weeks of Gestation

Characteristic	Likelihood Ratio
Uterine artery mean PI	
0.1	0.42
0.2	0.45
0.3	0.50
0.4	0.54
0.5	0.59
0.6	0.64
0.7	0.70
0.8	0.77
0.9	0.83
1.0	0.91
1.1	0.99
1.2	1.08
1.3	1.18
1.4	1.29
1.5	1.40
1.6	1.53
1.7	1.67
1.8	1.82
1.9	1.98
2.0	2.16
2.1	2.36
2.2	2.57
2.3	2.81
2.4	3.06
BMI	
Less than 25	0.63
25–29.9	1.35
More than 30	1.36
Ethnicity	
Non-African American	0.85
African American	1.59

PI, pulsatility index; BMI, body mass index.
Population risk of stillbirth over this interval was 2 per 1,000.
Logistic model was log odds = –7.806 + (0.867×mean PI) + (0.768×BMI 25-29.9) + (0.768×BMI ≥ 30) + (0.624×African American ethnicity), where categorical outcomes were expressed as yes=1 and no=0.

prolonged, maceration of the fetus may occur. Consequently, the birth weight of the stillborn infant may not accurately reflect growth in fetal life. Moreover, dichotomizing infants as small or appropriate for gestational age on the basis of birth weight does not identify those infants that were constitutionally small. Moreover, infants with an apparently appropriate birth weight for gestational age may not have achieved their true growth potential. Therefore, classification of unexplained stillbirths by birth weight does not perfectly discriminate between those that were growth restricted and those that were not. Indeed, failure of correct classification may account for the association between unexplained stillbirth and abnormal uterine artery Doppler. Further studies may be able to address this using more sophisticated indicators of intrauterine growth restriction, such as serial antenatal scanning or neonatal anthropometry.

In conclusion, we show that a high resistance pattern of flow in the uterine artery is associated with an increased risk of stillbirth. The association is strongest for stillbirths due to placental dysfunction and, since these tend to occur at earlier gestations, is strongest for stillbirths occurring at extreme preterm gestations. Uterine artery Doppler is a relatively poor predictor of unexplained stillbirth unrelated to fetal growth restriction.

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Section 4. Biochemical predictors of pregnancy outcome

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Early Pregnancy Levels of Pregnancy-Associated Plasma Protein A and the Risk of Intrauterine Growth Restriction, Premature Birth, Preeclampsia, and Stillbirth

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The risk of adverse perinatal outcome among 8839 women recruited to a multicenter, prospective cohort study was related to maternal circulating concentrations of trophoblast-derived proteins at 8–14 wk gestation. Women with a pregnancy-associated plasma protein A (PAPP-A) in the lowest fifth percentile at 8–14 wk gestation had an increased risk of intrauterine growth restriction [adjusted odds ratio, 2.9; 95% confidence interval (CI), 2.0–4.1], extremely premature delivery (adjusted odds ratio, 2.9; 95% CI, 1.6–5.5), moderately premature delivery (adjusted odds ratio, 2.4; 95% CI, 1.7–3.5), preeclampsia (adjusted odds ratio, 2.3; 95% CI, 1.6–3.3), and stillbirth (adjusted odds ratio, 3.6; 95% CI, 1.2–11.0). The strengths of the associations were similar when the test was performed before 13 wk gestation or between 13 and 14 wk gestation. In contrast, levels of free β-human CG, another circulating protein synthesized by the syncytiotrophoblast, were not predictive of later outcome in multivariate analysis. PAPP-A has been identified as a protease specific for IGF binding proteins. We conclude that control of the IGF system in the first and early second trimester trophoblast may have a key role in determining subsequent pregnancy outcome. (*J Clin Endocrinol Metab* 87: 1762–1767, 2002)

INTRAUTERINE GROWTH RESTRICTION and preterm birth are major determinants of perinatal morbidity and mortality. Much of routine prenatal care involves detecting women at increased risk of these adverse events and targeting intensive monitoring and interventions. Standard reviews of fetal physiology suggested that variation in human fetal growth was largely a phenomenon of the second half of pregnancy (1), and it is during this phase of pregnancy when women receive the bulk of prenatal care. However, a previous study showed that embryos and fetuses that were smaller than expected in the first trimester of pregnancy were more likely to have pregnancy complications, including intrauterine growth restriction and preterm birth (2). In the present study, we investigated whether circulating concentrations of two trophoblast-derived proteins in early pregnancy [pregnancy-associated plasma protein A (PAPP-A) and free β-subunit human CG (FβhCG)] might identify women at increased risk of subsequent adverse perinatal outcomes.

Materials and Methods

Blood samples were obtained from women between 8 and 14 wk gestation, attending 15 maternity hospitals in southern Scotland, as part of a prospective, nonintervention multicenter study on combined ultrasound and biochemical screening for Down's syndrome, which is being reported elsewhere (Crossley *et al.*, submitted for publication). Women were sent an information leaflet along with their booking notification and were invited to participate in the study when first attending for prenatal care. Gestational age at the time of recruitment was assessed by crown-rump length (CRL) and/or biparietal diameter, as recommended, using previously described protocols (3). Signed consent was obtained from all patients, and ethical approval was obtained from the institutional committees of all participating centers and from the regional multicenter ethics committee. No results were reported to either the obstetrician or patient, and prenatal care was not modified in any way by participation in the study.

Abbreviations: BMI, Body mass index; BW, birth weight; CI, confidence interval; CRL, crown-rump length; FβhCG, free β-human CG; IGFBP, IGF binding protein; MOM, multiple of the median.

Seven data collection

Relevant patient and pregnancy information were entered on the study data form, which was sent along with a clotted blood sample to the study coordinating center, where the data were entered into the study database. Samples were assayed for PAPP-A and FβhCG using the *Kryptor* immunoassay analyzer (Brahms, Berlin, Germany; formerly supplied by CIS-Bio International, Burgess Hill, UK). Kryptor assays are based on time- resolved amplified cryptate emission technology. PAPP-A exists complexed 2:2 with the precursor of eosinophil major basic protein, and the PAPP-A assay measures this PAPP-A/precursor of eosinophil major basic protein complex. The detection limit of the assay is 0.004 IU/liter (International reference preparation 78/610), and the coefficient of variation was found to be 3.5% at 4.58 IU/liter and 5.7% at 12.90 IU/liter. The FβhCG assay is specific for the unbound β-subunit of hCG and measures both nicked and unnicked forms. The detection limit of the assay is 0.1 IU/liter (International reference preparation 75/551), and the coefficient of variation was found to be 4.3% at 17.6 IU/liter and 3.5% at 48.4 IU/liter. FβhCG and PAPP-A levels were converted to multiples of the median (MOMs) using the CRL or biparietal diameter measurement when the sample was obtained as an estimate of gestation. Because PAPP-A levels are reduced in smokers by around 15%, when compared with nonsmokers (4), separate medians were used for each group. PAPP-A and FβhCG MOM values were corrected for maternal weight using reciprocal-linear regression (5). Outcome data were gathered from each woman's clinical record, after

delivery, using predefined criteria and coded by a team of two research midwives, two obstetricians, and two clinical scientists.

Selection of study cohort

The database included 9002 records of singleton pregnancies where values for PAPP-A, FβhCG, and gestational age at the time of sampling were documented and outcome data were available. We excluded 121 (1.3%) records with missing values for birth weight (BW), 68 (0.8%) with missing values for perinatal outcome (*i.e.* stillbirth or livebirth), 99 (1.1%) records where the gestational age at delivery was outside the range of 24–43 wk, and 26 (0.3%) records where the karyotype was abnormal or missing. This left a study group of 8839 (some records had multiple exclusions or missing values).

Definitions and denominators

Nulliparous women were defined as women either having their first pregnancy or women whose births were preceded only by pregnancies that resulted in abortion before 24 wk gestation. Gestational age was defined as the number of completed weeks of gestation. A small-for-gestational-age baby was defined as a liveborn baby that was less than the fifth percentile of BW for the given week of gestation, using percentiles derived from 409,541 live births in Scotland between 1992–1998 (G. C. S. Smith, unpublished data). The denominator was all live births. Very preterm delivery was defined as birth of a live-born baby between 24 and 32 wk gestation inclusive and the denominator was all live births at or after 24 wk gestation. Moderately preterm delivery was defined as live births between 33 and 36 wk gestation inclusive and the denominator was all live-births at or after 33 wk gestation. Spontaneous preterm birth was defined as vaginal delivery of a liveborn baby between 24–36 wk where labor had not been induced. The denominator was spontaneous preterm births plus term births. Stillbirth was defined as delivery of a dead baby at or after 24 wk gestational age and the denominator was all births at or after 24 wk gestational age. Preeclampsia was defined as pregnancy-induced hypertension with proteinuria. Maternal age was defined as the age of the mother, in completed years, at term. Maternal height was measured in centimeters, maternal weight was measured in kilograms at the time of blood sampling, and body mass index (BMI) was calculated using weight divided by height squared. Nonsmoking was defined as never having smoked, at the time of first attendance for prenatal care; exsmokers were defined as women who stopped smoking either before or during pregnancy; and smokers were defined as women who smoked throughout pregnancy.

Statistical analyses

Separate analyses were undertaken for five dichotomous outcomes: delivery of a small-for-gestational-age baby, moderately preterm delivery, extremely preterm delivery, preeclampsia, and stillbirth. Univariate comparisons of dichotomous data were performed using the chi-square test (more than five observations in all cells) or Fisher's exact test (five or fewer observations in one or more cells). Ordinal data were compared using the chi-square test for trend. The *P* values for all hypotheses tests were two-sided. Crude and adjusted odds ratios were obtained using logistic regression analysis (6). Height and BMI were categorized into strata, age was dichotomized into <35 and ≥ 35, and gestational age at the time of sampling was dichotomized into <13 wk and ≥ 13 wk. The statistical significance of interaction terms was assessed using the likelihood ratio test. The goodness quality of fit of models was assessed using the Hosmer and Lemeshow test based on deciles of probability. All statistical analyses were performed using the Stata software package (Stata Corporation, College Station, TX), version 7.0.

Results

Among the study group, there were missing values for parity in 512 records (5.8%), for height in 739 (8.4%), for BMI in 814 (9.2%), for smoking status in 342 (3.9%), for ethnicity in 557 (6.3%), and for maternal age in 49 (0.6%). The basic demographic and outcome data are given in Table 1. Values of PAPP-A measured in the study ranged from 0.09–27.70 IU/liter, and values of FβhCG ranged from 3.2–265 IU/liter.

When the proportion of adverse events was compared among deciles of PAPP-A, the lowest decile of PAPP-A consistently had the highest proportion of adverse outcomes (Fig. 1). Moreover, there was an association between intrauterine growth restriction and moderately premature delivery across the whole range of PAPP-A (Fig. 1). When outcomes were compared in relation to FβhCG, there was a trend for increased proportions of growth-restricted babies with decreasing FβhCG, but not with any of the other outcomes (Fig. 2). The number of stillbirths was too small to test for trend, but the highest proportion of stillbirths was seen in the lowest deciles of both PAPP-A and FβhCG (Figs. 1 and 2).

We then determined the ability of the lowest 5% of MOMs

TABLE 1. Characteristics and outcomes of study group (n = 8839)

Study group characteristics		
Age (yr)	Median (IQR)	30.7 (26.9–34.0)
	Age > 35 yr	1693 (19.2%)
Parity	Median (IQR)	1 (0–1)
	Nulliparous	3924 (44.4%)
Ethnicity	Non-Caucasian	221 (2.5%)
Smoking status	Nonsmokers	5976 (67.6%)
	Exsmokers	703 (8.0%)
	Current smokers	1818 (20.6%)
Height (cm)	Median (IQR)	163 (159–168)
Weight (kg)	Median (IQR)	63.9 (57.5–72.1)
BMI	Median (IQR)	23.8 (21.7–26.6)
Gestational age at sampling	Median (IQR) (in days)	87 (81–93)
	<13 wk	5388 (60.4%)
Outcome data		
BW (g)*	Median (IQR)	3450 (3110–3780)
Less than 5th percentile[a]		370 (4.2%)
Gestational age at delivery[a]	24–32 wk	86 (1.0%)
	33–36 wk	326 (3.7%)
	37–43 wk	8405 (95.3%)
Stillbirths		22 (0.3%)

Data are number (%) unless stated otherwise. IQR, Interquartile range.
[a] Excludes stillbirths.

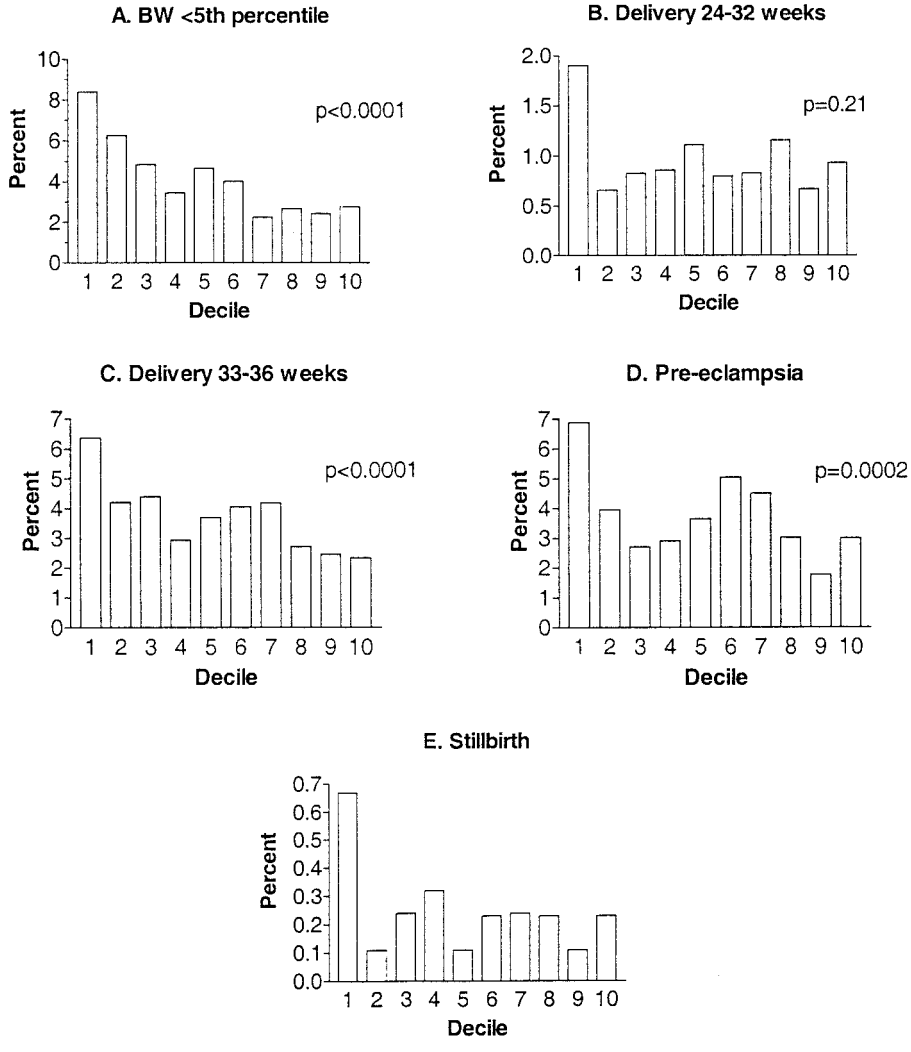

FIG. 1. Proportion of adverse perinatal outcomes related to PAPP-A decile. The *P* value is the chi-square test for trend. When data from the smallest decile were excluded, the test for trend remained statistically significant for BW less than fifth percentile ($P < 0.0001$) and delivery between 33–36 wk ($P = 0.006$) but was no longer statistically significant for preeclampsia ($P = 0.22$). The chi-square test was not performed on stillbirth data, because of the small number of adverse events.

for each serum marker to identify women at increased risk of adverse outcomes in later pregnancy (Table 2). Women with the lowest 5% of PAPP-A MOMs were at increased risk of intrauterine growth restriction, moderately and extremely premature birth, preeclampsia, and stillbirth. Women with the lowest 5% of FβhCG MOMs were at increased risk of intrauterine growth restriction but none of the other outcomes.

In multivariate analysis (Table 3), PAPP-A remained highly significantly predictive of all adverse outcomes when adjusted for FβhCG, BMI, height, ethnicity, parity, smoking status, maternal age, and gestational age at the time of sampling. There were no statistically significant interactions between PAPP-A and the other covariates. FβhCG was no longer significantly positively predictive of any adverse outcome when adjusted for PAPP-A, BMI, height, ethnicity, parity, smoking status, maternal age, and gestational age at the time of sampling. There were no statistically significant interactions between FβhCG and any of these other covariates. When the analysis was confined to spontaneous preterm births, there was a positive association with the lowest 5% of PAPP-A MOMs [adjusted odds ratio, 2.0; 95% confidence interval (CI), 1.2–3.3; $P = 0.005$] but no association with the lowest 5% of FβhCG MOMs (adjusted odds ratio, 0.7; 95% CI, 0.4–1.4; $P = 0.32$).

Discussion

In this study, we demonstrate that maternal circulating concentrations of PAPP-A at 8–14 wk gestation are significantly predictive of adverse perinatal outcome in later pregnancy. The strength of the association between PAPP-A and outcome before 13 wk gestation was similar to that at ≥13 wk gestation. These data indicate that, in a proportion of women, adverse pregnancy outcome is determined in the first trimester of pregnancy.

We had previously studied ultrasonic measurement of the CRL of the fetus and found that embryos and fetuses that were smaller than expected in the first trimester were more likely to be low BW, low BW at term, in the smallest fifth percentile of weight for gestational age, and born extremely prematurely (2). That study had certain weaknesses. First, the fetus might be smaller than expected because of variation in the assumed day of ovulation. Second, we were able to obtain an ideal menstrual history and early ultrasound in only approximately 10% of women, which meant that the

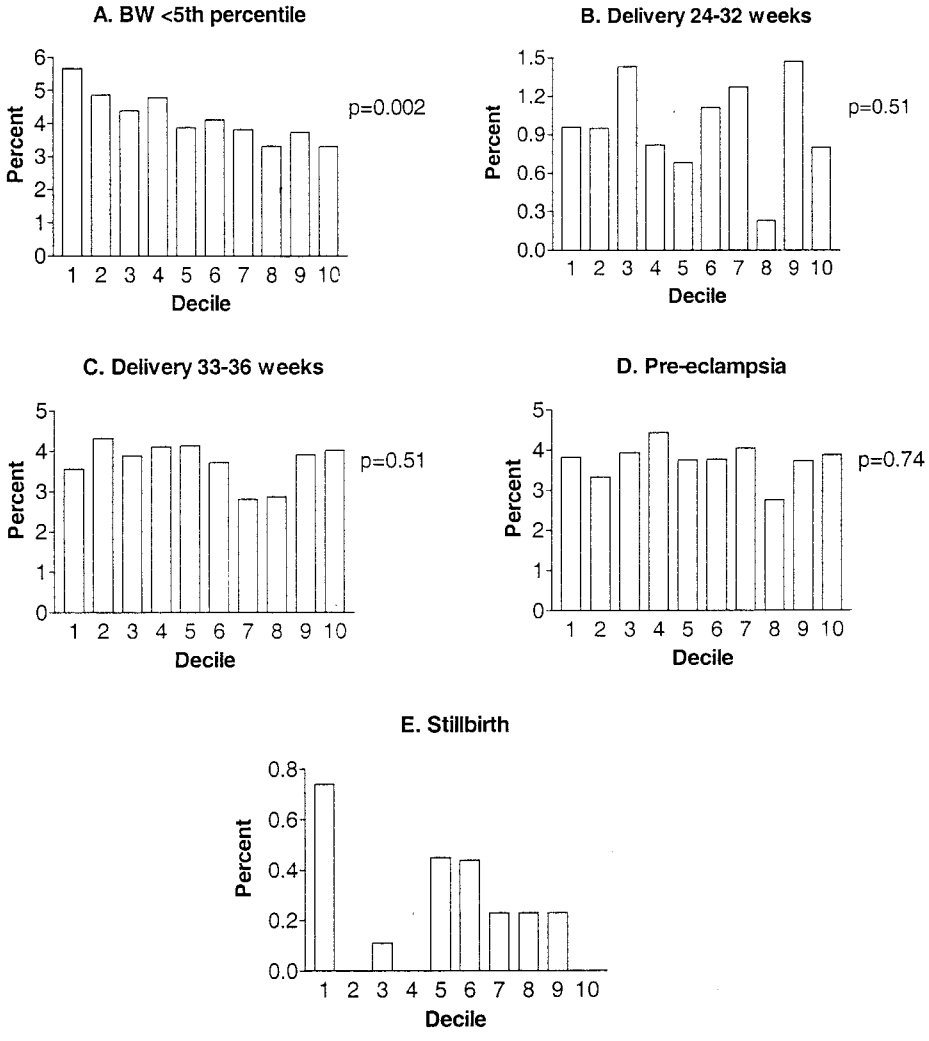

FIG. 2. Proportion of adverse perinatal outcomes related to FβhCG decile. The *P* value is the chi-square test for trend. When data from the smallest decile were excluded, the test for trend remained statistically significant for BW less than fifth percentile ($P = 0.03$). The chi-square test was not performed on stillbirth data, because of the small number of adverse events.

TABLE 2. Univariate analysis of first-trimester biochemistry and perinatal outcomes

	PAPP-A				FβhCG			
	Smallest 5th percentile (n = 461)	>5th Percentile (n = 8378)	Odds ratio (95% CI)	*P*	Smallest 5th percentile (n = 456)	>5th Percentile (n = 8383)	Odds ratio (95% CI)	*P*
BW < 5th percentile for gestational age	46 (10.0%)	324 (3.9%)	2.8 (2.0–3.8)	<0.0001	30 (6.6%)	340 (4.1%)	1.7 (1.1–2.5)	0.008
Delivery, 24–32 wk	12 (2.6%)	74 (0.9%)	3.0 (1.6–5.5)	0.0002	6 (1.3%)	80 (1.0%)	1.4 (0.6–3.1)	0.44
Delivery, 33–36 wk	35 (7.9%)	291 (3.5%)	2.2 (1.6–3.4)	<0.0001	10 (2.2%)	316 (3.8%)	0.6 (0.3–1.1)	0.09
Preeclampsia	35 (7.6%)	296 (3.5%)	2.1 (1.6–3.2)	<0.0001	19 (4.1%)	312 (3.7%)	1.1 (0.7–1.8)	0.63
Stillbirth	4 (0.9%)	18 (0.2%)	4.0 (1.4–11.5)	0.03	3 (0.7%)	19 (0.2%)	2.9 (0.9–9.8)	0.10

Statistical comparison by χ^2 test or Fisher's exact test, as appropriate.

technique could not be used as a screening test. Our current findings of an association between low PAPP-A and adverse outcome provide additional weight to our hypothesis that adverse perinatal outcome may be determined in early pregnancy. These observations suggest that measurement of specific circulating trophoblast-derived proteins in the first trimester of pregnancy may provide a potential screening tool to identify women at increased risk of subsequent adverse pregnancy outcome.

There is an extensive literature on the use of trophoblast-derived steroids and proteins, including PAPP-A, as biochemical tests of fetal well-being in the third trimester of pregnancy (7), although these are not currently widely used in antepartum monitoring. Previous studies of first-trimester measurement of PAPP-A and perinatal outcome have reported inconsistent results. One study compared first-trimester PAPP-A levels in 73 babies ultimately born less than the fifth percentile for gestational age and 87 babies ultimately born preterm with matched controls. There was no statistically significant difference between the groups (8). However, another study found a positive correlation between PAPP-A at 8–14 wk and eventual BW (9), and an

TABLE 3. Adjusted odds ratios for adverse perinatal outcomes associated with first-trimester PAPP-A and FβhCG in the lowest 5th percentile

Outcome	PAPP-A <5th percentile		FβhCG <5th percentile	
	Adjusted odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
BW < 5th percentile	2.9 (2.0–4.1)	<0.001	1.3 (0.9–2.0)	0.15
Delivery, 24–32 weeks	2.9 (1.6–5.5)	0.001	1.1 (0.5–2.7)	0.77
Delivery, 33–36 weeks	2.4 (1.7–3.5)	<0.001	0.5 (0.3–1.0)	0.04
Preeclampsia	2.3 (1.6–3.3)	<0.001	1.1 (0.7–1.8)	0.64
Stillbirth	3.6 (1.2–11.0)	0.02	2.3 (0.7–8.2)	0.18

Odds ratios are adjusted for BMI, height, smoking status, ethnicity, parity, maternal age, gestational age at the time of sampling, PAPP-A, and FβhCG. Odds ratios for delivery wk 33–36 are also adjusted for interaction between age ≥35 and height.

analysis of 60 *in vitro* fertilization pregnancies described lower concentrations of PAPP-A in the first trimester among 8 women who eventually delivered preterm (10). Another study of 5297 women demonstrated lower PAPP-A levels at 10–14 wk gestation among women who miscarried, delivered babies small for gestational age, and developed preeclampsia (11). However, PAPP-A was used in these women to estimate the risk of the fetus having Down's syndrome, and the study failed to take into account the effect of invasive procedures, which may well have explained the association with loss before 24 wk. Moreover, none of these studies took into account smoking status. Because smoking is associated with many of these outcomes (12) and is also associated with low PAPP-A (4), these studies are difficult to interpret. The advantages of the present study are: that it was a prospective cohort study, that the levels of serum markers did not influence clinical management, that key maternal factors such as weight and smoking were taken into account, and that it included much larger numbers of women who ultimately experienced adverse events.

The pattern of the association varied for different outcomes (Fig. 1). In the case of preeclampsia, stillbirth, and extremely premature birth, the association was only with the smallest decile of PAPP-A. In the case of growth restriction and moderately premature delivery, the association was observed across the whole range of PAPP-A. Moreover, low FβhCG was also associated with growth restriction, although this was lost after adjusting for PAPP-A, whereas low FβhCG was not significantly associated with the other outcomes, even in univariate analysis (Tables 2 and 3). Both PAPP-A and FβhCG are produced by the syncytiotrophoblast (13, 14). It seems likely that these different patterns of association may reflect different pathophysiological mechanisms relating first-trimester trophoblast function and later adverse perinatal outcome. The fact that the strength and pattern of the association differed for the two trophoblast-derived proteins suggests that PAPP-A is not acting as a simple marker of the volume or health of the trophoblast but that the association reflects a specific property of PAPP-A in the physiological regulation of trophoblast function.

The precise mechanisms linking first-trimester levels of trophoblast-derived proteins and adverse outcomes will require further study. PAPP-A has been identified as a protease for IGF binding protein (IGFBP)-4 (15). IGFBPs bind IGF-I and IGF-II, inhibiting their interaction with cell surface receptors and have, therefore, a key role in modulating IGF activity (16). Because PAPP-A breaks down IGFBP (15), low levels of PAPP-A would be expected to be associated with high levels of IGFBP and, therefore, low levels of free IGF. The IGFs have a key role in regulating fetal growth (17). The IGFs have also been shown to control uptake of glucose and amino acids in cultured trophoblast (18) and are thought to have an important role in the autocrine and paracrine control of trophoblast invasion of the decidua (19). The current observation that PAPP-A was predictive of a range of adverse obstetric outcomes implies a fundamental role of this system in development of the placenta in early pregnancy, and the observed association between low PAPP-A and poor perinatal outcome is clearly biologically plausible.

In summary, first-trimester serum concentrations of PAPP-A, a trophoblast-specific protein regulating IGF function, is highly predictive of a range of subsequent adverse pregnancy outcomes. These observations imply that adverse outcome in late pregnancy may be determined in the first trimester of pregnancy, that control of the IGF system in early pregnancy may be critical in normal placental development, and that women at high risk of adverse pregnancy outcome may be identified in very early pregnancy.

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Competing financial interests: declared none.

Development

Early-pregnancy origins of low birth weight

Low birth weight is a significant cause of morbidity and mortality among newborns, and may result from impaired placental function during the first trimester of pregnancy[1]. Here we show that the risk of delivering a low-birth-weight baby at term after an uncomplicated pregnancy varies with maternal circulating concentrations of a placental protein, pregnancy-associated plasma protein-A (PAPP-A) in the first 10 weeks after conception. Poor fetal growth may therefore already have been determined by the time obstetric monitoring begins after completion of the first trimester.

PAPP-A acts as a protease on the binding proteins of insulin-like growth factor (IGF)[2,3] and may therefore increase the known stimulatory effects of placental IGFs[4]. Circulating concentrations of PAPP-A increase during the first three months of pregnancy, and this protein is highly expressed in trophoblasts[5]. We therefore investigated a possible link between the birth weight of a baby at term and maternal levels of PAPP-A during the first trimester. We determined the specificity of associations with PAPP-A by comparing it with the free β-subunit of human chorionic gonadotrophin (β-CG), another trophoblast-derived protein whose circulating levels change in the first trimester[6] but which is functionally unrelated to the IGF system.

As part of a prospective, multicentre, non-interventional cohort study, we obtained serum from 4,288 women at 8–12 weeks of gestation (dated by ultrasound, equivalent to 6–10 weeks after conception), who ultimately had uncomplicated singleton pregnancies and delivered normal, live babies at full term. We had complete data for these women on maternal age, parity, height, body-mass index, race and smoking status.

Serum levels of PAPP-A and free β-CG were measured using a Kryptor immunoassay analyser (Brahms Diagnostica) and converted to multiples of the appropriate gestational median (MOM), corrected for smoking status[7] and maternal weight[8].

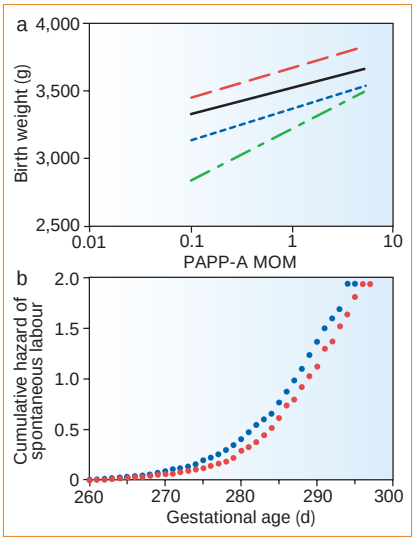

Figure 1 Association between pregnancy-associated plasma protein-A (PAPP-A), birth weight at 38–41 weeks of gestation and timing of labour at full term. **a,** Eventual birth weight plotted against PAPP-A multiples of the median (MOM; on a $\log_{10}$ scale) from a linear regression analysis. Curves (from bottom to top) represent gestational ages of 38, 39, 40 and 41 weeks. Coefficients (95% CI) for change in birth weight associated with a one $\log_{10}$ unit change in PAPP-A MOM: 38 weeks, 380 (209–552); 39 weeks, 231 (113–349); 40 weeks, 196 (104–289); 41 weeks, 221 (112–331); $P < 0.0001$ in each case. Coefficients were virtually unchanged after adjusting for age, parity, body-mass index, height, smoking status and race. **b,** Cumulative hazard (Nelson–Aelen cumulative hazard function[10]) of spontaneous labour on each day of gestation at full term, comparing the lowest (top curve) and highest (bottom curve) quintiles of first-trimester PAPP-A MOMs. Univariate comparison, $P = 0.0003$ (log rank test).

There was a greater proportion of low-birth-weight infants (under 2,500 g) delivered to women with a first-trimester PAPP-A concentration in the lowest 5% (9 out of 201, 4.5%) compared with other women (65 out of 4,087, 1.6%; $P = 0.002$). Using multivariate logistic regression (adjusting for maternal height, race, body-mass index, smoking status and elective delivery), a one $\log_{10}$ unit increase in first trimester PAPP-A MOM (roughly equivalent to the range from the 1st to the 99th percentile) was associated with an 80% reduction in the risk of a low-birth-weight baby (adjusted odds ratio, 0.2; 95% CI, 0.1–0.6; $P = 0.002$). In contrast, there was no significant independent relationship in the case of free β-CG (adjusted odds ratio, 0.6; 95% CI, 0.2–1.3; $P = 0.17$).

The factors that determine variation in birth weight are fetal growth and the duration of pregnancy. We examined the relationship between PAPP-A concentration and fetal growth using multiple linear-regression analysis, and identified a strong, positive correlation between first-trimester levels of PAPP-A and eventual birth weight at 38–41 weeks of gestation (Fig. 1a). There was no strong association between free β-CG levels and birth weight at the same gestational age.

The relationship between first-trimester concentrations of PAPP-A or free β-CG and the timing of labour at full term was determined using time-to-event analysis[9]. Vaginal delivery after non-induced labour was taken as the event and all other modes of delivery were treated as censored. Lower concentrations of PAPP-A during the first trimester were associated with an earlier onset of spontaneous labour at full term (Fig. 1b).

In a multivariate proportional hazards model, there was a strongly additive and inverse relationship between levels of PAPP-A and free β-CG, and the likelihood of spontaneous labour on any given day of gestation at full term (adjusted hazard ratio for a one $\log_{10}$ unit change in MOM (95% CI): PAPP-A, 0.81 (0.69–0.96), $P = 0.003$; free β-CG, 0.79 (0.69–0.91), $P < 0.001$).

The association between PAPP-A levels, fetal growth and the timing of labour is biologically plausible, as PAPP-A is highly expressed in first-trimester trophoblasts[5] and may be responsible for activation of IGFs. Our results indicate that the risk of delivering a low-birth-weight baby at full term may be determined by the placental activity of IGFs in very early pregnancy.

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PRELIMINARY COMMUNICATION

First-Trimester Placentation and the Risk of Antepartum Stillbirth

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Context Preterm birth and low birth weight are determined, at least in part, during the first trimester of pregnancy. However, it is unknown whether the risk of stillbirth is also determined during the first trimester.

Objective To determine whether the risk of antepartum stillbirth varies in relation to circulating markers of placental function measured during the first trimester of pregnancy.

Design, Setting, and Participants Multicenter, prospective cohort study (conducted in Scotland from 1998 through 2000) of 7934 women who had singleton births at or after 24 weeks' gestation, who had blood taken during the first 10 weeks after conception, and who were entered into national registries of births and perinatal deaths.

Main Outcome Measures Antepartum stillbirths and stillbirths due to specific causes.

Results There were 8 stillbirths among the 400 women with levels of pregnancy-associated plasma protein A (PAPP-A) in the lowest fifth percentile compared with 17 among the remaining 7534 women (incidence rate per 10000 women per week of gestation: 13.4 vs 1.4, respectively; hazard ratio [HR], 9.2 [95% confidence interval {CI}, 4.0-21.4]; $P<.001$). When analyzed by cause of stillbirth, low level of PAPP-A was strongly associated with stillbirth due to placental dysfunction, defined as abruption or unexplained stillbirth associated with growth restriction (incidence rate: 11.7 vs 0.3, respectively; HR, 46.0 [95% CI, 11.9-178.0]; $P<.001$), but was not associated with other causes of stillbirth (incidence rate: 1.7 vs 1.1, respectively; HR, 1.4 [95% CI, 0.2-10.6]; $P=.75$). There was no relationship between having a low level of PAPP-A and maternal age, ethnicity, parity, height, body mass index, race, or marital status. Adjustment for maternal factors did not attenuate the strength of associations observed. There was no association between maternal circulating levels of the free β subunit of human chorionic gonadotropin and stillbirth risk.

Conclusion The risk of stillbirth in late pregnancy may be determined by placental function in the first 10 weeks after conception.

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STILLBIRTH AFFECTS APPROXIMATELY 1 in 200 pregnancies and is therefore approximately 10 times more common than sudden infant death syndrome.[1] In approximately 85% of stillbirths, death of the fetus occurs prior to labor.[2] The main epidemiological factors associated with an increased risk of stillbirth are advanced gestational age, advanced maternal age, nulliparity, high parity, smoking, obesity, and poor obstetric history.[3] However, most of these associations are relatively weak. Effective interventions have been described to reduce perinatal mortality, such as Doppler ultrasonography of umbilical artery blood flow[4] and induction of labor, which is used in prolonged pregnancy.[5] However, application of these interventions requires identification of women at high risk of stillbirth.

We have shown that the risk of a number of pregnancy complications, such as preterm birth and low birth weight, is determined, at least in part, during the first trimester of pregnancy.[6,7] However, it is not known whether the risk of stillbirth is also determined during the first trimester. In the present large-scale, multicenter, prospective cohort study, we determined the risk of antepartum stillbirth in relation to maternal serum levels of 2 proteins derived from the placenta—pregnancy-associated plasma protein A (PAPP-A) and the free β subunit of human chorionic gonadotropin (HCG)—measured during the first 10 weeks after conception.

METHODS

We used data from the Combined Ultrasound and Biochemical Screening (CUBS)[8] study, a prospective, multicenter study of screening for Down syndrome. The CUBS study evaluated the use of ultrasound measurement of fetal nuchal translucency in combination with analysis of maternal serum levels of PAPP-A and free β subunit of HCG as a first-trimester screening test for Down syndrome in a routine pre-

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natal clinic setting. Information leaflets about the study were sent to women with the notification of their first appointment for prenatal care. Those women whose first visit was within 14 weeks' gestation were invited to participate and those who agreed signed a consent form. Participation in the study involved obtaining a measurement of nuchal translucency at the time of the first ultrasound and an additional blood sample at the time of phlebotomy for routine prenatal investigations. No results were reported to either the obstetrician or patient and prenatal care was not modified in any way due to participation in the study. Ethical approval was obtained from the ethics committee for Scottish Multicenter Research. Fifteen Scottish maternity units participated during a 2-year period between 1997 and 1999 and 98.6% of records came from births in 11 of the hospitals. Ninety-eight percent of the births occurred between May 1998 and July 2000. Births to women recruited to the study constituted 28.6% of all births in the 11 hospitals during that period.

Pregnancy outcome was ascertained by record linkage to the Scottish Morbidity Record[9] and the Scottish Stillbirth and Infant Death Enquiry.[1] The Scottish Morbidity Record is a national registry of pregnancy outcome data and the Scottish Stillbirth and Infant Death Enquiry is a national registry that routinely classifies all perinatal deaths in Scotland. Both registries are close to 100% complete and are described in detail elsewhere.[1,9] The study cohort for the current analysis was defined by women who participated in the CUBS study, had a PAPP-A level recorded prior to 91 days' gestation (equivalent to <77 days after conception) assessed by crown-rump length, and were linked to the Scottish Morbidity Record in which singleton birth occurred at or after 24 weeks' gestation. This cutoff was chosen because ascertainment of stillbirths at less than 24 weeks' gestation is incomplete and the causes are not defined in the Scottish Stillbirth and Infant Death Enquiry.[1] There were no data on spontaneous and therapeutic abortions.

Definitions and Denominators

Maternal height, smoking status, marital status, ethnicity, and body mass index (weight in kilograms divided by the height in meters squared) were ascertained at the time of the first prenatal visit. Maternal age was defined as the age at delivery. Socioeconomic status was estimated based on the postcode of residence, using Carstairs socioeconomic deprivation categories[10] (based on 1991 Census data on car ownership, unemployment, overcrowding, and social class within postcode sectors of residence, which contain approximately 1600 residents). Women were categorized into quintiles of socioeconomic deprivation. The gestational age at birth was defined as completed weeks of gestation. Race was self-reported by questionnaire (options were white and other). Many studies have shown disparity in stillbirth risk comparing racial groups, but our population had a small proportion of nonwhite women.

The cause of perinatal death was classified by a modified version of the Wigglesworth system.[8] Explained stillbirths were defined as those in which there was an apparent direct cause, such as fetal abnormality, placental abruption, or maternal diabetes. All other stillbirths were classified as unexplained. Unexplained stillbirths were subdivided into those that were small for gestational age (SGA; in the smallest fifth percentile for sex and week of gestation) and those appropriate for gestational age. Unexplained SGA stillbirths were assumed to reflect chronic placental insufficiency. Therefore, stillbirths due to abruption or SGA unexplained stillbirths were considered collectively as stillbirths due to placental causes.

Statistical Analyses

Levels of PAPP-A and free β subunit of HCG were expressed as multiples of the median for gestational age, which is the convention for biochemical indices in pregnancy that vary with week of gestation. Because PAPP-A levels vary inversely with maternal weight, multiples of the median were corrected for maternal weight using reciprocal-linear regression. This method is widely used in prenatal screening and is described in detail elsewhere.[11] Separate multiples of the median for PAPP-A level were estimated for smokers because PAPP-A level is reduced by 15% among smokers.[8] Univariate comparison of continuous variables was performed using the Mann-Whitney test and of categorical data using the Fisher exact test. All *P* values were 2-sided. Statistical significance was assumed at $P<.05$.

The association between PAPP-A level and stillbirth was assessed by comparing women with levels in the lowest fifth percentile with women in other percentiles. We previously showed that a low PAPP-A level was associated with a range of adverse outcomes. However, we also studied PAPP-A level as a continuous variable and categorized it by quintiles. The risk of stillbirth was compared between groups using time to event analyses in which week of gestation from 24 weeks onward was used as the time scale. The gestational age at delivery was taken as the time of the event in the case of antepartum stillbirth or the time of censoring in the case of all other births. This method uses ongoing pregnancies as the denominator, as previously suggested,[12] but accounts for censoring due to birth and allows multivariate analysis[2] and can be used in situations in which not all individuals would ultimately experience the event.[13] This analytic approach allows assessment of the relative risk accounting for variation in the duration of pregnancy. Survival data were plotted as a cumulative percentage of the event, which is recommended for rare outcomes,[14] and univariate statistical comparisons were made using the log-rank test. Crude and adjusted hazard ratios were estimated using a Cox proportional hazards model.[15] The proportional hazards assumption was tested using the global test of Grambsch

and Therneau.[16] Goodness of fit was assessed by the global test described by May and Hosmer.[17] Missing values were imputed using multiple imputation.[18] All statistical analyses were performed using STATA statistical software (version 8.2, STATA Corp, College Station, Tex).

RESULTS

The linked database contained 11 729 records of women who had a PAPP-A level recorded and had an entry in the Scottish Morbidity Record. In 3 records (<0.1%), the gestational age at delivery was less than 24 weeks, leaving a cohort of 11 726 singleton births at or after 24 weeks' gestation. Among these, 7934 (67.7%) were assayed prior to 13 weeks' gestation (equivalent to <77 days after conception). The median gestational age at sampling was 11.9 weeks (69 days after conception; interquartile range [IQR], 65-73 days). There was no relationship between low PAPP-A level and maternal characteristics (TABLE 1). Circulating serum levels of PAPP-A (expressed in multiples of the median for gestational age) were lower in male fetuses compared with female (median [IQR], 0.97 [0.67-1.41] vs 1.03 [0.71-1.46], respectively; $P<.001$).

There were 25 (0.3%) antepartum stillbirths in the study group. An autopsy was performed on 19 (76%) of the stillborns. Ten stillbirths were attributed to placental causes—4 due to

Table 1. Maternal Characteristics in Relation to Levels of PAPP-A in the First 10 Weeks After Conception*

	Percentile of PAPP-A Level		
	≤Fifth (n = 400)†	>Fifth (n = 7534)	*P* Value
Age, median (IQR), y	29 (25-33)	30 (26-33)	.26
Marital status			
Married	244 (61.0)	4597 (61.0)	.39
Other	135 (33.8)	2416 (32.1)	
Missing data	21 (5.2)	521 (6.9)	
Deprivation quintile			
1 (Least deprived)	82 (20.5)	1653 (21.9)	.60
2	61 (15.2)	1177 (15.6)	
3	78 (19.5)	1613 (21.4)	
4	102 (25.5)	1645 (21.8)	
5 (Most deprived)	77 (19.2)	1440 (19.1)	
Missing data	0	6 (0.1)	
Ethnicity			
White	373 (93.2)	6912 (91.7)	.44
Other	6 (1.5)	182 (2.4)	
Missing data	21 (5.2)	440 (5.8)	
Smoking status			
Nonsmoker	277 (69.2)	5161 (68.5)	.91
Former smoker	31 (7.8)	615 (8.2)	
Current smoker	89 (22.3)	1719 (22.8)	
Missing data	3 (0.8)	39 (0.5)	
No. of previous births			
None	226 (56.5)	4158 (55.2)	.61
≥1	174 (43.5)	3376 (44.8)	
No. of previous abortions			
None	276 (69.0)	5363 (71.2)	.35
≥1	124 (31.0)	2171 (28.8)	
Height, median (IQR), cm	163 (159-168)	163 (159-168)	.53
Missing data	10 (2.5)	151 (2.0)	.49
Body mass index, median (IQR)‡	23.7 (21.6-27.1)	23.9 (21.6-26.9)	.91
Missing data	43 (10.8)	644 (8.6)	.13

Abbreviations: IQR, interquartile range; PAPP-A, pregnancy-associated plasma protein A.
*Values are presented as number (percentage) unless otherwise indicated.
†The lowest fifth percentile of PAPP-A was equivalent to <0.4 multiples of the median.
‡Calculated as weight in kilograms square of height in meters.

Table 2. Low PAPP-A in the First 10 Weeks After Conception and the Risk of Stillbirth*

Stillbirth Category	No. (%) in ≤Fifth Percentile of PAPP-A Level (n = 400)	Incidence Rate†	No. (%) in >Fifth Percentile of PAPP-A Level (n = 7534)	Incidence Rate†	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)‡	*P* Value
All cause	8 (2.0)§	13.4	17 (0.2)	1.4	9.2 (4.0-21.4)	<.001	9.4 (4.1-21.9)	<.001
Due to abruption	3 (0.8)	5.0	1 (<0.1)	0.1	58.0 (6.0-557.3)	<.001	60.5 (6.1-597.0)	<.001
All unexplained	4 (1.0)	6.7	12 (0.2)	0.9	6.6 (2.1-20.4)	.001	7.2 (2.3-22.4)	.001
Unexplained SGA	4 (1.0)	6.7	2 (<0.1)	0.2	40.0 (7.3-218.3)	<.001	46.6 (8.3-262.1)	<.001
All placenta-related	7 (1.8)‖	11.7	3 (<0.1)	0.3	46.0 (11.9-178.0)	<.001	52.6 (13.3-207.8)	<.001
Not related to placental dysfunction	1 (0.2)	1.7	14 (0.2)	1.1	1.4 (0.2-10.6)	.75	1.4 (0.2-10.9)	.73

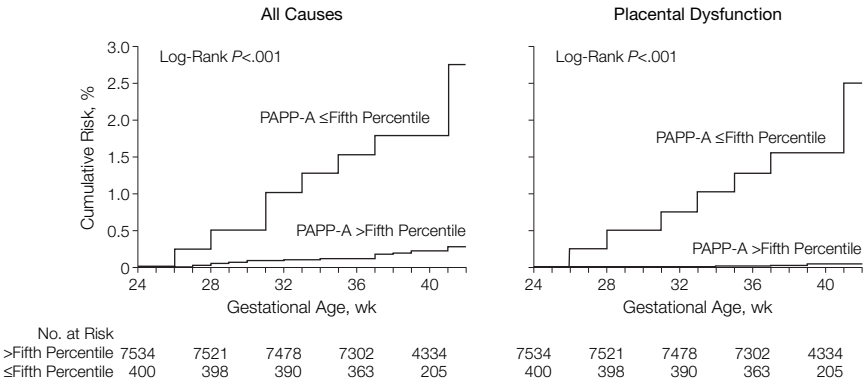
Abbreviations: CI, confidence interval; HR, hazard ratio; PAPP-A, pregnancy-associated plasma protein A; SGA, small for gestational age.
*The earliest stillbirth occurred at 24 weeks and the latest occurred at 41 weeks.
†Incidence expressed per 10 000 women per week of gestation from 24 weeks.
‡Adjusted for maternal age, height, body mass index, marital status, ethnicity, socioeconomic deprivation category, smoking, and fetal sex.
§Attributable fraction = 28.4%.
‖Attributable fraction = 68.4%.

abruption and 6 were SGA unexplained stillbirths. An autopsy was performed on all of the SGA unexplained stillbirths. Among the 400 women with PAPP-A levels in the lowest fifth percentile (<0.4 multiples of the median), 8 (2%) had a stillbirth due to any cause, 3 (0.8%) had a stillbirth due to abruption, 4 (1.0%) had a stillbirth due to SGA unexplained stillbirth, and 7 (1.8%) had a stillbirth due to placental causes. When compared with the rest of the population, a low PAPP-A level was associated with a 9.2-fold risk of all-cause stillbirth (TABLE 2, FIGURE 1A), a 58.0-fold risk of stillbirth due to abruption, a 40.0-fold risk of SGA unexplained stillbirth, and a 46.0-fold risk of stillbirth due to placental dysfunction (Figure 1B). There were 2 stillbirths due to chromosomal abnormality in the study group and one of these was to a mother with a low PAPP-A level. This was the sole stillbirth among this group not due to a placental cause.

The proportion of stillbirths due to placental dysfunction was 7 of 8 among women with a low PAPP-A level compared with 3 of 17 in the other women ($P=.002$). FIGURE 2 illustrates the relationship between quintiles of PAPP-A level and the risk of stillbirth due to placental dysfunction. There were no stillbirths due to placental dysfunction among women with PAPP-A levels in the upper 3 quintiles. There was no relationship between free β subunit of HCG quintile and the risk of all-cause stillbirth ($P=.59$) or stillbirth due to placental dysfunction (Figure 2).

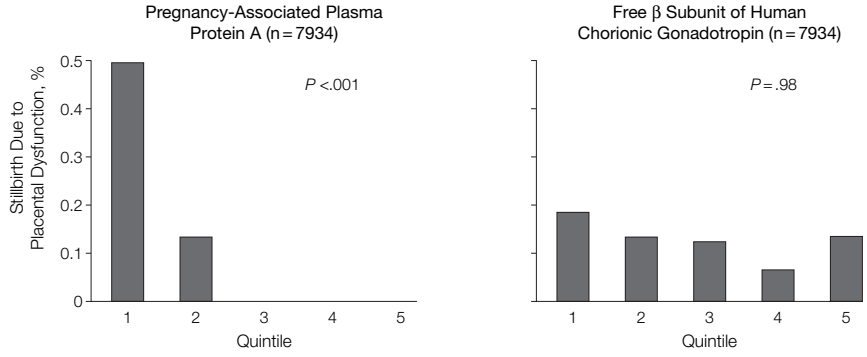
The numbers of all-cause stillbirths were sufficient to test the goodness of fit of the multivariate model, to test the proportional hazards assumption, and to determine whether there were any interactions between PAPP-A and the other factors. There was no evidence of poor fit ($P=.93$), there was no evidence of nonproportionality ($P=.25$), and there were no statistically significant interactions between PAPP-A level and the other maternal characteristics (all $P>.01$). When treated as a continuous variable, the hazard ratio associated with an increase in multiples of the median for PAPP-A level was 0.13 (95% confidence interval [CI], 0.04-0.40) and for free β subunit of HCG was 1.06 (95% CI, 0.67-1.69). The multiples of the median of PAPP-A level among stillbirths caused by placental dysfunction was 0.34 (IQR, 0.27-0.45) and for other births was 1.00 (IQR, 0.69-1.43) ($P<.001$).

Figure 1. Cumulative Risk of Stillbirth Among Women With Normal or Low Levels of Pregnancy-Associated Plasma Protein A (PAPP-A)



Normal indicates higher than the fifth percentile for gestational age and low is the fifth percentile or lower for gestational age. Hazard ratios are given in Table 2.

Figure 2. Placental Stillbirths in Relation to Level of Pregnancy-Associated Plasma Protein A and Level of Free β Subunit of Human Chorionic Gonadotropin



P value is from the Fisher exact test (virtually identical *P* values obtained when estimated using log-rank test of survival comparing the 5 quintiles). The upper limits of the quintiles of pregnancy-associated plasma protein A level are 0.63, 0.87, 1.15, 1.55, 9.1. The upper limits of the quintiles of free β subunit of human chorionic gonadotropin are 0.61, 0.87, 1.18, 1.72, 9.53.

COMMENT

The main finding of this study is that women in the first 10 weeks after conception with circulating levels of PAPP-A in the lowest fifth percentile had a greater than 40-fold risk of having an intrauterine fetal death due to placental dysfunction, which was independent of maternal characteristics. There was no relationship between maternal circulating levels of free β subunit of HCG and stillbirth due to any cause. The strengths of the present study are that all data were collected prospectively and all outcomes were defined independently of the study. Because level of PAPP-A was not used in the clinical estimation of Down syndrome risk, there is no potential for confounding due to bias in the use of invasive procedures. The study design excluded women who had a therapeutic

abortion due to a chromosomal abnormality. It is likely that some of these women would have had low PAPP-A levels. However, because chromosomal abnormalities are relatively rare, excluding these women would have virtually no effect on the strength of the association between stillbirth and placental dysfunction. Our data suggest that the placental dysfunction causing stillbirth may be an end point of impaired placental function in the first 10 weeks after conception.

We had previously described a 3.6-fold risk of all-cause stillbirth among women with low levels of PAPP-A.[19] This was based on partial follow-up of the CUBS cohort.[8] However, 40% of the 8839 women in that analysis were sampled in the second trimester and the partial follow-up included insufficient numbers of women sampled in the first trimester for subanalysis. Moreover, it was not a prior hypothesis that levels of PAPP-A would be associated with stillbirth and detailed information on the cause of stillbirth was not retrieved in our previous study. We addressed these weaknesses in the present study by linking the entire CUBS cohort to a national database of perinatal deaths. Consequently, in the present study, we had data for almost 8000 women sampled before 13 weeks' gestation and stillbirths could be classified according to the cause. This is the first study, to our knowledge, which demonstrates an association between a biochemical measurement in the first trimester and the risk of stillbirth. Moreover, the strength of the association between PAPP-A level and stillbirth caused by placental dysfunction is one of strongest described for this outcome.

The main weakness of this study is the relatively small number of events, which leads to wide 95% CIs. However, the lower limit of the 95% CI of the hazard ratio for placental causes of stillbirth was 12 and this study is, therefore, powered to demonstrate a strong association. Many studies of stillbirth are limited by incomplete ascertainment of cases. However, in the present study ascertainment of events is likely to be close to 100% because it is a legal requirement to register a stillbirth in Scotland and the perinatal death database used is virtually 100% complete when compared against death registries.[1] The present study could be criticized because the women received prenatal care relatively early so the CUBS cohort may not be representative of the general population. However, the study was prospective and ascertainment of stillbirth and definition of its cause for the present analysis was completely independent of the CUBS study. It is unlikely, therefore, that there are biases among women with low levels of PAPP-A that might lead to a spurious association with stillbirth. Moreover, adjustment for a range of maternal characteristics, including all the previously described maternal characteristics associated with stillbirth,[3] did not affect the strength of the association with PAPP-A level. Given the above, it is unlikely that the association between PAPP-A level and stillbirth is due to confounding. The primary purpose of the CUBS study was to assess methods for Down syndrome screening and the association described with stillbirth is the result of a secondary analysis. However, the strength and statistical significance of the associations observed make it unlikely that these are chance findings.

The current study focused on stillbirths at or after 24 weeks' gestation because the data available on these events are close to 100% complete. The data sources used in the present study are less robust for fetal losses between 20 and 23 weeks' gestation.[1] Further studies will be required to determine the association between PAPP-A level and losses at earlier gestational ages. However, the present study is clinically relevant because the stillbirths occurred at gestational ages in which the fetus is viable. Interventions have been described that have been shown to reduce perinatal mortality among high-risk women, specifically, Doppler ultrasonography of umbilical artery blood flow[4] and induction of labor in prolonged pregnancy.[5] This raises the possibility that PAPP-A level might be clinically useful when combined with an intervention. The positive predictive value for placental causes of stillbirth was 1.8% among women with a PAPP-A level in the lowest fifth percentile. Although low, given the rarity of this event, this may justify closer prenatal surveillance and elective delivery prior to 40 weeks' gestation. However, further studies are required to confirm this association before clinical practice is changed. Furthermore, it may be that other proteins derived from the placenta in the first trimester have a higher positive predictive value. This is an area that we are currently studying.

A specific association between PAPP-A level and stillbirth is biologically plausible. PAPP-A has been identified as a protease for insulinlike growth factor binding proteins 4 and 5.[20] Messenger RNA for PAPP-A has been identified in placental X cells and syncytiotrophoblast and the protein has been localized to placental septae, anchoring villi, and chorionic villi.[21] Low levels of PAPP-A would be expected to lead to lower levels of free insulinlike growth factor. The insulinlike growth factor 2 is thought to have a key role in trophoblast function[22] and, therefore, it is plausible that low levels of PAPP-A reflect poor placental function in early pregnancy. Consistent with this, it has recently been shown that mice homozygous for targeted disruption of the PAPP-A gene exhibit severe early onset intrauterine growth restriction.[23] Level of PAPP-A is unlikely to be acting simply as a marker of placental volume. There was no association between stillbirth risk and levels of free β subunit of HCG, which is a protein derived from the placenta that is not involved in the control of the insulinlike growth factor system. The current findings indicate that catastrophic complications of late pregnancy may be determined by impaired placental function in the first 10 weeks after conception, which precedes prenatal care.

Author Contributions: Dr Smith had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Smith, Crossley, Aitken, Connor.
Acquisition of data: Crossley, Aitken, Cameron, Dobbie.
Analysis and interpretation of data: Smith, Crossley, Pell.
Drafting of the manuscript: Smith.
Critical revision of the manuscript for important intellectual content: Smith, Crossley, Aitken, Pell, Cameron, Connor, Dobbie.
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Circulating Angiogenic Factors in Early Pregnancy and the Risk of Preeclampsia, Intrauterine Growth Restriction, Spontaneous Preterm Birth, and Stillbirth

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OBJECTIVE: To estimate the relationship between maternal serum levels of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) in early pregnancy with the risk of subsequent adverse outcome.

METHODS: A nested, case–control study was performed within a prospective cohort study of Down syndrome screening. Maternal serum levels of sFlt-1 and PlGF at 10–14 weeks of gestation were compared between 939 women with complicated pregnancies and 937 controls. Associations were quantified as the odds ratio for a one decile increase in the corrected level of the analyte.

RESULTS: Higher levels of sFlt-1 were not associated with the risk of preeclampsia but were associated with a reduced risk of delivery of a small for gestational age infant (odds ratio [OR] 0.92, 95% confidence interval [CI] 0.88–0.96), extreme (24–32 weeks) spontaneous preterm birth (OR 0.90, 95% CI 0.83–0.99), moderate (33–36 weeks) spontaneous preterm birth (OR 0.93, 95% CI 0.88–0.98), and stillbirth associated with abruption or growth restriction (OR 0.77, 95% CI 0.61–0.95). Higher levels of PlGF were associated with a reduced risk of preeclampsia (OR 0.95, 95% CI 0.90–0.99) and delivery of a small for gestational age infant (OR 0.95, 95% CI 0.91–0.99). Associations were minimally affected by adjustment for maternal characteristics.

CONCLUSION: Higher early pregnancy levels of sFlt-1 and PlGF were associated with a decreased risk of adverse perinatal outcome.

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LEVEL OF EVIDENCE: II

Preeclampsia, intrauterine growth restriction, and preterm birth account for a large proportion of perinatal mortality. There are currently very few interventions in routine clinical practice that have been clearly shown to reduce perinatal deaths due to these complications. The lack of available interventions reflects continuing uncertainty regarding the underlying biologic processes that lead to these outcomes. Recently, a novel approach to preeclampsia has been proposed. Human and animal studies have suggested that a protein released from the placenta, soluble fms-like tyrosine kinase-1 (sFlt-1), may cause the maternal endothelial dysfunction which is characteristic of preeclampsia.[1–3] Recent animal studies have suggested that administration of vascular endothelial growth factor A_{121} (VEGF-A_{121}) to bind and inactivate sFlt-1 may attenuate the preeclamptic phenotype in the animal model.[4] This approach may have promise as a means of treating preeclampsia or preventing its onset in high-risk women. However, there are minimal data on the association between circulating angiogenic factors and other complications of pregnancy. Here we report the association between maternal serum levels of sFlt-1 and placental growth

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factor (PlGF) at 10–14 weeks of gestation and the risk of preeclampsia, delivery of a small for gestational age (SGA) infant, spontaneous preterm birth, or stillbirth

MATERIALS AND METHODS

We performed a nested case–control study using serum samples that were stored as part of the Combined Ultrasound and Biochemical Screening study, a prospective, noninterventional, multicenter study of screening for Down syndrome.[5] The Combined Ultrasound and Biochemical Screening study evaluated the use of ultrasound measurement of fetal nuchal translucency in combination with analysis of maternal serum pregnancy-associated plasma protein A and the free subunit of hCG as a first trimester screening test for Down syndrome in a routine prenatal clinic setting. Information leaflets about the study were sent to women with the notification of their first appointment for prenatal care. Those women with a singleton pregnancy whose first visit was at 14 weeks of gestation or less were invited to participate, and those who agreed signed a consent form. Participation in the study involved measurement of nuchal translucency at the time of the first ultrasonography and obtaining additional blood at the time of phlebotomy for routine prenatal investigations. Serum was analyzed for pregnancy-associated plasma protein A and free β-hCG, and the remainder of the sample was frozen and stored. No results were reported to either the obstetrician or patient, and prenatal care was not modified in any way by participation in the study.

Ethical approval for the cohort study and the subsequent nested case–control study was obtained from the Scottish Multicenter Research Ethics Committee. Fifteen Scottish maternity units participated,[5] recruiting women over a 2-year period between 1997 and 1999. A total of 96.6% of records came from births in 11 hospitals (see Appendix). Ninety-eight percent of the births occurred between May 1998 and July 2000. Births to women recruited to the study constituted 28.6% of all births in these 11 hospitals over that period of time.

The outcome of the pregnancy was ascertained in two ways. First, case notes were manually retrieved from approximately 75% of the cohort, and they were used to identify women diagnosed with preeclampsia.[6] Preeclampsia was defined as women for whom the diagnosis was documented in the clinical record, and this was performed by trained midwives. To obtain outcome data on birth weight percentile, spontaneous preterm birth, and stillbirth for the entire cohort, records were linked to the Scottish Morbidity Record, a national register of pregnancy outcome data,[7] and the Scottish Stillbirth and Infant Death Enquiry, a national register that routinely classifies all perinatal deaths in Scotland.[8] Both registries are close to 100% complete and are described in detail elsewhere.[7,8]

Maternal height, smoking status, marital status, ethnicity, and body mass index (weight in kg divided by the height in meters squared) were ascertained at the time of the first prenatal visit. Maternal age was defined as the age at delivery. Socioeconomic status was estimated based on the post code of residence, using Carstairs socioeconomic deprivation categories[9] (based on 1991 Census data on car ownership, unemployment, overcrowding, and social class within post code sectors of residence, which contain, on average, around 1,600 residents), and women were categorized into quintiles of socioeconomic deprivation. The gestational age at birth was defined as completed weeks of gestation and was based on ultrasound dating performed between 10 weeks and 14 weeks of gestation. Cases were defined as women who had one or more of the following: a diagnosis of preeclampsia; an SGA infant (a liveborn infant with a birth weight less than the 3rd percentile for sex and gestational age); and spontaneous preterm delivery, which was divided into extreme (between 24 weeks and 32 weeks of gestational age) and moderate (between 33 weeks and 36 weeks of gestational age), or stillbirth. Spontaneous preterm deliveries were defined as those where 1) the birth was vaginal or there was a documented duration of labor and 2) labor was not documented as having been induced. All other preterm births were regarded as indicated. Indicated preterm birth was not analyzed as a separate outcome, but was used in the subclassification of preeclampsia: complicated preeclampsia was defined as cases where the mother was had a medically indicated preterm birth or where the fetus was SGA.

Stillbirths excluded those due to congenital abnormality or rhesus disease. The cause of perinatal death was classified by a modified version of the Wigglesworth system.[8] Explained stillbirths were defined as those where there was an apparent direct cause, such as placental abruption. All other stillbirths were classified as unexplained. Unexplained stillbirths were subdivided into those that were SGA and those appropriate for gestational age. Unexplained SGA stillbirths were assumed to reflect chronic placental insufficiency. Therefore, stillbirths due to placental abruption and SGA unexplained stillbirths were also considered collectively as stillbirths due to placental causes, as previously described.[10] Controls were selected at random from among cohort mem-

bers who delivered a liveborn infant of birth weight between the 10th and 90th percentile at or after 37 weeks of gestation.

Assays were performed by enzyme-linked immunosorbent assay for human sFlt-1 and free PlGF using commercial kits (product numbers DVR100 and DPG 00, respectively; R&D Systems, Abingdon, United Kingdom). All analyses were performed within the West of Scotland Regional Genetics Service of the Institute of Medical Genetics, Glasgow, which performs all prenatal biochemical screening assays for the West of Scotland.[11] The minimal detectable concentrations in the assays for sFlt-1 and PlGF were 5 and 7 pg/mL. The interassay and intra-assay coefficients of variation were 14.9% and 10.4%, respectively, for sFlt-1 and 13.7% and 11.3%, respectively, for PlGF.

Maternal serum levels of sFlt-1 and PlGF were expressed as multiples of the median (MoM) for gestational age, as is conventional for biochemical indices in pregnancy which vary with week of gestation. The gestational age–specific medians were calculated from the control group. Multiples of the median values were corrected for maternal weight using reciprocal-linear regression. This is widely employed in standardizing biochemical tests for Down syndrome screening and is described in detail elsewhere.[12] Where levels of an analyte varied in relation to maternal smoking, MoMs were adjusted for smoking status using the data from controls. Cut points for deciles were estimated from the controls and used to classify the levels of the analytes for both cases and controls into deciles. Univariable comparison of continuous variables was performed using the Mann-Whitney *U* test and categorical data using the χ^2 and the χ^2 for trend.[13] All *P* values were two-tailed. Statistical significance was assumed at $P<.05$. Comparison of cases and controls was by odds ratios and 95% confidence intervals (CIs). Multivariable analysis was by logistic regression. Interactions were assessed using the likelihood ratio test[14] and statistical significance of interactions was assumed at $P<.05$, after correcting for the number of comparisons using the Bonferroni method. Due to the rarity of the event, exact logistic regression was used for the analysis of stillbirth data.[15] All statistical analyses were performed using the Stata 8.2 software package (StataCorp LP, College Station, TX), LogExact 5 (Cytel Corporation, Cambridge, MA) or SPSS 12.0 (SPSS Inc., Chicago, IL).

RESULTS

The study group consisted of 939 cases and 937 controls. Among the cases, 309 had a diagnosis of preeclampsia, 65 were spontaneous preterm births between 24 and 32 weeks of gestation, 227 were spontaneous preterm births between 33 and 36 weeks of gestation, 333 had a birth weight less than the 3rd percentile, and 26 were stillbirths, 14 of which had a placental cause. Twenty-one women had two of the preceding diagnoses. Among the 309 women with preeclampsia, 3 (1.0%) had a spontaneous preterm birth, 58 (18.8%) had an indicated preterm birth, and of the 248 births at term, 16 (6.4%) had a birth weight less than the 3rd percentile.

Blood was obtained between 70 and 104 days of gestation in 1,876 (99.5%) of the study group. The median gestational age at sampling was 87 days of gestation (interquartile range 82–92 days). Median sFlt-1 concentration declined from 996 pg/mL at 10 weeks to 834 pg/mL at 14 weeks gestational age. Median PlGF concentrations rose from 38.5 pg/mL at 10 weeks to 76.4 pg/mL at 14 weeks gestational age. There were weak inverse relationships between maternal weight and levels of both sFlt-1 and PlGF. The median MoM for PlGF was 36% higher among smokers whereas there was no significant difference in sFlt-1 between smokers and nonsmokers. Calculation of MoMs and the cutoff points for deciles and quintiles are described in the Appendix.

The characteristics of the cohort are tabulated by status as case or control (Table 1). Cases were younger, were less likely to be married, were more likely to live in an area of high socioeconomic deprivation, were less likely to be white, were more likely to smoke, were more likely to be primigravid, had more previous early pregnancy losses, and were shorter than controls. There were negative linear associations between decile of sFlt-1 and the risk of all adverse outcomes, delivery of an SGA infant, both extreme and moderate spontaneous preterm birth, and stillbirths due to a placental cause (Fig. 1 and Table 2). There was no association between sFlt-1 levels and the risk of preeclampsia. There were negative linear associations between decile of PlGF and the risk of preeclampsia and delivery of an SGA infant (Fig. 2 and Table 2). There was no relationship between levels of either analyte and nonplacental causes of stillbirth (data not shown). We repeated the analyses removing the top and bottom deciles of the given analyte to determine whether the odds ratios were strongly influenced by extreme values. In all but one case, the point estimate of the odds ratio fell

Table 1. Maternal Characteristics in Relation to Case or Control Status

	Controls (n=937)	Cases (n=939)	P*
Age (y)	30 (26-33)	29 (25-33)	.003
Missing	0 (0.0)	5 (0.5)	.02
Marital status			
Married	565 (60.3)	517 (55.1)	
Other	302 (32.2)	352 (37.5)	.05
Missing	70 (7.5)	70 (7.5)	
Deprivation quintile			
1 (least deprived)	204 (21.8)	165 (17.6)	
2	161 (17.2)	135 (14.4)	
3	189 (20.2)	204 (21.7)	.04
4	207 (22.1)	217 (23.1)	
5 (most deprived)	173 (18.5)	213 (22.7)	
Missing	3 (0.3)	5 (0.5)	
Ethnicity			
White	859 (91.7)	834 (88.8)	
Other	20 (2.1)	38 (4.1)	.04
Missing	58 (6.2)	67 (7.1)	
Smoking status			
Nonsmoker	671 (71.6)	544 (57.9)	
Ex-smoker	76 (8.1)	70 (7.5)	<.001
Current smoker	182 (19.4)	314 (33.4)	
Missing	8 (0.8)	11 (1.2)	
Number of previous births			
None	428 (45.7)	532 (56.7)	
One or more	509 (54.3)	402 (42.8)	<.001
Missing	0 (0.0)	5 (0.5)	
Number of previous early losses			
None	692 (73.8)	666 (70.9)	
One or more	245 (26.2)	268 (28.5)	.04
Missing	0 (0.0)	5 (0.5)	
Height (m)	1.63 (1.59–1.68)	1.62 (1.57–1.66)	<.001
Missing	14 (1.5)	30 (3.2)	.02
Body mass index	23.6 (21.6–26.5)	23.7 (21.3–27.2)	>.9
Missing	68 (7.3)	72 (7.7)	.7

Data are n (%) or median (interquartile range).
* *P* values calculated by Mann-Whitney *U* test, χ^2 test, or χ^2 test for trend, as appropriate.

within the 95% confidence intervals in Table 2, indicating that the results were consistent with those including the whole cohort. The exception was the association between sFlt-1 and extreme preterm birth. When the top and bottom deciles were excluded, the odds ratio for a 1-decile increase in sFlt-1 was 1.08 (95% confidence interval 0.94–1.24, *P*=.3).

Adjusting for the level of the other analyte and for maternal characteristics had a minimal effect on the nature and strength of associations (Table 2). There were no statistically significant interactions between decile of either analyte and maternal characteristics (all *P*>.05, adjusted for number of comparisons). There was a statistically significant interaction between decile of sFlt-1 and decile of PlGF in relation to all adverse outcome (odds ratio for the interaction 1.015, 95% CI 1.004–1.026, *P*=.007). The interaction was weaker for preeclampsia but stronger for all other outcomes. The interaction between sFlt-1 and PlGF was then assessed for a composite adverse outcome, namely all cases where there was no diagnosis of preeclampsia. This analysis demonstrated a highly statistically significant interaction between the two analytes (odds ratio for the interaction 1.018, 95% CI 1.006–1.031, *P*=.003). When the analysis of the relationship between sFlt-1 and this composite outcome was stratified by the level of PlGF, it was apparent that the association was stronger when PlGF was lower (Fig. 3).

The association between PlGF and preeclampsia was more marked among women with complicated preeclampsia (defined as being associated with preterm delivery or with an SGA infant; odds ratio 0.88, 95% CI 0.81 to 0.96) than among women with preeclampsia who delivered an infant with birth weight appropriate for gestational age at term (odds

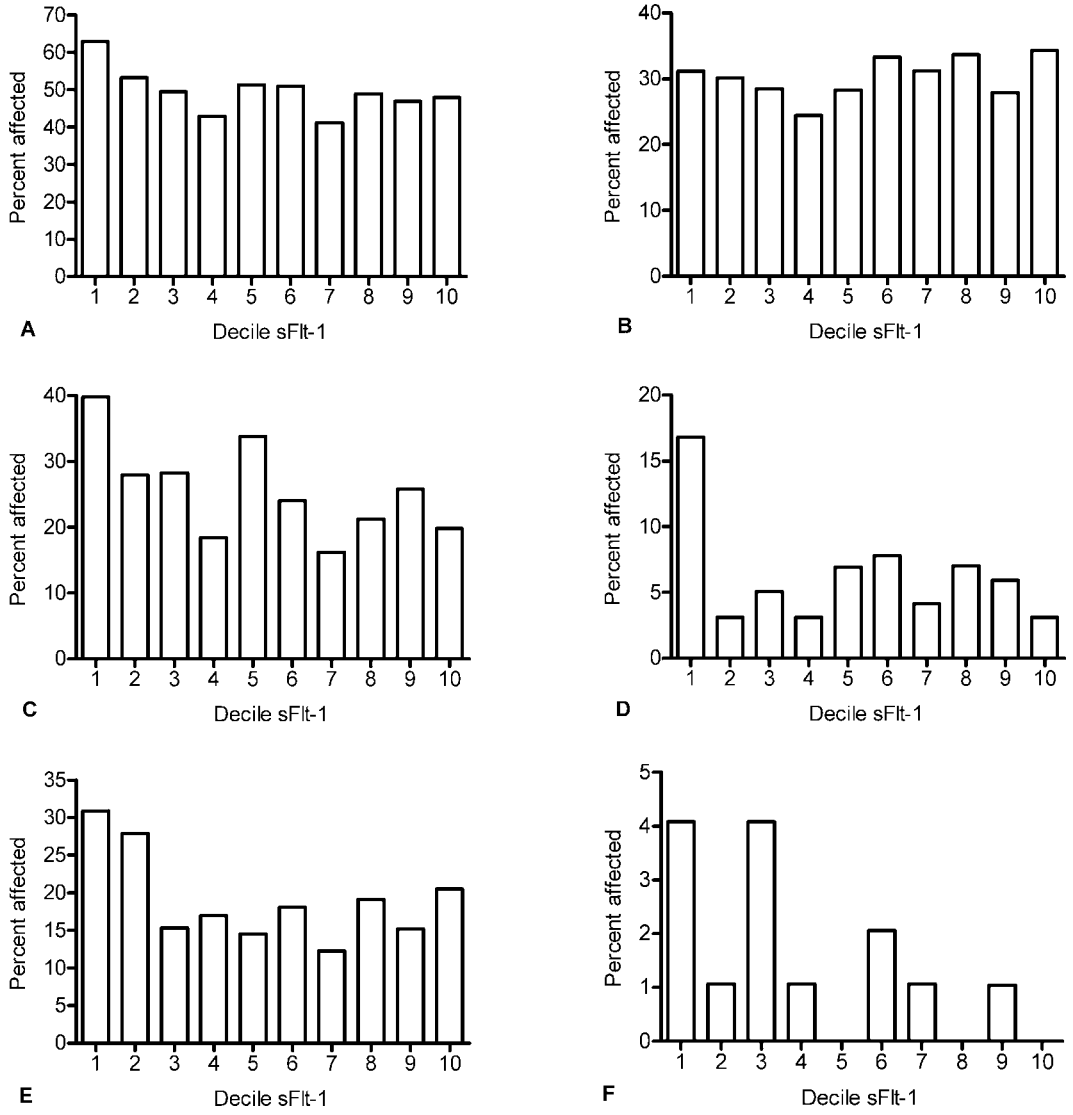

Fig. 1. Proportions of cases and controls in relation to decile of soluble fms-like tyrosine kinase-1 for all adverse outcome **(A)**, preeclampsia **(B)**, delivery of a small for gestational age infant **(C)**, extreme preterm delivery **(D)**, moderate preterm delivery **(E)**, and stillbirth **(F)**. *P* values of test for homogeneity were .001, .9, <.001, .001, .002, and .1, respectively. *P* values of test for trend were .001, .5, <.001, .02, .004, and .01, respectively. Outcomes are defined in the Materials and Methods section. Stillbirths are confined to those with a presumed placental cause. sFlt-1, soluble fms-like tyrosine kinase-1.
Smith. sFlt-1, PlGF, and Adverse Pregnancy Outcome. Obstet Gynecol 2007.

ratio 0.99, 95% CI 0.95 to 1.04). There was no significant association between sFlt-1 and either complicated (odds ratio 0.96, 95% CI 0.89–1.04) or uncomplicated preeclampsia (odds ratio 1.01, 95% CI 0.96–1.06). When the analyses were confined to women whose blood was obtained before 13 weeks of gestation, the pattern of associations was very similar to the findings for the whole population (Fig. 4).

DISCUSSION

We found no association between circulating levels of sFlt-1 at 10–14 weeks of gestation and the risk of preeclampsia, but a decreased risk of the disease among women with higher levels of PlGF. These findings are in complete agreement with a previous large-scale nested case–control study that found no association between maternal serum levels of sFlt-1 and the risk of preeclampsia in early pregnancy but a reduced risk of the disease among women with high levels of PlGF from 13 weeks onward.[3] However, we demonstrate that women with higher circulating levels of sFlt-1 at 10–14 weeks of gestation were at lower risk of other complications of pregnancy, specifically delivery of an SGA infant, spontaneous preterm birth,

Table 2. Associations Between Decile of Maternal Serum sFlt-1 and PlGF and the Risk of Adverse Outcome

	sFlt-1			PlGF		
Outcome	OR*	95% CI	*P*	OR*	95% CI	*P*
Univariable						
All	0.95	0.92–0.98	.001	0.97	0.94–1.00	.06
Preeclampsia	1.02	0.97–1.06	.5	0.95	0.90–0.99	.02
SGA	0.92	0.88–0.96	<.001	0.95	0.91–0.99	.02
Preterm delivery (wk)						
24–32	0.90	0.83–0.99	.02	1.02	0.93–1.11	.7
33–36	0.93	0.88–0.98	.004	0.99	0.95–1.04	.8
Stillbirth (placental)†	0.77	0.61–0.95	.01	0.91	0.74–1.10	.3
Adjusted for other analyte and maternal characteristics‡						
All	0.94	0.91–0.97	.001	0.98	0.94–1.01	.3
Preeclampsia	0.99	0.94–1.04	.7	0.93	0.88–0.98	.02
SGA	0.92	0.87–0.96	.001	0.93	0.89–0.98	.007
Preterm delivery (wk)						
24–32	0.90	0.82–1.00	.05	1.05	0.95–1.16	.3
33–36	0.93	0.88–0.98	.008	1.01	0.96–1.07	.6
Stillbirth (placental)†	0.71	0.53–0.91	.005	0.94	0.74–1.17	.6

sFlt-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; OR, odds ratio; CI, confidence interval; SGA, small for gestational age.

* Odds ratios are for a one decile increase in the level of the analyte.

† Associations with stillbirth estimated using exact logistic regression.

‡ Maternal characteristics were age, ethnicity, parity, body mass index, height, smoking status, and hospital of delivery. Due to computational constraints, multivariable analysis for stillbirth risk did not include hospital of delivery.

and stillbirth. Higher levels of PlGF at 10–14 weeks of gestation were associated with a decreased risk of delivery of an SGA infant but were not associated with the other outcomes.

The finding of improved outcome in association with higher levels of sFlt-1 is of particular interest. It could be that high circulating levels of sFlt-1 have some physiologic role in early pregnancy. Alternatively, it could be that high levels of sFlt-1 reflect some other aspect of placental function that is in turn associated with better outcome. It is unlikely that sFlt-1 is acting simply as a marker of placental mass, because we have previously related maternal serum levels of the free β-hCG at the same gestational age to the risk of later adverse outcome and failed to demonstrate any association.[6]

Previous studies have related maternal serum levels of sFlt-1 in pregnancy to the risk of adverse outcome for the offspring. Two demonstrated no association between maternal levels of sFlt-1 and the risk of delivering an SGA infant.[16,17] A further study demonstrated elevated levels of sFlt-1 at 23–25 weeks gestational age among women with high-resistance patterns of uterine artery flow velocimetry and established early onset growth restriction.[18] None of these studies corrected sFlt-1 levels for the gestational age at the time of sampling or for maternal weight, and none included more than 30 cases. Previous studies had demonstrated inconsistent relationships between levels of PlGF and the risk of delivering an SGA infant, with both higher[19] and lower[20,21] levels of PlGF reported.

We observed a statistically significant interaction between sFlt-1 and PlGF. There was no prior hypothesis that these factors would interact. We found that among women with low PlGF, elevated levels of sFlt-1 were significantly protective against adverse perinatal outcome, whereas there was no association between levels of sFlt-1 among women with PlGF levels in the upper two quintiles (Fig. 3). The assay employed in this study measured free PlGF. Soluble Flt-1 binds PlGF, and high levels of sFlt-1 would be anticipated to lead to low levels of free PlGF. The interaction could indicate that low circulating PlGF due to high levels of sFlt-1 is associated with better outcome than low circulating PlGF due to other causes, such as reduced placental production. Alternatively, it could indicate that a protective effect of sFlt-1 is antagonized by high circulating levels of PlGF.

Higher levels of sFlt-1 in late pregnancy are associated with an increased risk of preeclampsia. In contrast, we show that higher levels of sFlt-1 in very early pregnancy are associated with a decreased risk of other pregnancy complications. This finding is potentially clinically relevant. It has been hypothe-

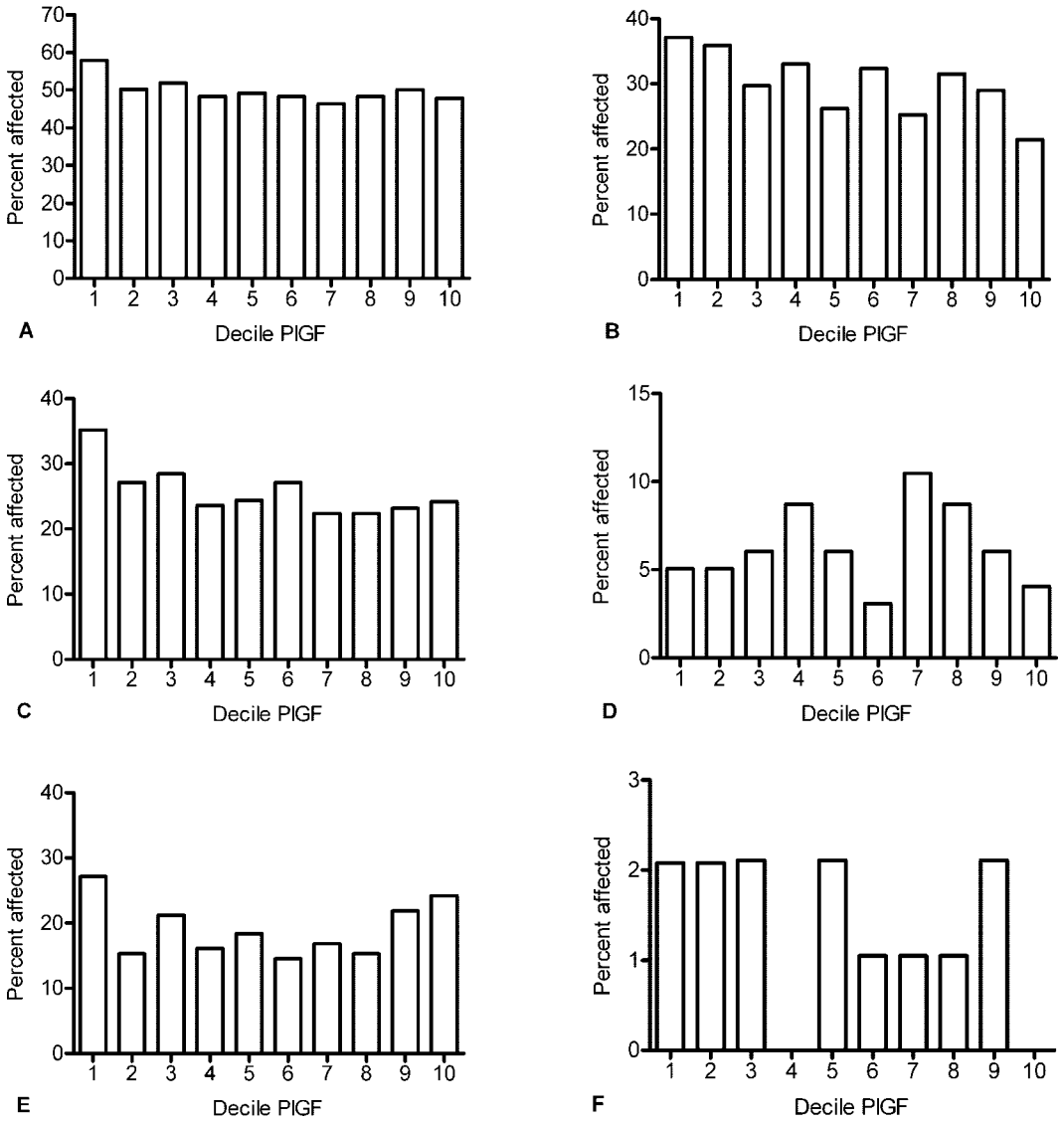

Fig. 2. Proportions of cases and controls in relation to decile of placental growth factor for all adverse outcome **(A)**, preeclampsia **(B)**, delivery of a small for gestational age infant **(C)**, extreme preterm delivery **(D)**, moderate preterm delivery **(E)**, and stillbirth **(F)**. *P* values of test for homogeneity were .6, .3, .4, .5, .2, and .9, respectively. *P* values of test for trend were .06, .02, .02, .7, .8, and .3, respectively. Outcomes are defined in the Materials and Methods section. Stillbirths are confined to those with a presumed placental cause. PlGF, placental growth factor.

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sized that there is a causal association between elevated maternal levels of sFlt-1 and preeclampsia.[3] It is proposed that sFlt-1 is released by the placenta into the maternal circulation and binds maternal PlGF and VEGF-A, leading to maternal endothelial dysfunction,[3] and animal studies are consistent with this model.[1,4] These data suggest that administration of VEGF-A_{121}, or alternative approaches to reducing maternal circulating levels of sFlt-1, may be therapeutically useful among women with established preeclampsia or among women who are at increased risk of the disease. The current data indicate that this has the potential to be harmful in early pregnancy. It may be prudent to conduct further observational studies of the associations in late pregnancy before evaluation of such treatments.

Haig[22] has advanced the hypothesis that "preeclampsia can be interpreted as an attempt by a poorly nourished fetus to increase its supply of nutrients by increasing the resistance of its mother's peripheral circulation." Given that high levels of sFlt-1 are associated with an increased risk of preeclampsia

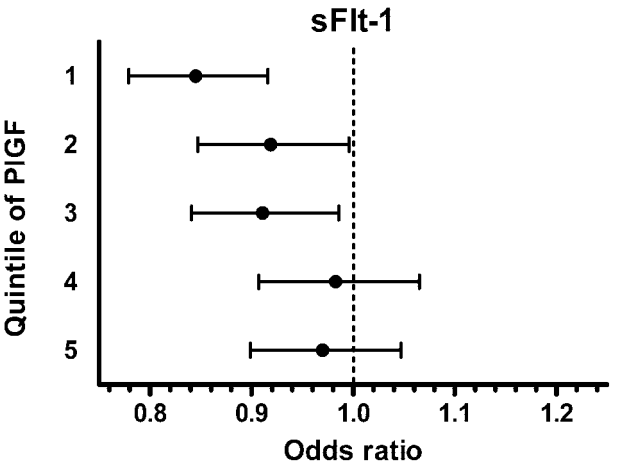

Fig. 3. Plot of odds ratio for a one decile increase in soluble fms-like tyrosine kinase-1 across quintiles of placental growth factor. The outcome is any case where there was no diagnosis of preeclampsia. Bars are 95% confidence intervals. Odds ratios and 95% confidence intervals were estimated using logistic regression. sFlt-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor.

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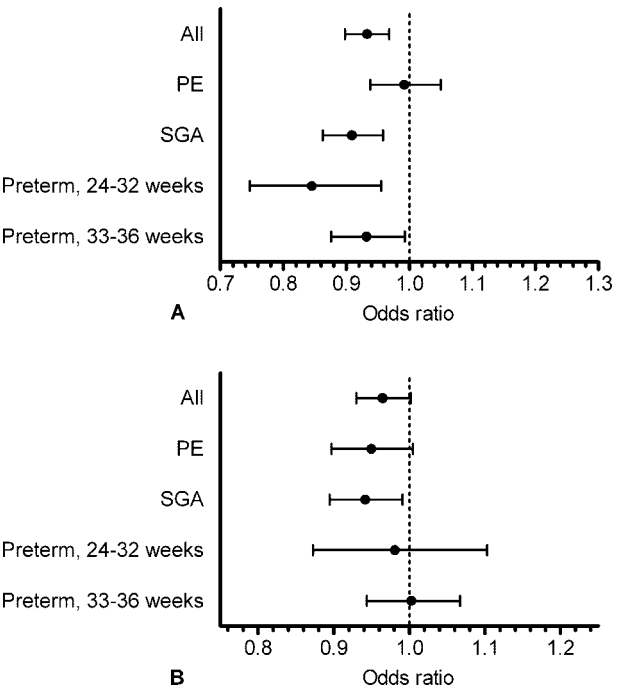

Fig. 4. Odds ratios for a one decile increase in soluble fms-like tyrosine kinase-1 **(A)** and placental growth factor **(B)** for all adverse outcome (All), preeclampsia (PE), delivery of a small for gestational age (SGA) infant, spontaneous preterm birth between 24–32 weeks of gestation (Preterm, 24–32 weeks), and spontaneous preterm birth 33–36 weeks of gestation (Preterm, 33–36 weeks). Analyses confined to cases and controls where serum obtained before 13 weeks of gestation. Points are odds ratios and bars are 95% confidence intervals, both estimated by logistic regression analysis.

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but a decreased risk of growth restriction, preterm birth, and stillbirth, it is possible that high levels of sFlt-1 in the maternal circulation represent a physiologic signal from the placenta to optimize uterine perfusion. Longitudinal assessment of sFlt-1 in pregnancy in combination with maternal blood pressure and assessment of uteroplacental blood flow would help determine whether sFlt-1 may have such a role.

The biologic basis for the association between sFlt-1 and preterm birth warrants further study. There are some data that indicate an association is biologically plausible. Studies of pregnant human uterus have demonstrated expression of VEGF-A in the myometrium.[23] Studies in the pregnant rat demonstrated expression of VEGF-A and its main functional receptor in the cervix. Moreover, VEGF-A expression peaks in association with ripening of the cervix.[24] If VEGF-A also had a role in human cervical ripening, low levels of sFlt-1 could result in increased free VEGF-A and hence promote preterm birth. There are no data on the possible effects of PlGF on the myometrium and cervix, and this should also be addressed.

In conclusion, higher levels of sFlt-1 in early pregnancy were associated with a decreased risk of intrauterine growth restriction, spontaneous preterm labor, and stillbirth. Strategies aimed at reducing the risk of preeclampsia by inactivating sFlt-1 in the maternal circulation may adversely affect perinatal outcome.

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APPENDIX

Regressed median of soluble fms-like tyrosine kinase-1 (sFlt-1) in relation to gestational age:

sFlt-1 (in pg/mL)=$e^{(6.389+33.366/x)}$, where x is the gestational age in days.

Regressed multiple of the median of sFlt-1 in relation to maternal weight:

Multiple of the median of sFlt-1=0.6944+18.2822/x, where x is the maternal weight in kilograms.

Regressed median of placental growth factor (PlGF) in relation to gestational age:

PlGF (in pg/mL)=$e^{(2.071+0.02288/x)}$, where x is the gestational age in days.

Regressed multiple of the median of PlGF in relation to maternal weight:

Multiple of the median of PlGF=0.8609+9.8629/x, where x is the maternal weight in kilograms.

Correction of multiple of the median of PlGF for maternal smoking:

Smokers: Multiples of the median (MoM) value divided by 1.29. Nonsmokers: MoM value divided by 0.95

Cut points for deciles of sFlt-1 (expressed as MoM):

0.572, 0.702, 0.814, 0.909, 1.016, 1.117, 1.219, 1.366, and 1.611.

Cut points for deciles of PlGF (expressed as MoM):

0.610, 0.720, 0.824, 0.907, 1.003, 1.092, 1.197, 1.332, and 1.575

Cut point for quintiles of PlGF (expressed as MoM):

0.720, 0.907, 1.092, and 1.332.

Eleven hospitals recruiting 98.6% of patients:

The Queen Mother's Hospital, Glasgow; Simpson Maternity, Edinburgh; Southern General Hospital, Glasgow; Royal Maternity Hospital, Glasgow; Royal Alexandria Hospital, Paisley; Ninewells, Dundee; Ayrshire Central Hospital, Irvine; Forth Park, Kikcaldy; Stirling Royal Infirmary, Stirling; Falkirk and District Royal Infirmary, Falkirk, and Inverclyde Royal Hospital, Greenock.

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Epidemiology

Maternal and biochemical predictors of antepartum stillbirth among nulliparous women in relation to gestational age of fetal death

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Objective To determine whether maternal serum levels of alphafetoprotein (α-FP) and human chorionic gonadotrophin (hCG) at 15–21 weeks provided clinically useful prediction of stillbirth in first pregnancies.

Design Retrospective study of record linkage of a regional serum screening laboratory to national registries of pregnancy outcome and perinatal death.

Setting West of Scotland, 1992–2001.

Population A total of 84 769 eligible primigravid women delivering an infant at or beyond 24 weeks of gestation.

Methods The risk of stillbirth between 24 and 43 weeks was assessed using the Cox proportional hazards model. Logistic regression models within gestational windows were then used to estimate predicted probability. Screening performance was assessed as area under the receiver operating characteristic (ROC) curve.

Main outcome measure Antepartum stillbirth unrelated to congenital abnormality.

Results The odds ratio (95% CI) for stillbirth at 24–28 weeks for women in the top 1% were 11.97 (5.34–26.83) for α-FP and 5.80 (2.19–15.40) for hCG. The corresponding odds ratios for stillbirth at or after 37 weeks were 2.44 (0.74–8.10) and 0.79 (0.11–5.86), respectively. Adding biochemical to maternal data increased the area under the ROC curve from 0.66 to 0.75 for stillbirth between 24 and 28 weeks but only increased it from 0.64 to 0.65 for stillbirth at term and post-term. Women in the top 5% of predicted risk had a positive likelihood ratio of 7.8 at 24–28 weeks, 3.7 at 29–32 weeks, 5.1 at 33–36 weeks and 3.4 at 37–43 weeks, and the corresponding positive predictive values were 0.97, 0.33, 0.47 and 0.63%, respectively.

Conclusions Maternal serum levels of α-FP and hCG were statistically associated with stillbirth risk. However, the predictive ability was generally poor except for losses at extreme preterm gestations, where prevention may be difficult and interventions have the potential to cause significant harm.

Keywords α-fetopcoteins, chorionic gonadotrophins, risk, stillbirth.

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Introduction

Intrauterine fetal death before the onset of labour (antepartum stillbirth) is one of the most common severe complications of pregnancy. It affects approximately 1 in 200 pregnancies and accounts for almost two-thirds of all perinatal deaths.[1] Antepartum stillbirth is potentially preventable by elective delivery.[2] The effect of this intervention depends on the gestational age. At extreme preterm gestations, delivery may result in either neonatal death or survival with long-term impairment.[3] However, elective delivery at term carries a low risk of infant or maternal morbidity and mortality.[4,5] Hence, assessment of stillbirth risk and knowledge of the gestational age where the risk is increased is clinically important.

Nulliparous women are at increased risk of antepartum stillbirth.[6] Moreover, the outcome of previous pregnancies is one of the most informative predictors of the risk of complications in future pregnancies,[7–9] and clearly, this information is not available among nulliparous women. Hence, developing novel predictors of stillbirth risk is particularly important for the care of nulliparous women. Elevated maternal serum levels of alphafetoprotein (α-FP) and human

chorionic gonadotrophin (hCG) are associated with an increased risk of antepartum stillbirth.[10,11] However, the gestational age dependence of these associations is currently unclear, as are the properties of these measurements as a screening test for stillbirth risk. Moreover, many maternal characteristics are also associated with stillbirth risk.[7] The gestational age dependence and screening performance of these, both in isolation and in combination with α-FP and hCG, are also currently unclear.

We obtained complete demographic and second-trimester biochemical screening data on approximately 85 000 nulliparous women and addressed the following aims: (1) to assess the relationship between maternal characteristics and serum screening data and the risk of stillbirth, (2) to determine whether the associations between maternal and biochemical factors varied according to gestational age and (3) to characterise the screening properties of a combined model at different gestational ages.

Methods

Data sources and woman selection

The Scottish Morbidity Record collects information on clinical and demographic characteristics and outcomes for all women discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been greater than 99% complete since the late 1970s.[12] The Scottish Stillbirth and Infant Death Enquiry is a national register that routinely classifies all perinatal deaths in Scotland.[1] All women attending for antenatal care in the West of Scotland are offered biochemical screening, using maternal serum levels of α-FP and hCG to assess their risk of having a fetus affected by Down syndrome and structural fetal abnormality, and approximately 81% of them accept screening.[13] The laboratory information management system for the West of Scotland antenatal screening programme in the Institute of Medical Genetics in Glasgow contains a database of the maternal information and biochemical screening results, and electronic storage of these data in their current form was commenced in September 1991. A probability-based matching approach[14] was employed using maternal identifiers to link the Scottish Morbidity Record, the Scottish Stillbirth and Infant Death Enquiry and the antenatal screening database in the Institute of Medical Genetics. We excluded multiple births and births outside the range 24–43 weeks of gestation. Ethical approval for the linkage was obtained from the Privacy Advisory Committee of the Information and Statistics Division of the NHS, Scotland.

Definitions

Maternal age, parity, postcode of residence and all outcome data were obtained solely from the Scottish Morbidity Record. Maternal weight was obtained solely from the biochemical database. Maternal height and smoking were obtained from the Scottish Morbidity Record, except in cases where they were missing from the Scottish Morbidity Record, the biochemical database was employed. The smoking status (current, past, never) was determined from information at the time of the first antenatal visit. Maternal age was defined as the age of the mother at the time of delivery. Body mass index (BMI) was calculated from the weight in kilogram recorded at the time of sampling for α-FP assay divided by the height in metres squared. Socio-economic status was estimated based on the postcode of residence, using Carstairs socio-economic deprivation categories[15] (based on 1991 Census data on car ownership, unemployment, overcrowding and social class within postcode sectors of residence which contain, on average, around 1600 residents).

The gestational age at birth was defined as the completed weeks of gestation on the basis of the estimated date of delivery in each woman's clinical record; standard national criteria exist for the estimation of date of delivery using menstrual and ultrasound data.[16] The gestational age has been confirmed by ultrasound scan in the first half of pregnancy in more than 95% of pregnancies in the UK from the early 1990s.[17] The birthweight was categorised into sex- and gestational-age-specific percentiles, as previously described in detail.[18] Small for gestational age (SGA) was defined as birthweight in the smallest 5% for sex and week of gestation of delivery, and those above this threshold were considered appropriate for gestational age (AGA). Maternal serum levels of α-FP and hCG were quantified as multiples of the median (MoM) for week of gestation, corrected for maternal weight.[19]

The cause of antepartum stillbirth was classified according to a modified version of the Wigglesworth hierarchical system which is described in detail elsewhere.[1] Stillbirths were defined as antepartum or intrapartum, and the cause of stillbirth was classified according to direct obstetric causes (in order): congenital abnormality, pre-eclampsia, haemorrhage (antepartum), mechanical, maternal, miscellaneous and unexplained. The hierarchy dictates that a perinatal death where there was severe pre-eclampsia complicated by abruption would be classified as being caused by pre-eclampsia, as pre-eclampsia is above haemorrhage in the hierarchy. Similarly, a stillbirth where the infant was SGA and the mother had pre-eclampsia would be defined as being caused by pre-eclampsia. Deaths caused by congenital anomaly were defined as 'any structural or genetic defect incompatible with life or potentially treatable but causing death' and were excluded. Hence, women who had a loss or therapeutic abortion where the fetus was affected by structural or chromosomal abnormalities associated with maternal serum screening were excluded from the analysis. Stillbirths caused by mechanical, maternal and miscellaneous causes were combined into the category of 'other'. There was no information on whether women had an amniocentesis. However, serum screening was performed no

later than 21 weeks, and all procedure-related losses would be expected to have occurred prior to 24 weeks. Classification is performed by a single, medically qualified individual (the Scottish Coordinator) with the results of postmortem investigations, where obtained.

Statistical analysis

Continuous variables were summarised by the median and interquartile range (IQR). Univariate comparisons were performed using the Mann–Whitney *U* test, the chi-square test and the chi-square test for trend, as appropriate. The *P* values for all the hypothesis tests were two sided, and statistical significance was assumed at $P < 0.05$. All the variables were treated as categorical. Biochemical data were categorised into quintiles, with the last quintile split into the top 5, 6–10 and 11–20%. For detailed analysis, the top 5% was further subdivided into the top 1, 2–3 and 4–5%. We preformed univariate and multivariate Cox regression using gestational age as the time scale, antepartum stillbirth as the event, and all other births as censored. The proportional hazards assumption was tested using the method of Grambsch and Therneau.[20] The rationale for and advantages of this approach are discussed in detail elsewhere.[21] Risk factors for stillbirth within four gestational windows were then explored using logistic regression analysis. Each woman contributed one record for each gestational window covered by her pregnancy. Stillbirth within the gestational window was taken to be the event, and all births at that or a later gestation were taken as the denominator. Factors whose associations with stillbirth had been shown in the proportional hazards model to vary significantly with gestation were included with an interaction term with gestational window, whereas the rest of the predictors were included without interactions. The predicted probability of stillbirth in each gestational window was obtained from the logistic model. The performance of the model in each gestational window was assessed via the area under the receiver operating characteristic (ROC) curve. Further, the positive predictive value, sensitivity, specificity and positive and negative likelihood ratios were estimated using different thresholds of predicted risk as screen positive, specifically, the top 5,

Table 1. Comparison of maternal and outcome characteristics by occurrence of antepartum stillbirths

	No antepartum stillbirth (*n* = 84 363)	Antepartum stillbirth (*n* = 406)	*P**
Maternal characteristics			
Age, median (IQR)	26 (22–30)	27 (22–31)	0.1
Height, median (IQR)	163 (158–167)	162 (157–167)	0.007
BMI, median (IQR)	23.5 (21.4–26.3)	24.0 (21.8–27.9)	<0.001
Deprivation category			
1 (least deprived)	3121 (3.7)	6 (1.5)	0.02
2	8729 (10.4)	33 (8.1)	
3	15 481 (18.4)	66 (16.3)	
4	20 979 (24.9)	108 (26.6)	
5	14 219 (16.9)	64 (15.8)	
6	13 143 (15.6)	79 (19.5)	
7 (most deprived)	8691 (10.3)	50 (12.3)	
Smoking status			
Never	52 202 (61.9)	185 (45.6)	<0.001
Current	24 258 (28.8)	185 (45.6)	
Former	7903 (9.4)	36 (8.9)	
Marital status			
Married	43 375 (51.4)	195 (48.0)	0.2
Other	40 988 (48.6)	211 (52.0)	
Maternal serum α-FP (multiple of the median), median (IQR)	1.03 (0.83–1.29)	1.16 (0.89 to 1.46)	<0.001
Maternal serum hCG (multiple of the median), median (IQR)	1.03 (0.74–1.45)	1.09 (0.74 to 1.59)	0.03
Gestational age at birth (weeks)			
24–28	328 (0.4)	106 (26.1)	<0.001
29–32	782 (0.9)	75 (18.5)	
33–36	4135 (4.9)	76 (18.7)	
37–43	79 118 (93.8)	149 (36.7)	

*Mann–Whitney *U* test, chi-square test or chi-square test for trend, as appropriate.

Table 2. Association between second-trimester maternal serum levels of α-FP and different causes of stillbirth

Causes of stillbirth	α-FP ≤ 95th percentile (n = 80 408)		α-FP > 95th percentile (n = 4361)		Odds ratio	95% CI	P*
	Experienced outcome	Percent	Experienced outcome	Percent			
All causes	353	0.43	53	1.21	2.79	2.09–3.73	<0.001
Pre-eclampsia	26	0.03	11	0.25	7.82	3.91–15.62	<0.001
Haemorrhage	43	0.05	7	0.16	3.00	1.38–6.55	0.005
Unexplained (All)	250	0.31	31	0.71	2.30	1.58–3.33	<0.001
Unexplained (SGA)	62	0.07	12	0.28	3.58	1.94–6.58	<0.001
Unexplained (AGA)	188	0.23	19	0.44	1.87	1.17–2.98	0.009
Other	34	0.04	4	0.09	2.17	0.80–5.87	0.1

CI, confidence interval.
*Chi-square test or Fisher's exact test as appropriate.

10 and 20%. All statistical analyses were performed using the Stata software package (Stata Corporation, College Station, TX, USA), version 8.2.

Results

There were 216 563 records of singleton births with a recorded value of maternal serum α-FP and hCG levels which could be linked to Scottish morbidity record 2, and 97 264 (44.9%) of these were first births. Among this group, we excluded 69 (0.1%) deliveries that were outside the range of 24–43 gestational weeks and 133 (0.1%) deaths caused by fetal abnormality or rhesus isoimmunisation. Of the remaining 97 062 records, 12 293 (12.7%) had missing data on one or more variable (2 [<0.1%] maternal age, 1297 [1.3%] height, 6927 [7.1%] BMI, 171 [0.2%] deprivation category, 5724 [5.9%] smoking status and 5 [0.01%] previous spontaneous early pregnancy losses), leaving a study group of 84 769 births (87.3% of eligible births).

The upper limits of percentiles (all expressed as MoM) for the 20th, 40th, 60th, 80th, 90th, 95th, 97th and 99th percentiles were 0.77, 0.93, 1.10, 1.35, 1.59, 1.83, 2.03 and 2.52, respectively, for α-FP and 0.66, 0.88, 1.13, 1.53, 1.92, 2.33, 2.65 and 3.44, respectively, for hCG. Women who experienced antepartum stillbirth in their first pregnancy were shorter, had higher median BMI, were more likely to live in an area of high socio-economic deprivation and were more likely to smoke (Table 1). There was no difference in median maternal age or marital status in relation to stillbirth. Women who experienced stillbirths had higher second-trimester levels of α-FP and hCG. An elevated value of α-FP was associated with an increased risk of stillbirth caused by pre-eclampsia, haemorrhage and of unexplained stillbirth (Table 2). The association with unexplained stillbirth was stronger where the birthweight was SGA. An elevated level of hCG was strongly associated with the risk of stillbirth caused by pre-eclampsia and weakly associated with unexplained stillbirth. The latter relationship was similar for AGA and SGA losses (Table 3).

When the risk of all-cause stillbirth was assessed using a Cox proportional hazards model, it was positively associated with maternal age, deprivation category and BMI and

Table 3. Association between second-trimester maternal serum levels of hCG and different causes of stillbirth

Causes of stillbirth	hCG ≤ 95th percentile (n = 80 408)		hCG > 95th percentile (n = 4361)		Odds ratio	95% CI	P*
	Experienced outcome	Percent	Experienced outcome	Percent			
All causes	365	0.45	41	0.94	1.93	1.39–2.66	<0.001
Pre-eclampsia	26	0.03	11	0.25	7.24	3.62–14.45	<0.001
Haemorrhage	45	0.06	5	0.11	1.90	0.78–4.64	0.2
Unexplained (All)	258	0.32	23	0.53	1.52	1.00–2.33	0.05
Unexplained (SGA)	68	0.08	6	0.14	1.51	0.67–3.40	0.3
Unexplained (AGA)	190	0.24	17	0.39	1.53	0.93–2.50	0.09
Other	36	0.04	2	0.05	0.95	0.00–3.57	>0.9

CI, confidence interval.
*Chi-square test or Fisher's exact test as appropriate.

Table 4. Risk of antepartum stillbirth in relation to maternal second-trimester serum biochemistry and demographic characteristics

Variables	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
α-FP percentile						
1–20	0.84	0.59–1.20		0.87	0.61–1.25	
21–40	0.96	0.68–1.36		0.99	0.70–1.39	
41–60	Reference			Reference		
61–80	1.34	0.98–1.84		1.30	0.95–1.78	
81–90	1.44	1.00–2.08		1.36	0.95–1.96	
91–95	1.49	0.94–2.35		1.33	0.84–2.10	
96–97	1.76	0.95–3.26		1.60	0.86–2.95	
98–99	2.86	1.70–4.81		2.48	1.47–4.17	
100	8.13*	5.07–13.06		6.34	3.92–10.25	
Trend test			<0.001			<0.001
Heterogeneity test			<0.001			<0.001
hCG percentile						
1–20	1.21	0.88–1.66		1.08	0.79–1.48	
21–40	0.83	0.59–1.17		0.80	0.57–1.13	
41–60	Reference			Reference		
61–80	1.04	0.76–1.43		1.10	0.80–1.51	
81–90	1.16	0.80–1.67		1.27	0.87–1.84	
91–95	1.29**	0.82–2.01		1.44**	0.91–2.25	
96–97	1.53	0.83–2.81		1.70	0.92–3.15	
98–99	2.11*	1.25–3.58		2.28*	1.34–3.89	
100	3.03*	1.65–5.58		3.10*	1.67–5.77	
Trend test			0.002			<0.001
Heterogeneity test			<0.001			<0.001
Age (years)						
<20	1.12	0.82–1.53		0.89	0.63–1.25	
20–24	1.03	0.78–1.35		0.86	0.65–1.15	
25–29	Reference			Reference		
30–34	1.20	0.92–1.57		1.28	0.98–1.67	
35–39	1.74	1.19–2.53		1.79	1.23–2.61	
>39	2.49	1.02–6.09		2.29	0.94–5.62	
Trend test			0.04			<0.001
Heterogeneity test			0.02			0.004
Deprivation category						
1 (least deprived)	0.38	0.17–0.86		0.42	0.19–0.97	
2	0.73	0.50–1.08		0.77	0.52–1.14	
3	0.83	0.61–1.13		0.86	0.63–1.16	
4	Reference			Reference		
5	0.88	0.64–1.20		0.85	0.63–1.16	
6	1.18	0.88–1.58		1.14	0.85–1.53	
7 (most deprived)	1.15	0.82–1.60		1.05	0.75–1.48	
Trend test			0.001			0.02
Heterogeneity test			0.02			0.09
Height (cm)						
<150	1.07	0.44–2.62		0.88	0.36–2.16	
150–154	1.59	1.12–2.26		1.47	1.03–2.10	
155–159	1.48	1.12–1.95		1.44	1.10–1.90	
160–164	Reference			Reference		
165–169	1.18	0.90–1.55		1.20	0.92–1.58	
170–174	0.85	0.59–1.24		0.89	0.61–1.29	
>174	1.08	0.64–1.83		1.12	0.66–1.90	
Trend test			0.006			0.045
Heterogeneity test			0.01			0.05

(*continued*)

Table 4. (*Continued*)

Variables	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Smoking						
Nonsmoker	Reference			Reference		
Current smoker	2.19	1.78–2.68		2.48	1.98–3.11	
Ex-smoker	1.28	0.90–1.83		1.40	0.98–2.01	
Heterogeneity test			<0.001			<0.001
BMI (kg/m^2)						
<20	1.43	1.05–1.97		1.36	0.99–1.87	
20–24	Reference			Reference		
25–29	1.47	1.16–1.86		1.44	1.13–1.82	
>30	2.12	1.60–2.81		1.96	1.47–2.60	
Trend test			<0.001			<0.001
Heterogeneity test			<0.001			<0.001
Marital status						
Married	Reference			Reference		
Other	1.15	0.95–1.40		1.03	0.82–1.29	
Heterogeneity test			0.2			0.82

CI, confidence interval.
Test of proportional hazards assumption: $*P < 0.05$, $**P < 0.01$, all others $P \geq 0.05$.
Global test of proportional hazards assumption for multivariate model: $P = 0.05$.

negatively associated with height (Table 4). The strength of association with these maternal characteristics did not significantly vary over the range of gestation from 24 to 43 weeks. The risk of stillbirth was also positively associated with second-trimester maternal serum levels of α-FP and hCG. The cumulative probability of stillbirth associated with elevated levels of these analytes is plotted, and the strength of association varied with gestational age (Figure 1). High levels of α-FP and hCG were strongly associated with stillbirth between 24 and 28 weeks of gestation. In both cases, the strength of association became weaker with advancing gestational age, and there was no statistically significant association between levels of these analytes and the risk of stillbirth at or after 37 weeks of gestation (Table 5).

There were no statistically significant interactions between α-FP and hCG and maternal characteristics and no significant interactions between the two analytes. Because of the large number of comparisons, the threshold for statistical significance was set at $P < 0.01$. There was a trend towards an interaction between α-FP levels in the top 5% and hCG levels in the top 5%: the hazard ratio for the interaction term was 2.20 (95% CI 1.06–4.56, $P = 0.03$). Four hundred and seventy-nine women had levels of both analytes in the top 5%, and 14 (2.9%) of these pregnancies ended in stillbirth. The hazard ratio for stillbirth among this group was 7.3 (95% CI 4.3–12.5, $P < 0.001$). Again, the association declined significantly with advancing gestational age ($P < 0.05$), and there was no statistically significant association at term (OR 3.0, 95% CI 0.7–12.1, $P = 0.1$), although the numbers were too small to exclude a significant association.

The screening characteristics of the model were assessed at the different gestational ages using the predicted probability of stillbirth from the logistic regression models (Table 6). The top 5% of the population for predicted risk had a likelihood ratio for stillbirth of more than seven for 24–28 weeks. The likelihood ratio associated with the top 5% of predicted risk steadily declined with advancing category of gestational age and was lowest for stillbirth at or beyond 37 weeks, being approximately three. The screening characteristics of the predicted probabilities were then assessed using the area under the ROC curve, and models containing only maternal variables were compared with those which also included second-trimester serum screening results (Table 7). Adding biochemical data significantly increased the area under the ROC curve for stillbirth between 24–28 weeks and 29–32 weeks but had a minimal effect for stillbirth prediction at term.

Discussion

The main finding of this paper is that women with elevated serum levels of α-FP and hCG in the second trimester of pregnancy were at increased risk of stillbirth and that these associations were strongest for stillbirth at extreme preterm gestations. In contrast, the association between stillbirth and maternal characteristics was similar over the period of 24–43 weeks. Consequently, a model combining maternal

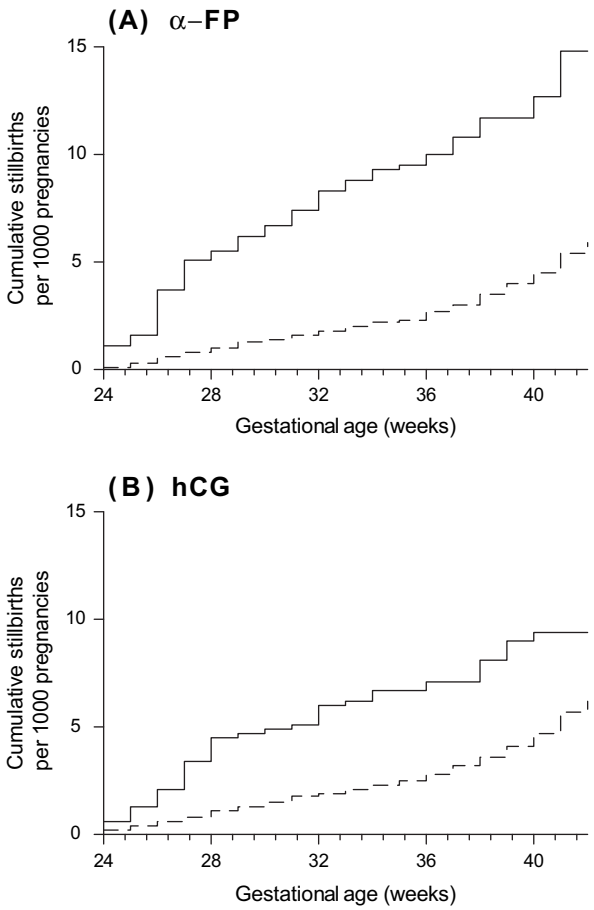

Figure 1. Kaplan–Meier plot of cumulative probability of stillbirth from 24 to 43 weeks of gestation comparing women with elevated (top 5%) maternal serum levels (solid line) with all other women (dashed line): (A) α-FP and (B) hCG. Hazard ratio for top 5% (95% CI) is 3.33 (2.32–4.77) for α-FP and 2.06 (1.41–3.02) for hCG. Test of proportional hazards assumption: $P < 0.05$ for both and remained statistically significant when included in multivariate Cox model with all other maternal characteristics.

characteristics and biochemical data performed reasonably well in predicting stillbirth risk at extreme preterm gestations (24–28 weeks): women in the top 5% of predicted risk had a positive likelihood ratio of seven and included 36% of all losses between 24 and 28 weeks of gestation. In contrast, a model combining maternal characteristics and biochemical data performed poorly at predicting stillbirth at term: women in the top 5% of predicted risk had a positive likelihood ratio of three and only included 15% of losses at or after 37 weeks of gestation.

These findings are of clinical relevance. Measurement of α-FP and hCG is in widespread use as a well validated method of screening for Down syndrome.[13] It is generally recognised that elevated levels of these proteins are associated with an increased risk of other adverse outcomes, including stillbirth. Some authors suggest that women with elevated levels of α-FP or hCG should have close surveillance of their pregnancies, such as growth scans at intervals of 2–4 weeks.[22] However, the current data suggest that if surveillance is thought to be beneficial, it should commence at 24 weeks. Moreover, if serial scans are reassuring up to 36 weeks, it may well be safe to discontinue further assessment.

The current analysis also addresses whether selecting women for further fetal assessment on the basis of second-trimester serum screening data is justifiable. There are no studies that directly indicate that the use of α-FP and hCG measurements to screen for stillbirth improves outcome. A successful screening programme has two major components, namely (1) effective assessment of risk and (2) application of an effective intervention among women who screen positive. The primary intervention to prevent stillbirth is delivery of the infant prior to intrauterine demise. In assessing the effect of delivery of high-risk infants on overall perinatal mortality, the gestational age where the fetus is presumed to be at risk is crucial. The risk of neonatal death is around 30–40% at 24–25 weeks[23] and less than 0.1% at term.[5] Therefore, at term, elective delivery of an infant at high risk of stillbirth carries a small risk of increasing overall perinatal mortality. Hence, if a risk factor is strongly predictive of stillbirth at term, elective delivery at term is likely to be beneficial and is unlikely to cause serious harm. This practice is widespread in clinical obstetrics. Women with risk factors such as insulin-dependent diabetes mellitus or a history of stillbirth are commonly offered elective delivery at around 38 weeks of gestation. However, the current data do not suggest that routine elective delivery at term is indicated on the basis of elevated levels of α-FP or hCG in the second trimester.

The stronger association with stillbirth at preterm gestations raises the possibility that α-FP and hCG measurements may be used to screen for fetuses at risk of stillbirth at preterm gestations. However, the management of a pregnancy where the fetus is thought to be at increased risk of stillbirth at preterm gestations is more complex. Elective delivery at extreme preterm gestations would clearly not simply be on the basis of a raised α-FP or hCG level. Rather, women with a raised α-FP or hCG would have an increased level of fetal surveillance (such as ultrasound scanning and computerised cardiotocography), and those with severely abnormal findings would be considered for delivery. However, no assessment of fetal wellbeing is completely accurate. Therefore, identifying and delivering fetuses at risk of stillbirth between 24 and 28 weeks could lead to neonatal deaths as a consequence of iatrogenic prematurity among infants who would not have died had they been left *in utero*. Moreover, even if the infants survived, elective delivery could lead to long-term severe disability as approximately 40% of long-term survivors of extreme preterm birth may be severely disabled.[3] It is possible that some parents would prefer a stillbirth to occur than have delivery of an infant

Table 5. Adjusted odds ratios for the risk of antepartum stillbirth in relation to maternal serum levels of α-FP and hCG for four different gestational age categories

Variables	Gestational age of 24–28 weeks, *n* = 84 769			Gestational age of 29–32 weeks, *n* = 84 335			Gestational age of 33–36 weeks, *n* = 83 478			Gestational age of 37–43 weeks, *n* = 79 267		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Maternal serum α-FP percentile												
1–20	0.78	0.33–1.82	0.6	0.87	0.40–1.91	0.7	1.29	0.61–2.71	0.5	0.75	0.42, 1.35	0.3
21–40	1.18	0.55–2.51	0.7	0.61	0.25–1.45	0.3	0.58	0.23–1.44	0.2	1.29	0.78, 2.13	0.3
41–60	Reference		—	Reference		—	Reference		—	Reference		—
61–80	1.41	0.70–2.83	0.3	1.07	0.52–2.20	0.8	1.53	0.77–3.07	0.2	1.24	0.75–2.03	0.4
81–90	2.12	1.02–4.42	0.04	1.03	0.43–2.47	0.9	1.54	0.69–3.45	0.3	1.00	0.54–1.88	>0.9
91–95	2.42	1.06–5.54	0.04	1.52	0.58–3.96	0.4	0.55	0.12–2.44	0.4	0.94	0.41–2.16	0.9
96–97	3.04	1.08–8.55	0.04	2.45	0.80–7.48	0.1	—	—	—	1.01	0.30–3.32	>0.9
98–99	4.06	1.61–10.23	0.003	2.57	0.84–7.86	0.10	2.12	0.60–7.47	0.2	1.45	0.51–4.15	0.5
100	11.97	5.34–26.83	<0.001	4.79	1.54–14.86	0.007	5.76	1.85–17.96	0.003	2.44	0.74–8.10	0.1
Maternal serum hCG percentile												
1–20	0.80	0.37–1.71	0.6	1.68	0.80–3.53	0.2	0.89	0.46–1.73	0.7	1.07	0.65–1.75	0.8
21–40	0.96	0.47–2.00	0.9	1.11	0.49–2.53	0.8	0.50	0.22–1.11	0.09	0.76	0.44–1.31	0.3
41–60	Reference		—	Reference		—	Reference		—	Referent		—
61–80	1.20	0.60–2.39	0.6	1.20	0.54–2.68	0.7	0.80	0.40–1.61	0.5	1.20	0.74–1.96	0.5
81–90	1.99	0.97–4.09	0.06	1.12	0.41–3.04	0.8	1.16	0.53–2.52	0.7	1.01	0.53–1.90	>0.9
91–95	2.86	1.31–6.26	0.009	2.58	0.99–6.67	0.05	0.70	0.21–2.38	0.6	0.71	0.28–1.84	0.5
96–97	3.87	1.49–10.05	0.005	1.86	0.41–8.45	0.4	0.59	0.08–4.40	0.6	1.13	0.34–3.70	0.8
98–99	5.20	2.25–12.01	<0.001	1.71	0.38–7.78	0.5	1.13	0.26–4.90	0.87	1.48	0.52–4.22	0.5
100	5.80	2.19–15.40	<0.001	4.90	1.34–17.94	0.02	2.16	0.49–9.47	0.3	0.79	0.11–5.86	0.8

CI, confidence interval, HR, hazard ratio; OR, odds ratio.

The OR for the other variables were virtually identical to the adjusted hazard ratios listed in Table 4. The only OR which differed from the HR at the first decimal place was for maternal age greater than 39 years: the HR was 2.29 and the adjusted OR was 2.14.

Table 6. Screening performance of the predicted probability from multivariate logistic regression models containing maternal and biochemical data

Gestational age and predicted risk	Positive predicted value (%)	Sensitivity (%)	Specificity (%)	Positive LR	Negative LR
24–28 weeks					
Top 5%	0.97	36.68	95.04	7.80	0.65
Top 10%	0.52	41.51	90.04	4.17	0.65
Top 20%	0.34	54.72	80.04	2.74	0.57
29–32 weeks					
Top 5%	0.33	18.67	95.01	3.74	0.86
Top 10%	0.28	32.00	90.02	3.21	0.76
Top 20%	0.20	44.00	80.02	2.20	0.70
33–36 weeks					
Top 5%	0.47	25.00	95.13	5.13	0.79
Top 10%	0.32	34.21	90.23	3.50	0.73
Top 20%	0.21	46.05	80.45	2.36	0.67
37–43 weeks					
Top 5%	0.63	16.78	95.02	3.38	0.88
Top 10%	0.42	22.15	90.03	2.22	0.86
Top 20%	0.33	35.57	80.03	1.78	0.81

LR, likelihood ratio.
The risk (per 1000 subsequent births) of antepartum stillbirth is as follows: 1.25 (95% CI 1.01–1.49) for gestational age group 24–28 weeks, 0.89 (95% CI 0.69–1.09) for gestational age group 29–32 weeks, 0.91 (95% CI 0.71–1.11) for gestational age group 33–36 weeks and 1.88 (95% CI 1.58–2.18) for gestational age 37–43 weeks.

which would be severely disabled in the long term. Furthermore, delivery at extreme preterm gestations also carries issues of maternal morbidity. Delivery would usually be by caesarean section, often using the classical method. This carries immediate risks of maternal morbidity and is associated with significant risks in future pregnancies.[24] Thus, the beneficial effects of preventing stillbirth in those who would have died may be offset by the harmful effects among those who were false positives. Finally, the use of α-FP and hCG measurements to screen for stillbirth has not been subjected to an economic analysis. From the above, even if it did result in decreased perinatal mortality, the costs of preventing each stillbirth may be substantial, including costs of fetal monitoring, elective preterm delivery, neonatal intensive care and long-term costs, including management of future pregnancy (e.g. after classical caesarean section) and care of disabled infants. We conclude that although statistical associations can be shown between stillbirth risk and both biochemical and maternal data, population-based screening for stillbirth risk on the basis of these associations should not be undertaken without direct evidence that screening and intervention improve outcome and are economically justifiable, particularly when performed at extreme preterm gestations.

The current data are also of biological interest. This is the first large-scale study of α-FP and hCG which had detailed information on the cause of antepartum stillbirth and it considerably extends the understanding of the association between maternal serum markers in the second trimester of pregnancy and the risk of stillbirth. An elevated level of α-FP was most strongly associated with stillbirth caused by

Table 7. Area under the ROC curve from the two multivariate logistic regression models for the four different gestational age groups

Model predictors	Gestational age, 24–28 weeks		Gestational age, 29–32 weeks		Gestational age, 33–36 weeks		Gestational age, 37–43 weeks	
	Area*	95% CI	Area*	95% CI	Area*	95% CI	Area*	95% CI
Maternal only	0.66	0.61–0.71	0.69	0.64–0.75	0.64	0.58–0.70	0.64	0.60–0.68
Maternal and biochemical	0.75	0.70–0.80	0.74	0.69–0.79	0.71	0.65–0.77	0.65	0.61–0.69

CI, confidence interval.
*Area under the ROC curve.

pre-eclampsia (seven- to eight-fold risk), was moderately associated with stillbirth associated with haemorrhage (primarily abruption) and SGA unexplained stillbirth (three- to four-fold risk) and weakly associated with unexplained stillbirths which had AGA birthweight (two-fold risk). Elevated levels of hCG were also strongly associated with stillbirth caused by pre-eclampsia (seven- to eight-fold risk) and weakly associated with unexplained stillbirth (1.5-fold risk) The latter seemed to be unrelated to fetal growth. Finally, there was a trend towards a synergistic association between elevated α-FP and hCG and the risk of antepartum stillbirth. These data indicate the complexity of placental determinants of stillbirth caused by different causes. The biochemical data employed in the present study did not perform well as uterine artery Doppler flow velocimetry as a predictor of stillbirth. A recent study of more than 30 000 women has shown that the area under the ROC curve for this modality was 0.84 for losses before 32 weeks, and the women in the top 5% of predicted risk on the basis of Doppler alone had a positive likelihood ratio of 12.1.[25] However, similar to α-FP and hCG, adding uterine artery Doppler data to a model including maternal characteristics had a minimal effect (increase of 0.02) on the area under the ROC curve for stillbirths at later gestations.

In conclusion, we show that elevated levels of α-FP and hCG were strongly associated with stillbirth at extreme preterm gestations, and the strength of association with stillbirth declined with advancing gestational age. These findings have implications for the clinical use of second-trimester maternal serum levels of α-FP and hCG in obstetric risk assessment.

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Maternal and biochemical predictors of spontaneous preterm birth among nulliparous women: a systematic analysis in relation to the degree of prematurity

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Background Nulliparous women are at increased risk of spontaneous preterm birth. Other maternal and biochemical risk factors have also been described. However, it is unclear whether these associations are strong enough to offer clinically useful prediction. It is also unclear whether the predictive power of these factors varies in relation to the degree of prematurity.

Methods The risk of spontaneous preterm birth associated with maternal characteristics and second trimester serum screening data was analysed in a dataset of 84 391 first births in Scotland between 1992 and 2001 using Cox and logistic regression. Variation in the relative risk of preterm birth over the period 24–36 weeks was assessed using a test of the proportional hazards assumption.

Results The risk of spontaneous preterm birth was positively associated with maternal serum levels of alpha-fetoprotein, socioeconomic deprivation, number of previous therapeutic abortions, smoking, and being unmarried and was negatively associated with height and body mass index. The risk of preterm birth at 24–28 weeks, but not later gestations, was increased in association with maternal levels of human chorionic gonadotrophin >95th percentile, maternal age <20, and two or more previous miscarriages. The area under the receiver operating characterise curve (95% CI) for models based on these factors was 0.67 (0.63–0.71) for 24–28 weeks, 0.65 (0.62–0.68) for 29–32 weeks, and 0.62 (0.61–0.63) for 33–36 weeks.

Conclusions Time to event analytic methods can identify factors that are differentially associated with spontaneous preterm birth according to the degree of prematurity. However, models based on maternal and biochemical data perform poorly as a screening test for any degree of spontaneous preterm birth.

Keywords alpha-Fetoproteins, chorionic gonadotrophin, labour, premature, proportional hazards models, risk

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Preterm birth is a major source of morbidity and mortality in the neonatal period and in infancy and later childhood.[1–4] One of the major clinical risk factors for spontaneous preterm birth is a previous pregnancy that ended in this event. Self evidently, this information is not available for woman having a first birth, making risk assessment in this substantial proportion of the population problematic. A number of other factors have, however, been shown to be associated with the risk of spontaneous preterm birth, and these have been reviewed elsewhere.[5,6] However, it remains unclear

whether the combined information available from such characteristics provides useful predictive information.

A further complication in assessing risk factors for spontaneous preterm birth is the degree of prematurity. Whereas birth between 33 and 36 weeks gestation carries a relatively favourable short-term and long-term prognosis, extreme preterm birth is associated with high absolute risks of death and severe disability.[1,4] The profoundly different consequences of extreme, moderate, and mild prematurity mean that interventions to reduce the risk of these events should be targeted at the clinically important extreme cases. However, many analyses of factors associated with the risk of preterm birth fail to distinguish between different degrees of prematurity. Moreover, we are unaware of any widely utilized approach to determine objectively whether the relative risk associated with a given factor significantly varies across the range of gestational age.

We have previously proposed that time to event analytic methods, specifically Cox proportional hazards regression, might be employed in assessing the factors associated with the spontaneous onset of labour.[7] Tests have been developed using residuals estimated from the Cox model, which allow a formal test of the assumption that the relative risk of an event associated with a given factor is the same across a period of time.[8] This analytic approach could also be used to determine whether the strength of association between the risk of spontaneous preterm birth and maternal or obstetric factors varies in relation to the degree of prematurity. We are unaware of any study that has previously performed such an analysis.

In the present study, we analysed data from over 80 000 women having first pregnancies in the West of Scotland and sought to determine (i) which maternal and biochemical factors are associated with the relative risk of spontaneous preterm birth over the period 24–36 weeks gestation, (ii) whether the relative risks associated with these factors significantly varied over the period 24–36 weeks, and (iii) whether these factors could yield clinically useful prediction of risk.

Methods

Data sources and patient selection

The Scottish Morbidity Record collects information on clinical and demographic characteristics and outcomes for all women discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been >99% complete since the late 1970s.[9] The Scottish Stillbirth and Infant Death Enquiry is a national register, which routinely classifies all perinatal deaths in Scotland.[10] All women attending for prenatal care in the West of Scotland are offered biochemical screening, using maternal serum levels of alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG), to assess their risk of having a fetus affected by Down syndrome and/or structural fetal abnormality.[11] The laboratory information management system for the West of Scotland prenatal screening programme in the Institute of Medical Genetics in Glasgow contains a database of the maternal information and biochemical screening results, and electronic storage of these data in their current form was commenced in September 1991. A probability-based matching approach[12] was employed using maternal identifiers to link the Scottish Morbidity Record, the Scottish Stillbirth and Infant Death Enquiry, and the prenatal screening database in the Institute of Medical Genetics. We excluded multiparous patients, multiple births, stillbirths, and births outside the range 24–43 weeks gestation. Ethical approval for the linkage was obtained from the Privacy Advisory Committee of the Information and Statistics Division of the National Health Service, Scotland.

The maternal age, parity, previous miscarriages and therapeutic abortions, postcode of residence, and all outcome data were obtained solely from the Scottish Morbidity Record. Maternal weight was obtained solely from the biochemical database. Maternal height and smoking were obtained from the Scottish Morbidity Record except in cases where they were missing from the Scottish Morbidity Record and the biochemical database was employed. The smoking status (current, past, never) was determined from information at the time of the first prenatal visit. The maternal age was defined as the age of the mother at the time of delivery. The body mass index was calculated from the weight in kilograms recorded at the time of sampling for serum screening assay divided by the height in metres squared. Socioeconomic status was estimated based on the postcode of residence, using Carstairs socioeconomic deprivation categories[13] (based on 1991 Census data on car ownership, unemployment, overcrowding, and social class within postcode sectors of residence containing, on average, ~1600 residents).

Definitions

Previous miscarriage was defined as previous delivery of a conceptus showing no signs of life before 24 weeks gestation, excluding therapeutic abortions. Previous therapeutic abortion was defined as previous therapeutic termination of pregnancy by any means prior to 24 weeks gestation. Spontaneous birth was defined as all births that were vaginal or had a documented duration of labour but were not recorded as having had labour induced. Elective births were taken to be all other births. The gestational age at birth was defined as the completed weeks of gestation on the basis of the estimated date of delivery in each woman's clinical record; standard national criteria exist for the estimation of date of delivery using menstrual and ultrasound data.[14] The gestational age has been confirmed by ultrasound scan in the first half of pregnancy in >95% of pregnancies in the UK from the early 1990s.[15] Maternal serum levels of AFP and hCG were quantified as multiples of the median for week of gestation, corrected for maternal weight.[16]

Statistical analysis

Continuous variables were summarized by the median and inter-quartile range. Univariate comparisons were performed using the Kruskal–Wallis test, the chi-squared test, and the chi-squared test for trend, as appropriate. The *P*-values for all hypothesis tests were two-sided, and we set statistical significance at $P < 0.05$. All the variables were treated as categorical. Biochemical data were categorized into quintiles with the highest quintile split into a decile and vigesimals. We preformed univariate and multivariate Cox regression using gestational age as the time scale, spontaneous labour as the event, elective preterm deliveries as censored at the gestation of

birth, and all term deliveries censored at the start of the 37th week. The proportional hazards assumption was tested using the method of Grambsch and Therneau.[8] This was used to determine whether the relative risk of spontaneous preterm birth associated with a given factor varied across the range 24–36 weeks gestation. Preterm delivery was then divided into extreme (24–28 weeks), moderate (29–32 weeks), and mild (33–36 weeks), thus, dividing the span of gestation into approximate thirds. Logistic regression analysis was used to estimate adjusted odds ratios associated with the different degrees of prematurity using spontaneous preterm birth within the given range as the event, excluding elective preterm births within the gestational age range, and using spontaneous preterm birth within the age range and all births at later gestations as the denominator. Factors which had been shown in the proportional hazards model to vary significantly with gestation, were allowed to vary in the three preterm gestational age groups, whereas the rest of the predictors remained fixed. The predicted probability of each outcome was obtained from the logistic model. The screening performance of the model was assessed using the predicted probability to estimate the area under the receiver operating characteristic (ROC) curve. Further, the positive predictive value, sensitivity, specificity, and positive and negative likelihood ratios were estimated using different thresholds of predicted risk as screen positive (predicted probability in the top 1, 5, 10, or 20%). All statistical analyses were performed using the Stata software package (Stata Corporation, TX, USA), version 8.2.

Results

There were 216 563 records of singleton births with a recorded value of maternal serum AFP and hCG, which could be linked to the Scottish Morbidity Record, and 97 264 (44.9%) of these were first births. Among this group we excluded 69 (0.1%) deliveries that were outside the range of 24–43 gestational weeks and 518 (0.5%) antepartum stillbirths. Of the remaining 96 677 records, 12 286 (12.7%) had missing data on one or more variable [47 (0.1%) maternal age, 1290 (1.3%) height, 6907 (7.1%) body mass index, 171 (0.2%) deprivation category, 5691 (5.9%) smoking status, and 5 (0.01%) previous miscarriages] leaving a study group of 84 391 births.

When categorized by gestational age at birth, there were significant differences in the proportion of spontaneous births, maternal height, deprivation category, smoking status, previous miscarriages, previous therapeutic abortions, marital status, and second trimester levels of AFP and hCG (Table 1). The risk of spontaneous preterm birth over the range 24–36 weeks was then assessed using a multivariate Cox model (Table 2). There were linear trends between the risk of spontaneous preterm birth and second trimester maternal serum levels of AFP and hCG. The risk of spontaneous preterm birth also varied according to maternal age, marital status, and smoking status; decreased linearly with height and body mass index; and, increased linearly with maternal deprivation category, number of previous miscarriages, and number of previous therapeutic abortions. The relative risk of preterm birth varied across the range 24–36 weeks in association with high levels of hCG ($P = 0.008$), maternal age <20 ($P = 0.0001$), and the number of previous miscarriages ($P = 0.006$).

The nature of variation across the range of gestational ages was then assessed using logistic regression for each of the categories of spontaneous preterm birth (Table 3). Separate odds ratios were estimated within each of the windows of gestational age for each of the variables where the relative risk had been shown to vary over the range 24–36 weeks. For the other variables where Cox modelling had shown the relative risk was constant, a single odds ratio was estimated across the range 24–36 weeks. Using this approach, high levels of hCG and age <20 were associated with extreme preterm birth but not moderate or mild preterm birth. The number of previous miscarriages was associated with all categories of preterm birth, but the association was strongest for extreme prematurity and weakest for mild prematurity.

The screening performance of the multivariate logistic regression models were then assessed for the different degrees of prematurity assuming classification of the top 1, 5, 10, or 20% of predicted risk as having screened positive (Table 4). The positive likelihood ratios were highest for extreme prematurity (5.5 for women in the top 1% of predicted risk). However, owing to the fact that mild prematurity was much more common, the positive predictive value was greatest for the model of mild prematurity. In no case did any positive predictive value exceed 10%. Finally, the predictive ability of the models was assessed using the area under the ROC curve. Values were highest for extreme preterm birth and lowest for mild preterm birth. Adding AFP and hCG to the maternal characteristics resulted in an increase in the area under the ROC of 0.04 at all gestations (Table 5).

Discussion

In the present study, we demonstrated in a large population of primigravid women that the risk of spontaneous preterm birth was significantly associated with marital status, smoking status, height, body mass index, socioeconomic deprivation category, previous miscarriages and therapeutic abortions, and with maternal serum levels of AFP in the second trimester. We also demonstrated significant variation in the relative risk of spontaneous birth across the range 24–36 weeks gestation associated with maternal age <20, elevated levels of hCG, and with number of previous miscarriages. Each of these factors was strongly associated with extreme preterm birth but not associated, or only weakly associated, with moderate or mild spontaneous preterm birth.

The results of the current study expand considerably on previous studies. In relation to elevated hCG, a number of studies had shown increased rates of preterm delivery,[17–21] but others had shown no association[22] or only a very weak association.[23] However, these analyses did not distinguish between spontaneous and elective preterm birth. A study, which did make this distinction, demonstrated that elevated hCG was associated with elective preterm birth, but there was no significant association with spontaneous preterm birth.[24] However, no attempt was made to analyse this outcome in relation to the degree of severity of preterm delivery. In relation to maternal age <20, we had previously analysed routinely data from Scotland and shown no association between this characteristic and the risk of preterm birth at either 24–32 weeks or 33–36 weeks.[25] However, we also

Table 1 Maternal, demographic, and obstetrical characteristics in relation to gestation age among 84 391 first births in Scotland, 1992–2001

	Gestational age at delivery (weeks)				
Characteristics	24–28 (n = 335)	29–32 (n = 790)	33–36 (n = 4,150)	37–43 (n = 79,116)	***P* =**
Delivery					
Spontaneous birth	202 (60.3)	356 (45.1)	2,528 (60.9)	50 311 (63.6)	<0.001
Other	133 (39.7)	434 (54.9)	1622 (39.1)	28 805 (36.4)	
Age (years)	26 (21–30)	27 (22–31)	26 (22–30)	26 (22–30)	0.2
Height (cm)	162 (157–166)	162 (157–166)	162 (157–166)	163 (158–167)	<0.001
Body mass index	23.7 (21.2–27.1)	23.5 (21.2–26.5)	23.4 (21.1–26.4)	23.5 (21.4–26.3)	0.07
Deprivation category					
1 (least deprived)	12 (3.6)	18 (2.3)	147 (3.5)	2947 (3.7)	
2	35 (10.5)	75 (9.5)	388 (9.4)	8240 (10.4)	
3	48 (14.3)	132 (16.7)	737 (17.8)	14 565 (18.4)	
4	75 (22.4)	183 (23.2)	1010 (24.3)	19 715 (24.9)	<0.001
5	66 (19.7)	144 (18.2)	694 (16.7)	13 324 (16.8)	
6	48 (14.3)	146 (18.5)	680 (16.4)	12 268 (15.5)	
7 (most deprived)	51 (15.2)	92 (11.7)	494 (11.9)	8057 (10.2)	
Smoking status					
Non-smoker	206 (61.5)	481 (60.9)	2418 (58.3)	49 115 (62.1)	
Smoker	110 (32.8)	259 (32.8)	1388 (33.5)	22 512 (28.5)	<0.001
Ex-smoker	19 (5.7)	50 (6.3)	344 (8.3)	7489 (9.5)	
Previous miscarriages					
0	270 (80.6)	656 (83.0)	3497 (84.3)	68 961 (87.2)	
1	47 (14.0)	96 (12.2)	531 (12.8)	8541 (10.8)	<0.001
⩾2	18 (5.4)	38 (4.8)	122 (2.9)	1614 (2.0)	
Previous therapeutic abortions					
0	295 (88.1)	696 (88.1)	3709 (89.4)	71 567 (90.5)	
1	34 (10.2)	88 (11.1)	381 (9.2)	6837 (8.6)	<0.001
⩾2	6 (1.8)	6 (0.8)	60 (1.5)	712 (0.9)	
Marital status					
Married	153 (45.7)	381 (48.2)	2017 (48.6)	40 859 (51.6)	<0.001
Other	182 (54.3)	409 (51.8)	2133 (51.4)	38 257 (48.4)	
AFP (MoM)	1.18 (0.91–1.58)	1.17 (0.90–1.55)	1.13 (0.89–1.44)	1.02 (0.82–1.28)	<0.001
hCG (MoM)	1.15 (0.76–1.76)	1.14 (0.80–1.66)	1.04 (0.74–1.48)	1.03 (0.74–1.44)	<0.001

AFP denotes alpha-fetoprotein, hCG denotes human chorionic gonadotrophin and MoM denotes multiple of the median. Continuous data expressed as median (inter-quartile range) and continuous data expressed as n (%).

pooled spontaneous and elective preterm birth. With regard to prior miscarriages, a previous Swedish study had indicated a history of prior losses was more strongly associated with extreme preterm delivery.[26] However, there was no direct statistical test of whether the apparent variation in relation to the degree of prematurity was more than would be expected by chance. Finally, a previous analysis of spontaneous preterm birth in relation to the number of previous therapeutic abortions suggested that the association was stronger for extreme preterm delivery.[27] However, there was considerable overlap in the confidence intervals for odds ratios for the different degrees of prematurity and, again, that study lacked a specific test that the apparent variation between the groups was statistically significant. We confirm that the number of prior therapeutic abortions is associated with the risk of spontaneous preterm birth but show that the association is similar for different degrees of prematurity.

Many previous studies have analysed risk factors according to different degrees of prematurity. Variation in the strength of associations is critical since the consequences of preterm delivery vary profoundly in relation to the degree of prematurity. However, this is the first study, to our knowledge, to use Cox modelling and a test of the proportional hazards assumption to address whether the relative risk of spontaneous preterm birth associated with a given factor varies in relation to the degree of prematurity. Other approaches to this question are possible. First, categories of prematurity can be created and separate logistic regression models can be estimated, as we described in Table 3. Moreover, by stacking the datasets for the different outcomes and use of interaction terms, it can be determined whether odds ratios significantly vary among the categories. However, this requires deliberate selection of categories. In contrast, using the Cox method, gestational age is treated continuously. This will increase the power to

Table 2 Cox regression analysis of the risk of spontaneous preterm birth across the range 24–36 weeks gestation among 84 391 first births in Scotland, 1992–2001

	Univariate				Multivariate*			
Variables	HR	95% CI	*P* =	PH test	HR	95% CI	*P* =	PH test
AFP percentile								
0–20	0.86	0.76–0.97		0.7	0.85	0.75–0.96		0.8
21–40	0.95	0.84–1.07		0.7	0.95	0.84–1.07		0.7
41–60	(1.0)*	(1.0)*			(1.0)*			
61–80	1.29	1.15–1.45		0.2	1.29	1.16–1.45		0.1
81–90	1.41	1.23–1.61		0.3	1.40	1.23–1.61		0.3
91–95	1.83	1.57–2.13		0.1	1.83	1.57–2.13		0.1
96–100	2.44	2.12–2.81		0.07	2.45	2.12–2.82		0.1
Trend test			<0.001				<0.001	
Heterogeneity test			<0.001				<0.001	
hCG percentile								
0–20	1.05	0.94–1.17		0.9	1.04	0.93–1.16		0.9
21–40	0.97	0.87–1.08		0.4	0.97	0.87–1.09		0.4
41–60	(1.0)*	(1.0)*			(1.0)*			
61–80	0.94	0.84–1.06		0.8	0.95	0.85–1.06		0.8
81–90	0.88	0.76–1.01		0.7	0.88	0.77–1.02		0.7
91–95	0.82	0.68–0.99		0.7	0.81	0.67–0.98		0.8
96–100	1.07	0.90–1.27		0.047	1.02	0.86–1.21		0.008
Trend test			0.047				0.04	
Heterogeneity test			0.047				0.1	
Age (years)								
<20	1.32	1.18–1.46		0.0001	1.11	0.98–1.25		0.0001
20–24	1.03	0.93–1.13		0.3	0.92	0.83–1.02		0.3
25–29	(1.0)*	(1.0)*			(1.0)*			
30–34	1.03	0.94–1.14		0.07	1.05	0.95–1.16		0.1
35–39	1.08	0.92–1.27		0.06	1.07	0.91–1.26		0.1
>39	1.38	0.91–2.09		0.5	1.28	0.85–1.93		0.8
Trend test			0.004				0.5	
Heterogeneity test			<0.001				0.02	
Marital								
Married	(1.0)*	(1.0)*			(1.0)*			
Other	1.22	1.14–1.31		0.09	1.10	1.01–1.19		0.5
Heterogeneity test			<0.001				0.03	
Smoking								
Non	(1.0)*	(1.0)*			(1.0)*			
Current	1.36	1.26–1.46		0.4	1.19	1.09–1.29		0.1
Ex	0.93	0.81–1.06		0.3	0.92	0.80–1.05		0.2
Heterogeneity test			<0.001			<0.001		
Height (cm)								
<150	1.45	1.12–1.87		0.9	1.39	1.07–1.79		0.9
150–154	1.25	1.10–1.42		0.2	1.23	1.08–1.40		0.2
155–159	1.13	1.02–1.25		0.4	1.12	1.01–1.24		0.4
160–164	(1.0)*	(1.0)*			(1.0)*			
165–169	0.90	0.82–1.00		0.7	0.91	0.82–1.00		0.7
170–174	0.84	0.74–0.96		0.7	0.85	0.75–0.96		0.6
>174	0.62	0.50–0.78		0.8	0.62	0.49–0.78		0.9
Trend test			<0.001				<0.001	
Heterogeneity test			<0.001				<0.001	

Table 2 (continued)

	Univariate				Multivariate*			
Variables	HR	95% CI	*P* =	PH test	HR	95% CI	*P* =	PH test
Body mass index								
<20	1.48	1.34–1.64		0.4	1.43	1.30–1.59		0.8
20–24	(1.0)*	(1.0)*			(1.0)*			
25–29	0.91	0.83–0.99		0.6	0.89	0.81–0.97		0.5
>30	0.86	0.76–0.98		0.2	0.80	0.70–0.92		0.2
Trend test			<0.001				<0.001	
Heterogeneity test			<0.001				<0.001	
Deprivation category								
1 (least deprived)	1.02	0.84–1.25		0.9	1.10	0.90–1.35		0.8
2	0.92	0.80–1.06		0.3	0.96	0.84–1.10		0.2
3	0.99	0.89–1.11		0.5	1.02	0.92–1.15		0.6
4	(1.0)*	(1.0)*			(1.0)*			
5	1.09	0.97–1.22		0.3	1.06	0.95–1.18		0.4
6	1.12	1.00–1.26		0.4	1.08	0.96–1.21		0.4
7 (most deprived)	1.30	1.15–1.47		0.4	1.16	1.03–1.32		0.6
Trend test			<0.001				0.03	
Heterogeneity test			<0.001				0.2	
Previous miscarriages								
0	(1.0)*	(1.0)*			(1.0)*			
1	1.31	1.18–1.46		0.1	1.31	1.18–1.45		0.09
⩾2	1.53	1.25–1.88		0.006	1.50	1.22–1.84		0.005
Trend test			<0.001				<0.001	
Heterogeneity test			<0.001				<0.001	
Therapeutic abortions								
0	(1.0)*	(1.0)*			(1.0)*			
1	1.18	1.05–1.33		0.6	1.19	1.06–1.34		0.3
⩾2	1.91	1.46–2.51		0.3	1.90	1.44–2.49		0.2
Trend test			<0.001				<0.001	
Heterogeneity test			<0.001				<0.001	

HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein; hCG, human chorionic gonadotrophin; PH test, proportional hazards test (Grambsch and Therneau[8]). Global test of the proportional hazards assumption for multivariate model: $P = 0.007$. The six cut points (multiples of the median) for AFP were 0.78, 0.95, 1.12, 1.37, 1.60, and 1.84 i.e. AFP 96–100 was equivalent to MoM of ⩾1.84. The six cut points (multiples of the median) for hCG were 0.68, 0.91, 1.17, 1.57, 1.97, and 2.39.

* Referent category, i.e. hazard within each other category expressed as a ratio to hazard in referent category.

detect variation in the relative risk and removes the possibility of data-derived or investigator-derived categorization. We propose that this method may be useful in systematically determining whether an association varies in relation to the degree of prematurity. Such an approach is usefully combined with categorization, which then allows a simpler assessment of the pattern of variation in relation to the degree of prematurity. A further strength of the present study is its size. Deliveries prior to 28 weeks account for ~60% of all neonatal deaths of preterm infants.[10] However, extreme preterm birth is rare. In our study, the risk of spontaneous preterm birth between 24 and 28 weeks was 1 in 500. It follows, therefore, that very large-scale studies are required to address the factors associated with this outcome. In practice, many studies of preterm birth are insufficiently powerful to assess the risk of extreme preterm birth and, in effect, use moderate and mild preterm birth as proxies of this outcome. This approach is only valid if the relative risk of spontaneous preterm birth does not vary in relation to known risk factors over the range 24–36 weeks. In the present study we show that this is not the case.

Clinical prediction of the risk of spontaneous preterm birth among women with no previous births is an area of profound clinical interest. Recent studies have indicated that use of progesterone analogues may reduce the risk of spontaneous preterm birth among women deemed to be at high risk of this event.[28] The majority of women recruited to these trials are selected as high risk on the basis of previous preterm deliveries, as this is the maternal characteristic most strongly associated with the risk of spontaneous preterm birth.[5] This method of selection is clearly effective, as the rate of preterm birth in the control group in one major trial exceeded 50%.[29] Given the devastating consequences to the infant of extreme preterm

Table 3 Multivariate logistic regression analysis of factors associated with extreme, moderate, and mild spontaneous preterm birth among 84 391 first births in Scotland, 1992–2001

	Gestational age 24–28 ***n* = 202/84 258**			**Gestational age 29–32** ***n* = 790/83 622**			**Gestational age 33–36** ***n* = 4150/81 644**		
Variables	*Adjusted OR	95% CI	*P* =	*Adjusted OR	95% CI	*P* =	*Adjusted OR	95% CI	*P* =
hCG percentile									
0–20	1.20	0.74–1.94	0.5	1.06	0.78–1.44	0.7	1.03	0.91–1.17	0.6
21–40	1.56	0.99–2.47	0.06	0.64	0.45–0.91	0.01	0.99	0.87–1.12	0.9
41–60	(1.0)[a]			(1.0)[a]			(1.0)[a]		
61–80	1.29	0.80–2.08	0.3	0.84	0.61–1.16	0.3	0.95	0.84–1.08	0.4
81–90	1.27	0.72–2.26	0.4	0.79	0.52–1.19	0.3	0.88	0.75–1.03	0.1
91–95	1.07	0.49–2.35	0.9	0.73	0.42–1.27	0.3	0.81	0.66–1.01	0.06
96–100	2.74	1.57–4.81	<0.001	1.09	0.68–1.73	0.7	0.92	0.75–1.13	0.4
Age (years)									
<20	2.35	1.58–3.47	<0.001	1.19	0.86–1.64	0.3	1.02	0.90–1.17	0.7
20–24	1.20	0.80–1.80	0.4	0.92	0.68–1.24	0.6	0.90	0.80–1.00	0.06
25–29	(1.0)[a]			(1.0)[a]			(1.0)[a]		
30–34	1.21	0.80–1.85	0.4	1.24	0.93–1.66	0.1	1.02	0.91–1.14	0.8
35–39	1.36	0.72–2.56	0.4	1.34	0.86–2.10	0.2	1.02	0.85–1.23	0.8
>39	0.91	0.12–6.65	0.9	2.46	0.99–6.09	0.05	1.16	0.71–1.90	0.6
Previous miscarriages									
0	(1.0)[a]			(1.0)[a]			(1.0)[a]		
1	1.77	1.21–2.59	0.003	1.23	0.90–1.68	0.2	1.29	1.15–1.46	<0.001
⩾2	2.81	1.47–5.38	0.002	2.24	1.36–3.68	0.002	1.32	1.03–1.69	0.03

OR, odds ratio, CI, confidence interval, hCG, human chorionic gonadotrophin; *n*, number of spontaneous preterm births within the interval (numerator) and the number of spontaneous preterm births within the interval plus the number of all births at later gestations (denominator).

* Adjusted for AFP, hCG, maternal age, socioeconomic deprivation category, height, smoking status, body mass index, prior spontaneous miscarriages, prior therapeutic abortions, and marital status.

[a] Referent category, i.e. odds for each other category expressed as a ratio to odds in referent category.

Table 4 Screening performance of predictive models for extreme, moderate, and mild spontaneous preterm birth among 84 391 first births in Scotland, 1992–2001

Percentile of predicted risk	**PPV (%)**	**Sensitivity (%)**	**Specificity (%)**	**Positive LR**	**Negative LR**
24–28 weeks					
>99th percentile	1.31	5.45	99.01	5.51	0.96
>95th percentile	0.81	16.83	95.03	3.39	0.88
>90th percentile	0.65	27.23	90.04	2.73	0.81
>80th percentile	0.53	44.55	80.07	2.24	0.69
29–32 weeks					
>99th percentile	1.44	3.37	99.01	3.41	0.98
>95th percentile	1.29	15.17	95.04	3.06	0.89
>90th percentile	1.05	24.72	90.06	2.49	0.84
>80th percentile	0.84	39.61	80.08	1.99	0.75
33–36 weeks					
>99th percentile	9.80	3.16	99.07	3.40	0.93
>95th percentile	7.08	11.43	95.21	2.38	0.93
>90th percentile	6.22	20.09	90.32	2.08	0.88
>80th percentile	5.37	34.65	80.47	1.78	0.81

PPV denotes positive predictive value and LR denotes likelihood ratio. Analysis based on the predicted probability from multivariate logistic regression model where the associations with age, hCG, and number of previous miscarriages were allowed to vary over the gestational age groups, whereas all the other variables were fixed across the gestational age groups.

Table 5 ROC curve analysis of predictive models for extreme, moderate, and mild spontaneous preterm birth using maternal characteristics alone or in combination with AFP and hCG among 84 391 first births in Scotland, 1992–2001

	Gestational age 24–28 weeks		Gestational age 29–32 weeks		Gestational age 33–36 weeks	
Model	Area under ROC curve	95% CI	Area under ROC curve	95% CI	Area under ROC curve	95% CI
Maternal characteristics	0.63	0.60–0.67	0.61	0.58–0.64	0.58	0.57–0.59
Maternal characteristics + AFP and hCG	0.67	0.63–0.71	0.65	0.62–0.68	0.62	0.61–0.63

ROC, receiver operating characteristic; AFP, alpha-fetoprotein; hCG, human chorionic gonadotrophin; CI, confidence interval. Analysis based on the predicted probability from multivariate logistic regression model where the associations with age, hCG, and number of previous miscarriages were allowed to vary over the gestational age groups, whereas all the other variables were fixed across the gestational age groups.

birth and the possibility of an effective intervention, predictive tools to identify women at high risk of extreme preterm delivery in their first pregnancy are urgently required. However, characterization of the parameters used in the present study indicate that, in our population, the model employed performed poorly as a screening tool with positive predictive values of <10%. This suggests that maternal characteristics and second trimester maternal serum screening, although statistically associated with the risk of preterm birth, are insufficiently informative to be used to identify women at clinically significant risk of preterm birth. This may reflect the fact that spontaneous preterm birth has multiple aetiologies. If population-based screening and intervention to prevent preterm birth in nulliparous women is to be attempted, other specific methods will be required, such as cervical ultrasound or fetal fibronectin assay from vaginal swabs.[30]

In summary, we show that the risk of spontaneous preterm delivery among nulliparous women with no previous births is associated with a number of maternal characteristics and with second trimester maternal serum levels of placentally derived proteins. High levels of hCG, maternal age <20 and two or more previous miscarriages were more strongly associated with extreme preterm delivery than moderate or mild preterm delivery. However, models using maternal characteristics and second trimester serum screening results did not have the predictive ability for any degree of spontaneous preterm birth, which would allow useful population-based screening.

Acknowledgements

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KEY MESSAGES

- The risk of spontaneous preterm birth among nulliparous women was positively associated with maternal serum levels of AFP, socioeconomic deprivation, number of previous therapeutic abortions, smoking, and being unmarried and negatively associated with height and body mass index.
- High levels of hCG, maternal age <20, and two or more previous miscarriages were more strongly associated with extreme preterm delivery than moderate or mild preterm delivery.
- Models using maternal characteristics and second trimester serum screening results did not have the predictive ability for any degree of spontaneous preterm birth, which would allow useful population-based screening.

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Pregnancy-Associated Plasma Protein A and Alpha-fetoprotein and Prediction of Adverse Perinatal Outcome

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OBJECTIVE: To describe the association between pregnancy associated plasma protein A (PAPP-A), alpha-fetoprotein (AFP) and adverse perinatal outcome.

METHODS: We conducted a multicenter prospective cohort study of 8,483 women attending for prenatal care in southern Scotland between 1998 and 2000. The risk of delivering a small for gestational age infant, delivering preterm, and stillbirth were related to maternal serum levels of PAPP-A and AFP.

RESULTS: Women with a low PAPP-A were not more likely to have elevated levels of AFP. Compared with women with a normal PAPP-A and a normal AFP, the odds ratio for delivering a small for gestational age infant for women with a high AFP was 0.9 (95% confidence interval [CI] 0.5–1.6), for women with a low PAPP-A was 2.8 (95% CI 2.0–4.0), and for women with both a high AFP and a low PAPP-A was 8.5 (95% CI 3.6–20.0). The odds ratio for delivering preterm for women with a high AFP was 1.8 (95% CI 1.3–2.7), for women with a low PAPP-A was 1.9 (95% CI 1.3–2.7), and for women with both a low PAPP-A and a high AFP was 9.9 (95% CI 4.4–22.0). These interactions were statistically significant for both outcomes ($P = .03$ and .04, respectively). There was a nonsignificant trend toward a similar interaction in relation to stillbirth risk. Of the women with the combination of a low PAPP-A and high AFP, 32.1% (95% CI 15.9–52.4) delivered a low birth weight infant.

CONCLUSION: Low maternal serum levels of PAPP-A between 10 and 14 weeks and high levels of AFP between 15 and 21 weeks gestation are synergistically associated with adverse perinatal outcome.

(Obstet Gynecol 2006;107:161–6)

LEVEL OF EVIDENCE: II-2

Insulin-like growth factor II (IGF-II) is expressed in high levels in trophoblast and is thought to have a key role in the control of trophoblast invasion.[1] Recent evidence indicates that the activity of the IGF system may be important in very early human pregnancy. A number of studies have related maternal circulating concentrations of pregnancy-associated plasma protein A (PAPP-A), a trophoblast derived protease for IGF binding proteins 4 and 5, to eventual perinatal outcome. These studies have shown that low levels of PAPP-A are associated with increased risks of intrauterine growth restriction, preterm birth, and stillbirth.[2–4] These associations are evident even when confined to samples obtained in the first 10 weeks postconception.[5,6] Consistent with this, mice that are null mutant for the gene encoding PAPP-A have severe early onset intrauterine growth restriction.[7]

It has been appreciated for many years that, in the absence of congenital abnormality, high maternal serum levels of alpha-fetoprotein (AFP) in the second trimester of pregnancy are associated with an increased risk of adverse perinatal outcome.[8] AFP is the major fetal oncotic protein and, when the fetus is structurally normal, high maternal circulating levels are thought to reflect a defect in placentation. It is not

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yet known, however, whether the placental defect associated with increased placental permeability to AFP is related to the activity of the IGF system. The aim of this study was to describe the relationship between low PAPP-A, high AFP, and intrauterine growth restriction, preterm birth, and stillbirth.

MATERIALS AND METHODS

We used data from the Combined Ultrasound and Biochemical Screening[9] study, a prospective, noninterventional, multicenter study of screening for Down syndrome. The study evaluated the use of ultrasound measurement of fetal nuchal translucency in combination with analysis of maternal serum PAPP-A and the free β subunit of human chorionic gonadotrophin as a first trimester screening test for Down syndrome in a routine prenatal clinic setting. Information leaflets about the study were sent to women with the notification of their first appointment for prenatal care. Those women whose first visit was at 14 weeks of gestation or less were invited to participate, and those who agreed signed a consent form. Participation in the study involved measuring nuchal translucency at the time of the first ultrasound and obtaining additional blood at the time of phlebotomy for routine prenatal investigations. No results were reported to either the obstetrician or patient, and prenatal care was not modified in any way by participation in the study. Ethical approval was obtained from the Scottish Multicenter Research Ethics Committee. Fifteen Scottish maternity units participated in the Combined Ultrasound and Biochemical Screening study during a 2-year period between 1997 and 1999, and 98.6% of records came from births in 11 of the hospitals. Ninety-eight percent of the births occurred between May 1998 and July 2000. Births to women recruited to the study constituted 28.6% of all births in the 11 hospitals during that period.

Maternal levels of PAPP-A were measured from blood obtained at the time of the first prenatal visit (10–14 weeks) as part of the Combined Ultrasound and Biochemical Screening study. Maternal levels of AFP were determined by two methods. First, we performed record linkage of the Combined Ultrasound and Biochemical Screening database to the database of the laboratory information management system for the prenatal screening program of the West of Scotland Regional Genetics Service of the Institute of Medical Genetics in Glasgow. Second, part of the cohort was followed up by manual retrieval of the case notes, and the AFP level was obtained directly from the case record. PAPP-A was assayed between 10 and 14 weeks gestation and AFP between 15 and 21 weeks. The outcome of the pregnancy was ascertained by linkage of the Combined Ultrasound and Biochemical Screening database to the Scottish Morbidity Record[10] and the Scottish Stillbirth and Infant Death Enquiry.[11] The Scottish Morbidity Record is a national register of perinatal outcome data,[10] and the Scottish Stillbirth and Infant Death Enquiry is a national register that routinely classifies all perinatal deaths in Scotland.[11] The Scottish Stillbirth and Infant Death Enquiry has data on 100% of registered stillbirths,[11] and the Scottish Morbidity Record contains data on 99.6% of certified births.[10] The record linkage and the details of the other data sources and definitions are described in detail elsewhere.[6,12] The study cohort (N = 8,483) for the current analysis was defined by women who participated in the Combined Ultrasound and Biochemical Screening study, who had both PAPP-A and AFP results documented, and who could be linked to the Scottish Morbidity Record where singleton birth occurred at or after 24 weeks gestation.

Small for gestational age (SGA) was defined on the basis of centiles derived from the cohort, and preterm birth was defined as delivery before 37 completed weeks of gestation. Socioeconomic status was estimated on the basis of the postal code of the mother's residence, according to Carstairs socioeconomic-deprivation categories (based on 1991 Census data on car ownership, employment status, number of occupants per household room, and social class within postal-code sectors of residence that contain, on average, about 1,600 residents).[13] Higher scores indicate residence within areas of greater deprivation.

Maternal serum levels of PAPP-A and AFP were expressed as multiples of the median (MoM) for gestational age, as is conventional for biochemical indices in pregnancy that vary with week of gestation. Because PAPP-A and AFP levels vary inversely with maternal weight, MoM were corrected for maternal weight using reciprocal-linear regression. This is widely employed in prenatal screening and is described in detail elsewhere.[14] Separate PAPP-A MoM were estimated for smokers, because PAPP-A is reduced by 15% among smokers.[9] Low PAPP-A was defined as the lowest 5% of values for gestational age ($\leq$ 0.4 MoM), and high AFP was defined as the top 5% of values for gestational age ($\geq$ 1.7 MoM). Univariate comparison of continuous variables was performed using the Mann-Whitney *U* test and categorical data using the Fisher exact test. All *P* values were 2-tailed. Statistical significance was assumed at $P < .05$. Multivariate analysis was performed using logistic regression.[15] Cases with missing data on covariates

were dropped from the multivariate analysis. Interaction terms were assessed using the likelihood ratio test. All statistical analyses were performed using the Stata 8 software package (Stata Corporation, College Station, TX).

RESULTS

The linked database contained 11,729 records of women who had a PAPP-A documented and had a Scottish Morbidity Record. Three (0.03%) records were excluded because the gestational age at delivery was less than 24 weeks, 2 (0.02%) because of missing data on sex of the baby, and 3 (0.03%) because of missing data on weight. Of the remaining 11,721 births, 8,483 (72.4%) had an AFP level recorded, and these women constituted the study cohort. The characteristics of the study cohort are described in Table 1.

Low PAPP-A was associated with an increased risk of delivering an SGA infant, preterm birth, and stillbirth (Table 2). An elevated AFP was associated with an increased risk of preterm birth and stillbirth (Table 2). Women with a low level of PAPP-A were not at increased risk of having a high AFP (odds ratio 1.3, 95% confidence interval [CI] 0.9–1.9). Adjusting each factor for the other was without material effect on the strength of associations (Table 3). Similarly adjusting for maternal characteristics had a minimal effect on the strength of the associations (Table 3).

We then studied outcome for high AFP and low PAPP-A, either singly or in combination, with reference to women with normal values of both AFP and PAPP-A (this is a different referent category from Table 3 and thus odds ratios differ slightly from Table 3). The odds ratio for delivering a small for gestational age infant for women with a high AFP was 0.9 (95% CI 0.5–1.6), for women with a low PAPP-A was 2.8 (95% CI 2.0–4.0), and for women with both a high AFP and a low PAPP-A was 8.5 (95% CI 3.6–20.0). The odds ratio for delivering preterm for women with a high AFP was 1.8 (95% CI 1.3–2.7), for women with a low PAPP-A was 1.9 (95% CI 1.3–2.7), and for women with both a low PAPP-A and a high AFP was 9.9 (95% CI 4.4–22.0). The odds ratio for antepartum stillbirth for women with a high AFP was 2.5 (95% CI 0.6–10.9), for women with a low PAPP-A was 2.2 (95% CI 0.5–9.7), and for women with both a low PAPP-A and a high AFP was 36.7 (95% CI 8.0–167.6). Receiver operating characteristic curve analysis of PAPP-A, AFP, and maternal characteristics in predicting adverse outcome is shown in Table 4. There were statistically significant positive interactions (Fig. 1) between PAPP-A and AFP in the risk of delivering a SGA infant ($P = .03$), preterm birth ($P = .04$) and a trend toward a positive interaction in the risk of stillbirth ($P = .14$). Of the women with the combination of a low PAPP-A and high AFP, 32.1% (95% CI 15.9–52.4) delivered a low birth weight infant.

Table 1. Characteristics of Study Population (N = 8,483)

Characteristics	Normal Outcome (n = 7,715)	Adverse Outcome (n = 768)	P*
Median (IQR) age (y)	30 (27–33)	29 (25–33)	< .001
Parity† (nulliparous)	3,665 (47.5)	428 (55.7)	< .001
Ethnicity† (non-Caucasian)	180 (2.5)	28 (3.9)	.02
Smoking status†			
Nonsmokers	5,503 (71.8)	419 (55.0)	
Ex-smokers	643 (8.4)	57 (7.5)	< .001
Current smokers	1,522 (19.9)	286 (37.5)	
Median (IQR) height (cm)†	163 (159–168)	162 (156–166)	< .001
Median (IQR) BMI†	23.9 (21.8–26.8)	23.1 (21.0–25.9)	< .001
Deprivation category†			
1 (least deprived)	1,885 (24.5)	125 (16.3)	
2	1,299 (16.9)	104 (13.5)	
3	1,474 (19.1)	159 (20.7)	< .001
4	1,734 (22.5)	197 (25.7)	
5 (most deprived)	1,315 (17.1)	183 (23.8)	
Marital status† (married)	4,872 (67.5)	405 (57.1)	< .001

IQR, interquartile range; BMI, body mass index.

Normal outcome is defined as not small for gestational age, not preterm, not low birth weight, and not stillborn. Adverse outcome is defined as 1 or more of these outcomes. Values are n (%) unless otherwise specified.

* P from Mann-Whitney U test, χ^2 test or χ^2 test for trend as appropriate.

† Missing values n (%) of demographic variables as follows: ethnicity 510 (6.0), smoking status 53 (0.6) , parity 1 (0.01), height 191 (2.3), BMI 715 (8.4), deprivation category 8 (0.09), and marital status 559 (6.6).

Table 2. Univariate Associations Between Pregnancy-Associated Plasma Protein A and Alpha-fetoprotein and Outcome

	PAPP-A				AFP			
	≤ 5th Percentile (n = 457)	> 5th Percentile (n = 8,026)	OR (95% CI)	*P*	≤95th Percentile (n = 8,071)	>95th Percentile (n = 412)	OR (95% CI)	*P*
SGA	50 (10.9)	303 (3.8)	3.1 (2.3–4.3)	< .001	333 (4.1)	20 (4.9)	1.2 (0.7–1.9)	.47
Preterm birth	45 (9.9)	380 (4.7)	2.2 (1.6–3.0)	< .001	385 (4.8)	40 (9.7)	2.1 (1.5–3.0)	< .001
Stillbirth	4 (0.9)	18 (0.2)	3.9 (1.3–11.7)	.01	18 (0.2)	4 (1.0)	4.4 (1.5–13.0)	.008

PAPP-A, pregnancy-associated plasma protein A; AFP, alpha-fetoprotein; OR, odds ratio; CI, confidence interval; SGA, small for gestational age.

Data are expressed as n (%) and OR (95% CI). The difference in the number of births in the top fifth percentile of AFP (n = 412) and the lowest fifth percentile of PAPPA (n = 457) is due to their being ties in the data set. In an event of a tie, where percentiles are the same, they are grouped into the lower percentile category. As a result, the lowest fifth percentile of PAPPA has 5.4% births (greater than 5%) and the highest fifth percentile of AFP has 4.9% births (less than 5%).

Table 3. Multivariate Analysis of Association Between Pregnancy-Associated Plasma Protein A, Alpha-fetoprotein, and Maternal Characteristics in Predicting Adverse Perinatal Outcome

	PAPP-A		AFP	
Outcome/Adjustment	OR (95% CI)	*P*	OR (95% CI)	*P*
SGA				
Unadjusted	3.1 (2.3–4.3)	< .001	1.2 (0.7–1.9)	.47
Adjusted for each other	3.1 (2.3–4.3)	< .001	1.2 (0.7–1.8)	.54
Adjusted for each other and maternal characteristics*	2.8 (1.9–4.1)	< .001	0.9 (0.5–1.5)	.67
Preterm delivery				
Unadjusted	2.2 (1.6–3.0)	< .001	2.1 (1.5–3.0)	< .001
Adjusted for each other	2.2 (1.6–3.0)	< .001	2.1 (1.5–3.0)	< .001
Adjusted for each other and maternal characteristics*	2.4 (1.7–3.4)	< .001	1.8 (1.2–2.7)	.002
Stillbirth				
Unadjusted	3.9 (1.3–11.7)	.01	4.4 (1.5–13.0)	.008
Adjusted for each other	3.8 (1.3–11.3)	.02	4.2 (1.4–12.6)	.009
Adjusted for each other and maternal characteristics*†	–	–	–	–

PAPP-A, pregnancy associated plasma protein A; AFP, alpha-fetoprotein; OR, odds ratio; CI, confidence interval; SGA, small for gestational age.

Values are OR (95% CI). Odds ratios are for a low PAPP-A referent to a normal PAPP-A (irrespective of AFP) and for a high AFP referent to a normal AFP (irrespective of PAPP-A).

* Maternal characteristics included in the model were age, height, body mass index, deprivation category, marital status, smoking status, ethnicity, parity, and hospital where the birth took place.

† Number of events too small for estimation using full multivariate model.

Table 4. Receiver Operating Characteristic Curve Analysis of Pregnancy-Associated Plasma Protein A, Alpha-fetoprotein, and Maternal Characteristics in Predicting Adverse Outcome

	Small for Gestational Age Infant		Preterm Delivery	
Model	Area Under ROC Curve	95% CI	Area Under ROC Curve	95% CI
PAPP-A alone	0.55	0.49–0.60	0.53	0.49–0.57
AFP alone	0.50	0.46–0.55	0.52	0.48–0.57
PAPP-A and AFP	0.55	0.50–0.59	0.54	0.51–0.58
PAPP-A, AFP, and maternal characteristics*	0.77	0.74–0.80	0.64	0.61–0.67

ROC, receiver operating characteristic; CI, confidence interval; PAPP-A, pregnancy-associated plasma protein A; AFP, alpha-fetoprotein.

* Maternal characteristics included in the model were age, height, body mass index, deprivation category, marital status, smoking status, ethnicity, parity, and hospital where the birth took place.

DISCUSSION

A number of lines of evidence support an important role for the activity of the IGF system in the first trimester of pregnancy in determining perinatal outcome. Insulin-like growth factor II is highly expressed in trophoblast and is likely to control both maternal

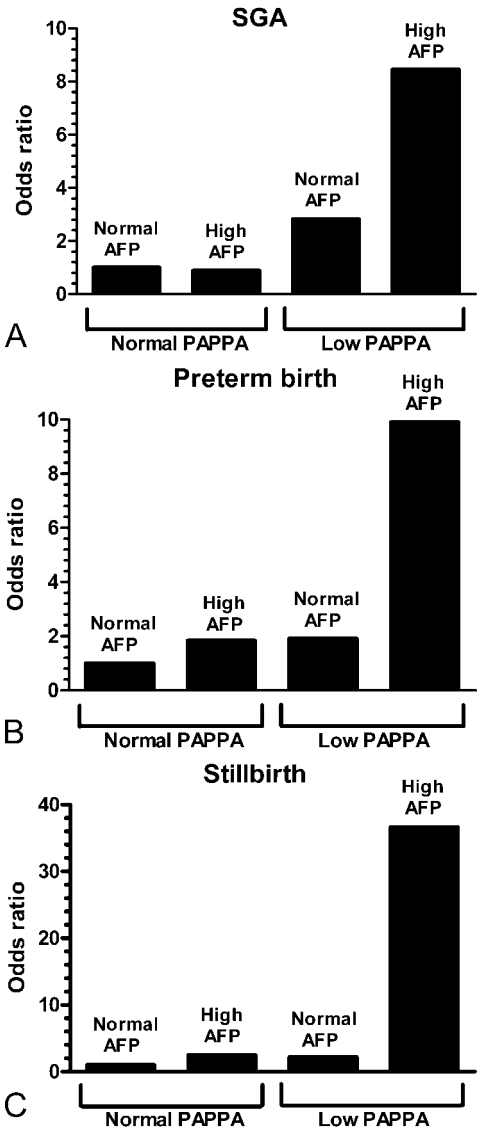

Fig. 1. Odds ratios for combinations of low pregnancy-associated plasma protein A and high alpha-fetoprotein in predicting delivery of a small for gestational age infant **(A)**, preterm delivery **(B)**, and stillbirth **(C)**. The odds ratios for interaction terms between a low pregnancy-associated plasma protein A and a high alpha-fetoprotein were 3.4 (95% CI 1.2–9.8, $P = .03$) for small for gestational age, 2.8 (95% CI 1.1–7.2, $P = .04$) for preterm birth and 6.6 (95% CI 0.5–78.9, $P = .14$) for stillbirth. All odds ratios are referent to women with both a normal pregnancy-associated plasma protein A and a normal alpha-fetoprotein. SGA, small for gestational age; AFP, alpha-fetoprotein; PAPPA, pregnancy-associated plasma protein A.

Smith. PAPP-A, AFP, and Perinatal Outcome. Obstet Gynecol 2006.

and placental tissues at the site of implantation.[1] Low maternal levels of PAPP-A, a trophoblast-derived protease for IGF binding proteins-4 and IGF binding proteins-5,[16] are associated with increased risks of intrauterine growth restriction, preterm birth, and stillbirth.[2–4] Mice which are null mutant for the PAPP-A gene are also at increased risk of early-onset intrauterine growth restriction,[7] which supports a causal role for PAPP-A in determining outcome.

Many previous studies had shown that high maternal levels of the fetal oncotic protein, AFP, were associated with an increased risk of complications in later pregnancy.[8] It was not apparent, however, whether PAPP-A was a marker for the same placental defect that leads to high rates of placental transfer of AFP. The present study had 3 major findings. First, we show that women who had low levels of PAPP-A were not more likely to have elevated levels of AFP in the second trimester of pregnancy. This suggests that the pathophysiologic process leading to high placental transfer rates of AFP is not related to the IGF system, insofar as it can be assessed by circulating levels of PAPP-A. Second, we show that adjustment for the levels of PAPP-A had a minimal effect on the strength of association between AFP and adverse outcome, and vice versa. If low levels of PAPP-A and high levels of AFP were markers of the same underlying defect in placental function, it would have been anticipated that adjustment of 1 factor for the level of the other would have resulted in a weaker association. The lack of an effect of such adjustment suggests that low PAPP-A and high AFP are consequences of distinct processes and that extreme levels indicate different aspects of placental dysfunction. Finally, we show the combination of a low PAPP-A and a high AFP was synergistically associated with adverse outcome. This indicates that the consequences of the 2 underlying processes must interact. These clinical observations indicate complexity in the placental determinants of adverse perinatal outcome and underline the importance of understanding the biology of trophoblast function in early pregnancy as a determinant of complications in late pregnancy.

The combination of low PAPP-A and high AFP is not likely to be clinically useful as a means of population-based screening to identify women at high risk of pregnancy complications. Relatively few women will have the combination of a low PAPP-A and a high AFP. Consequently, the sensitivity of this test will be low and would not, in itself, justify population-based screening for these outcomes. However, maternal serum levels of PAPP-A and AFP are used in Down syndrome screening, and inevitably, this process will identify women who have the combination of both a low PAPP-A and a high AFP. Women with this combination had a 32.1% risk of delivering a low

birth weight neonate (< 2,500 g), a composite outcome of poor growth and preterm birth. The current data justify very close surveillance of these women, because they have a high absolute risk of adverse outcome. Serial umbilical artery Doppler flow velocimetry may be the preferred method of surveillance, because its use has been shown to reduce perinatal mortality in high-risk pregnancies.[17]

The data sources employed in the present study also included measurement of the free β subunit of human chorionic gonadotrophin in the first trimester of pregnancy and human chorionic gonadotrophin in the second. We did not analyze whether these factors were associated with adverse outcome, because previous studies have shown the former is not independently associated with adverse outcome,[2] and the latter is only weakly associated.[18] Moreover, the number of cases in the present study were insufficient to study third- or fourth-order interactions or interactions associated with more extreme values of PAPP-A or AFP.

In conclusion, we show that low PAPP-A and high AFP synergistically predict preterm birth and intrauterine growth restriction. We speculate that the synergistic predictive ability of these tests reflects the combined effect of 2 independent pathophysiologic processes in early placental development.

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Section 5. Obstetric predictors of long term infant outcome

Risk of Sudden Infant Death Syndrome and Week of Gestation of Term Birth

Gordon C. S. Smith, MD, PhD*; Jill P. Pell, MD‡; and Richard Dobbie, BSc§

ABSTRACT. *Objective.* **We sought to determine if the risk of sudden infant death syndrome (SIDS) varied according to week of delivery at term among elective and nonelective births.**

Design. **Retrospective cohort study.**

Participants. **All single infants live born between 37 and 42 weeks gestation in Scotland between 1992 and 1995 documented in the Scottish Morbidity Record.**

Outcome. **Death in the first year of life where SIDS was in the principal position on the death certificate.**

Results. **There were 202 622 eligible births and 119 deaths attributed to SIDS. Among infants delivered electively, there was no significant association between risk of SIDS and week of delivery. Among those delivered nonelectively, the risk of SIDS declined significantly with each week of gestation (odds ratio .72, 95% confidence interval .60–.86). This trend was only minimally attenuated by adjustment for maternal age, parity, smoking and socioeconomic deprivation category, infant sex, Apgar score, mode of delivery, and birth weight decile (adjusted odds ratio .78, 95% confidence interval .65–.93).**

Conclusions. **We hypothesize that early spontaneous labor at term and SIDS may be linked because of a common association with suboptimal intrauterine environment.** *Pediatrics* **2003;111:1367–1371;** ***pregnancy, gestational age, labor, sudden infant death syndrome, smoking.***

ABBREVIATIONS. CI, confidence interval; HPAA, hypothalamopituitary adrenal axis; SIDS, sudden infant death syndrome.

Previous epidemiologic studies on the etiology of sudden infant death syndrome (SIDS) have identified a number of obstetric risk factors, such as maternal cigarette smoking in pregnancy, low birth weight, low maternal age and high parity, and a number of postnatal environmental factors, such as socioeconomic deprivation, parental cigarette smoking, sleeping position, and bedding material.[1–5] Identifying infants at increased risk of SIDS allows education and monitoring to be targeted toward high-risk families. Identification of modifiable environmental risk factors led to public information campaigns which have been followed by a dramatic decrease in the incidence of SIDS.[4,6] Despite these improvements, the pathophysiology of SIDS is still unclear and it remains the most common cause of postneonatal death in the first year of life.[7]

Moderate and severe preterm birth are associated with an increased risk of SIDS and account for a significant etiologic fraction of all SIDS deaths.[8] We have recently shown that early pregnancy levels of circulating placental proteins are associated both with spontaneous preterm birth[9] and with the earlier onset of labor at term.[10] We hypothesize that in some pregnancies the early onset of labor at term reflects a suboptimal intrauterine environment. The aim of the present study was to determine if the risk of SIDS varied with the timing of spontaneous labor among infants born at term.

METHODS

Patient Selection

The Scottish Morbidity Record collects information on clinical and demographic characteristics and outcomes for all women discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been >99% complete since the late 1970s.[11] Data were extracted on all single live born infants delivered between 37 and 42 weeks gestation in Scotland between 1992 and 1995. Scottish Morbidity Record records were linked to the death database held by the Registrar General for Scotland's Office to determine the date and principal cause of death of those infants who died. We excluded from both the univariate and multivariate analyses those infants with missing values for any of the covariates of interest and those infants who died in their first year of life from a cause other than SIDS.

Definitions

SIDS was defined as the death of an infant for whom the principal cause of death on the death certificate was coded as 798.0 using the *International Classification of Diseases, Ninth Revision*. Over the period studied, a diagnosis of SIDS could only be written on a death certificate in Scotland following thorough investigation of the circumstances of the death including a postmortem examination performed by an approved pediatric pathologist.

Gestational age has been confirmed by ultrasound scan in the first half of pregnancy in >95% of pregnancies in the United Kingdom from the early 1990s.[12] Gestational age at birth was defined as completed weeks of gestation on the basis of the estimated date of delivery in each woman's clinical record and standard national criteria exist for the estimation of date of delivery using menstrual and ultrasound data.[13] Smoking status was defined as the smoking status of the woman at the time of first attendance for antenatal care. Maternal age was defined as the age of the mother at the time of delivery. Birth weight was categorized into sex and gestational age-specific deciles, as previously described in detail.[14] Elective delivery was defined as delivery by planned cesarean section or delivery by any mode following induction of labor. Postal code of residence was used to derive Carstairs socioeconomic deprivation categories.[15] These are based on 1991 Census data on car ownership, unemployment, over-

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crowding, and social class within postal code sectors of residence which contain, on average, ~1600 residents.

Statistical Analyses

Continuous variables were summarized by the median and interquartile range, and comparisons between groups were performed using the Mann-Whitney *U* test. Correlation was tested using Spearman's ρ. Univariate comparisons of dichotomous data were performed using the χ^2 test. Ordinal data were compared using the χ^2 test for trend. The *P* values for all hypothesis tests were 2-sided. Crude and adjusted odds ratios were obtained using logistic regression analyses. Maternal age, height, socioeconomic deprivation score and mode of delivery, and the offspring's birth weight decile, Apgar score, and sex were categorized and treated as dummy variables. Week of gestation at term was treated as a continuous variable and linearity or nonlinearity (in the log odds scale) was assessed using fractional polynomials.[16] The possible effect of deaths attributed to other causes was taken into account using a proportional hazards model, where age was the time scale, death attributed to SIDS was the event, deaths in the first year of life attributed to causes other than SIDS were treated as censored, as were all survivors at 1 year of life. Regression techniques employed robust standard errors to allow for dependence within individuals using a maternal identifier. The statistical significance of interaction terms was assessed using the likelihood ratio test and significance assumed at $P < .01$. The goodness of fit of models was assessed using the Hosmer and Lemeshow[17] test based on deciles of probability. All statistical analyses were performed using the Stata software package (Stata Corporation, College Station, TX), version 7.0.

RESULTS

Between 1992–1995, there were 241 846 single live births in Scotland. Gestational age at birth was missing in 666 (.3%), and recorded but outside the range of 37 to 42 weeks in 13 714 (5.7%). Among the remaining 227 466 births, there were missing values for parity in 155 (.1%), deprivation category in 741 (.3%), birth weight in 62 (<.1%), and maternal smoking in 23 626 (10.4%). Overall, 24 413 had 1 or more missing values, leaving 203 053 live births between 37 and 42 weeks gestation with complete data. Within this group, there were 431 (.2%) deaths before the first year of life attributed to causes other than SIDS, leaving a study group of 202 622. There were 119 deaths attributed to SIDS in the group which equated to a rate of 5.9 per 10 000 (95% confidence interval [CI] 4.9–7.0) for the study cohort. The proportion of infants dying from SIDS did not change significantly between 1992 and 1995 ($P = .98$, χ^2 test for trend).

Table 1 compares the maternal demographic and obstetric characteristics of those infants who died from SIDS with those who did not (Table 1). On univariate analysis, the mothers of infants who died from SIDS were younger at delivery, of higher parity,

TABLE 1. Comparison of Maternal, Demographic, and Obstetric Characteristics by Occurrence of SIDS

	SIDS ($N = 119$)	Non-SIDS ($N = 202\,503$)	*P Value
Maternal characteristics	median (IQR)	median (IQR)	
Age	24 (20–29)	28 (24–31)	<.001
Height (cm)	161 (156–166)	162 (157–167)	.19
Parity	number (%)	number (%)	
Nulliparous	43 (36.1)	89 588 (44.2)	
Para 1–2	63 (52.9)	100 176 (49.5)	
Para 3–4	11 (9.2)	11 388 (5.6)	
Parity ≥5	2 (1.7)	1351 (.7)	<.001
Deprivation category			
1 (least deprived)	2 (1.7)	10 584 (5.2)	
2	5 (4.2)	25 963 (12.8)	
3	18 (15.1)	42 357 (20.9)	
4	32 (26.9)	50 243 (24.8)	
5	18 (15.1)	32 606 (16.1)	
6	17 (14.3)	24 527 (12.1)	
7 (most deprived)	27 (22.7)	16 223 (8.0)	<.001
Smoker	80 (67.2)	63 578 (31.4)	<.001
Obstetric characteristics			
Week of gestation of delivery			
37	13 (10.9)	10 216 (5.0)	
38	23 (19.3)	26 721 (13.2)	
39	24 (20.2)	41 466 (20.5)	
40	36 (30.2)	69 050 (34.1)	
41	19 (16.0)	44 537 (22.0)	
42	4 (3.4)	10 513 (5.2)	.02
Male	77 (64.7)	102 873 (50.8)	.002
Elective delivery	33 (27.7)	59 950 (29.6)	.65
Mode of delivery			
Spontaneous vaginal	96 (80.7)	149 172 (73.4)	
Operative vaginal	7 (5.9)	24 221 (12.0)	
Prelabor cesarean section	9 (7.6)	16 691 (8.2)	
Postlabor cesarean section	7 (5.9)	12 372 (6.1)	.21
Missing	0	47	
Birth weight decile for sex and gestational age			
Lowest decile	24 (20.2)	20 190 (10.0)	<.001
Highest decile	7 (5.9)	19 875 (9.8)	.15
	median (IQR)	median (IQR)	
Birth weight (g)	3180 (2880–3540)	3400 (3120–3760)	<.001

IQR indicates interquartile range.
* *P* value is from the Mann-Whitney *U* test, the χ^2 test or the χ^2 test for trend as appropriate.

were more likely to live in an area of high socioeconomic deprivation and were more likely to smoke. Infants who died from SIDS were of lower absolute birth weight, lower birth weight decile for sex and gestational age, were more likely to deliver at earlier weeks of gestation, and were more likely to be male. The median age of death attributed to SIDS was 78 days (interquartile range: 42–138 days). There was no association between gestation at delivery and age of death attributed to SIDS among infants born electively (Spearman's $\rho = -.06$, $P = .75$) or following spontaneous labor (Spearman's $\rho = .19$, $P = .08$).

The relationship between the risk of SIDS and the week of gestation at delivery was then examined separately for elective and nonelective births. There was no significant trend between week of delivery at term and the risk of SIDS among infants delivered electively, whereas among infants delivered nonelectively the risk of SIDS decreased with increasing gestational age at delivery (Fig 1). The relationship between week of gestation and risk of SIDS was explored further using logistic regression. The odds ratio for each week of gestation at term for SIDS among nonelective births was .72 (95% CI .60–.86, $P < .001$) and for elective births was .90 (95% CI .70–1.15, $P = .41$). Addition of a polynomial term did not significantly improve either model ($P = .38$ and $P = .36$). Adjusting for potential confounders (maternal age, parity, deprivation category, mode of delivery, smoking status, birth weight decile, Apgar score, and sex) only slightly attenuated the association among nonelective births (adjusted odds ratio .78, 95% CI .65–.93) and minimally altered the odds ratio for week of gestation among elective births (adjusted odds ratio .88, 95% CI .68–1.13). The odds ratio of SIDS at each week of gestation among nonelective births is tabulated (Table 2).

The association between week of gestation and the risk of SIDS among nonelective births was very similar when confined to women who booked before 20 weeks gestation (odds ratio .74, 95% CI .60–.91) or before 13 weeks gestation (odds ratio .69, 95% CI .50–.96). The association was also very similar when the risk of SIDS was calculated having taken into account infant deaths attributed to other causes using a proportional hazards model for both nonelective (hazard ratio .72, 95% CI .60–.86) and elective births (hazard ratio .90, 95% CI .70–1.15). There were no statistically significant interactions between week of delivery at term among either elective or nonelective births and the other factors in predicting the risk of SIDS (all $P > .01$). Goodness of fit tests were performed for logistic models and these were not statistically significant for either nonelective ($P = .96$) or elective births ($P = .72$).

There was limited information available on the indication for elective delivery. However, we could identify women who were delivered by planned cesarean section who had an infant presenting by the breech and women having planned repeat cesarean births. The incidence of SIDS in this group (4 of 9766, 4.1 per 10 000) was very similar to the other women delivered electively (29 of 50 217, 5.8 per 10 000; $P = .52$).

DISCUSSION

The factors predisposing to SIDS have been the subject of intense study for many years. The incidence of SIDS declined in many countries in the early 1990s as the importance of postnatal environmental factors, such as sleeping position and cigarette smoke, was recognized. The sharp decline in incidence took place between 1989–1991 in Scotland,[6] and over the period of the present study the rate of SIDS was relatively stable. A number of obstetric factors are known to affect the risk of SIDS, including preterm birth. The main finding of the present study is that even within gestational ages regarded as term (from 37 weeks onwards), the risk of SIDS decreased progressively with advancing gestational age at delivery (Fig 1 and Table 2). This association was not explained by known risk factors for SIDS, such as maternal cigarette smoking, fetal sex, fetal growth, maternal age, parity, and socioeconomic deprivation. There was no comparable trend among infants delivered electively, and the differing patterns of association persisted after adjusting for mode of delivery. This suggests that the increased risk was not attributed to early delivery, but to the early onset of labor. We hypothesize that the factors which predispose to earlier onset of spontaneous labor at term may also predispose to SIDS.

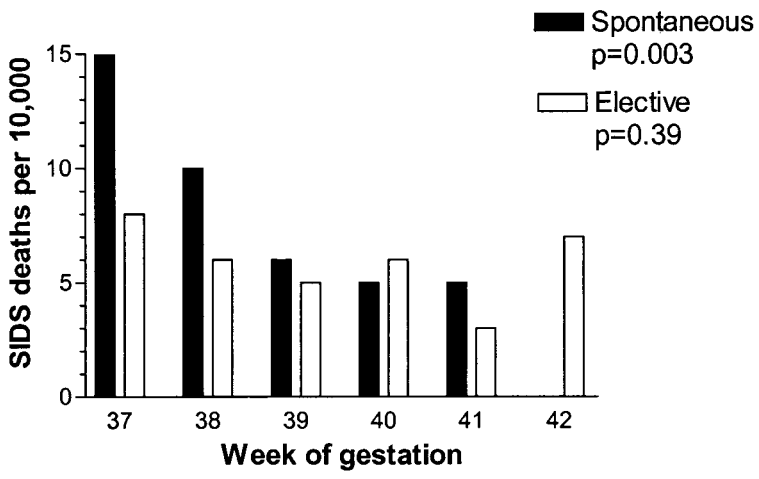

Fig 1. Death rates for SIDS in relation to week of delivery among women delivered electively ($N = 59\,983$) and nonelectively ($N = 142\,639$). P value is the χ^2 test for trend.

TABLE 2. Crude and Adjusted Odds Ratios for SIDS Associated With Week of Delivery at Term Among Infants Born Following the Onset of Spontaneous Labor

Week of Gestation	Births (*N*)	SIDS Deaths *N* (%)	Crude Odds Ratio* (95% CI)	*P* Value§	Adjusted Odds Ratio† (95% CI)	*P* Value§
37	654	10 (.15)	3.1 (1.5–6.4)	.002	2.5 (1.2–5.2)	.015
38	15 722	16 (.10)	2.1 (1.1–3.8)	.02	1.8 (.9–3.3)	.075
39	32 285	19 (.06)	1.2 (.7–2.2)	.54	1.1 (.6–2.1)	.66
40*	54 981	27 (.05)	(1.0)		(1.0)	
41	28 492	14 (.05)	1.0 (.5–1.9)	>.99	1.1 (.6–2.1)	.80
42	4611	0 (0)	–	.27	–	

* Referent category.
† Adjusted for maternal age, parity, deprivation category, birth weight decile, male sex, maternal smoking, and mode of delivery.
§ *P* value from Wald test except comparison between 40 weeks and 42 weeks, which was by Fisher's exact test.

It is possible that the lack of association between gestational age and risk of SIDS could be explained by bias. If infants born electively before 40 weeks had an increased risk of SIDS, then it is possible that those allowed to proceed to 40 weeks and beyond were selected and had a lower risk of SIDS. Therefore, a false relationship between gestational age and SIDS might be observed. However, the infants born electively before 40 weeks had a very similar risk of SIDS to infants born nonelectively at or after 40 weeks gestation. The excess of deaths occurred among infants nonelectively delivered at the earlier weeks of term. The rate of death in this group was higher than elective births at all gestational ages and spontaneous births at later weeks of gestation. It is possible that the association with early term birth reflected misclassification of gestational age and increased numbers of truly preterm infants at the earlier weeks of gestation at term. However, this is unlikely since confining the analysis to women who booked in the first trimester of pregnancy, when ultrasound estimation of gestational age is most accurate,[13] tended to strengthen rather than weaken the association.

This study focused on the relationship between obstetric factors and the risk of SIDS. Although this analysis is retrospective, these data were collected during pregnancy and immediately following delivery and were thus prospective in relation to SIDS; this is one of the main strengths of our study design. However, we lacked information on some other factors which are thought to influence the risk of SIDS. For example, the method of infant feeding was unknown. It is possible that differences in successful breastfeeding in relation to week of delivery may account for some of the observed association. However, this would not explain the observed difference between elective and nonelective births. There were missing values for ~10% of the population, principally smoking status. This is unlikely to bias the analysis and the proportion with missing values is comparable to other national databases.[18]

A number of studies have demonstrated an increased risk of SIDS following preterm birth.[4,19] Because SIDS is independently associated with admission to neonatal intensive care,[19] it is difficult to determine if the association with preterm birth was a consequence of preterm delivery or was associated with the factors which led to the preterm delivery. Our study is the first to demonstrate an association between earlier onset of labor at term and the risk of SIDS in the infant. Although the biological determinants of the onset of labor at term are not yet fully understood, activation of the fetal hypothalamopituitary adrenal axis (HPAA) is thought to be a key physiologic event precipitating the process.[20] The factors controlling the fetal HPAA are complex, and possibly include corticotrophin-releasing hormone from the placenta[21] and suppression of the fetal HPAA by maternal steroids.[22] However, a number of physiologic stresses activate the fetal HPAA.[23] Previous studies have also shown an association between spontaneous preterm birth and intrauterine growth restriction.[24–26] We hypothesize that early activation of the fetal HPAA and the resultant early onset of labor at term may reflect an adverse intrauterine environment. Consistent with this, we have recently demonstrated that low levels of placentally derived proteins in early pregnancy are associated with earlier onset of labor at term.[10] We hypothesize that the association demonstrated between early onset of spontaneous labor and risk of SIDS may result from a suboptimal intrauterine environment predisposing to both events.

It has been hypothesized, on the basis of postmortem findings, that SIDS forms a continuum with unexplained death of the fetus in utero.[27] Consistent with this, the conditions share a number of risk factors, such as maternal cigarette smoking during pregnancy,[28] poor fetal growth,[29] and male sex.[14] However, the risk of unexplained fetal death increases with advancing gestational age,[30,31] whereas the risk of SIDS declined (Table 2). Moreover, the risk of SIDS is lower among first pregnancies,[4,19] whereas the risk of unexplained fetal death is higher among first pregnancies.[31] We hypothesize that the differences in risk factors for SIDS and unexplained fetal death may be explained by the initiation of labor. We propose that if the suboptimal intrauterine environment prematurely initiates the endocrine cascade leading to parturition, the infant is live born but is at increased risk of subsequent SIDS. If the fetus is exposed to a suboptimal intrauterine environment but labor is not initiated, there is an increased risk of intrauterine death. We hypothesize that the lower risk of SIDS and higher risk of unexplained fetal death among nulliparous women may reflect a higher threshold for activation of the fetal HPAA to

initiate labor. Consistent with this, the onset of spontaneous labor at term is later among nulliparous women.[32]

CONCLUSIONS

The earlier onset of spontaneous labor at term is associated with an increased risk of subsequent SIDS. We hypothesize that this may reflect a common association with suboptimal intrauterine environment.

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ORIGINAL ARTICLE

Second-Trimester Maternal Serum Levels of Alpha-Fetoprotein and the Subsequent Risk of Sudden Infant Death Syndrome

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ABSTRACT

BACKGROUND

Unexplained stillbirth and the sudden infant death syndrome (SIDS) share some features. A raised maternal serum level of alpha-fetoprotein during the second trimester of pregnancy is a marker of placental dysfunction and a strong predictor of the risk of unexplained stillbirth. It is unknown whether alpha-fetoprotein levels also predict the risk of SIDS.

METHODS

We linked a prenatal-screening database for women in western Scotland with databases of maternity, perinatal death, and birth and death certifications to assess the association between second-trimester levels of maternal serum alpha-fetoprotein and the subsequent risk of SIDS.

RESULTS

Among 214,532 women with singleton births, there were 114 cases of SIDS (incidence, 2.7 per 10,000 births among women with alpha-fetoprotein levels in the lowest quintile and 7.5 per 10,000 births among those with levels in the highest quintile). When the lowest quintile was used as a referent, the unadjusted odds ratios for SIDS for the second through fifth quintiles were 1.7 (95 percent confidence interval, 0.8 to 3.5), 1.8 (95 percent confidence interval, 0.9 to 3.7), 2.5 (95 percent confidence interval, 1.3 to 4.8), and 2.8 (95 percent confidence interval, 1.4 to 5.4), respectively (P for trend=0.001). The risk of SIDS varied inversely with the birth-weight percentile and the gestational age at delivery; after adjustment for these factors, the odds ratios for SIDS were 1.7 (95 percent confidence interval, 0.8 to 3.5), 1.7 (95 percent confidence interval, 0.8 to 3.5), 2.2 (95 percent confidence interval, 1.1 to 4.4), and 2.2 (95 percent confidence interval, 1.1 to 4.3), respectively (P for trend=0.01).

CONCLUSIONS

There is a direct association between second-trimester maternal serum alpha-fetoprotein levels and the risk of SIDS, which may be mediated in part through impaired fetal growth and preterm birth.

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THE SUDDEN INFANT DEATH SYNDROME (SIDS) is defined as the death of an infant during the first year of life in cases in which all identifiable causes of death can be ruled out by appropriate assessment. Observational studies have highlighted the prone sleeping position and environmental tobacco smoke in the infant's bedroom as factors that are associated with SIDS.[1] Widespread public health campaigns directed at modifying these behaviors have been followed by a sharp reduction in the incidence of SIDS. However, SIDS remains the most important single cause of infant death in the industrialized world.[1,2] A number of studies have identified obstetrical factors that are associated with an increased risk of SIDS, such as poor intrauterine growth and premature birth.[1] Moreover, as programs designed to address environmental risk factors have become widespread, the relative importance of obstetrical determinants has increased.[3]

The mechanisms linking complications of pregnancy and the risk of SIDS remain obscure. Previous studies have suggested similarities between unexplained stillbirth and SIDS with respect to clinical and pathological findings, suggesting that the two conditions may be related.[4,5] A raised maternal serum level of alpha-fetoprotein during the second trimester of pregnancy is one of the best biochemical predictors of the risk of unexplained stillbirth.[6] If SIDS and unexplained stillbirth have common pathophysiological determinants, there might be a direct association between maternal serum alpha-fetoprotein levels and the risk of SIDS. We designed this study to test the hypothesis that the risk of SIDS would increase with increasing maternal serum levels of alpha-fetoprotein in a large Scottish database linking biochemical, pregnancy, birth, and death records for 214,532 live-born singleton infants.

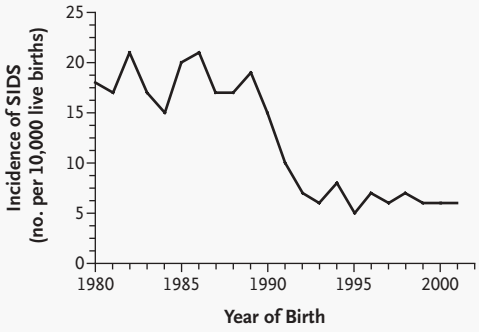

Figure 1. Incidence of SIDS According to the Year of Birth among 1,321,646 Live Singleton Births in Scotland, 1980 to 2001.

The range in the annual number of births was 48,740 to 65,688, and the range in the annual number of deaths attributed to SIDS was 29 to 131.

METHODS

SOURCES OF DATA

The Scottish Morbidity Record is a registry in which information on clinical and demographic characteristics and outcomes is collected for all women discharged from Scottish maternity hospitals. The registry is subjected to regular quality-assurance checks and has been more than 99 percent complete since the late 1970s.[7] The Scottish Stillbirth and Infant Death Enquiry is a national registry that routinely classifies all perinatal deaths in Scotland.[2] All women attending prenatal care in western Scotland are offered biochemical screening, with their serum levels of alpha-fetoprotein and human chorionic gonadotropin used to assess their risk of having a fetus affected by Down's syndrome or a structural abnormality.[8] The laboratory information management system for the prenatal screening program of the West of Scotland Regional Genetics Service of the Institute of Medical Genetics, in Glasgow, contains a database of maternal information and biochemical-screening results. Electronic storage of these data in their current form was started in September 1991. Although serum alpha-fetoprotein was measured during screening before this date, the data were not archived in a format that allowed weight-adjusted multiples of the median to be calculated. The General Register Office, Scotland, maintains electronic birth and death records.

We used a probability-based, matching approach[9] with maternal identifiers to link the Scottish Morbidity Record, the Scottish Stillbirth and Infant Death Enquiry database, the Institute of Medical Genetics prenatal screening database, and the General Register Office database of birth certificates. The birth certificates contained offspring identifiers that were then used to link biochemical data, pregnancy data, and data on perinatal deaths to the death-certificate registry to identify deaths among the offspring. We excluded multiple births, stillbirths, and births before or after 24 to 43 weeks of gestation. Approval of the study was obtained

Table 1. Demographic and Obstetrical Characteristics of the Cohort.*

Characteristic	SIDS (N=114)	No SIDS (N=214,418)	P Value†
Mother‡			
Age — yr			<0.001
Median	25	28	
Interquartile range	20–31	24–32	
Height — cm			0.002
Median	160	162	
Interquartile range	157–165	158–167	
Body-mass index§			0.008
Median	23.2	23.9	
Interquartile range	20.9–25.5	21.7–27.0	
Parity — no. (%)			0.005
Nulliparous	42 (36.8)	96,234 (44.9)	
1 or 2	57 (50.0)	106,175 (49.5)	
3 or 4	14 (12.3)	10,862 (5.1)	
≥5	1 (0.9)	1,123 (0.5)	
Carstairs deprivation category — no. (%)			<0.001
1 (least deprived)	2 (1.8)	8,909 (4.2)	
2	6 (5.3)	22,571 (10.5)	
3	14 (12.3)	41,147 (19.2)	
4	18 (15.8)	52,748 (24.6)	
5	20 (17.5)	34,412 (16.1)	
6	19 (16.7)	31,383 (14.7)	
7 (most deprived)	35 (30.7)	22,893 (10.7)	
Smoking status — no. (%)			<0.001
Never smoked	29 (27.1)	124,261 (61.9)	
Former smoker	4 (3.7)	15,302 (7.6)	
Current smoker	74 (69.1)	61,264 (30.5)	
Serum alpha-fetoprotein multiple of the median			0.002
Median	1.11	1.01	
Interquartile range	0.91–1.39	0.81–1.27	

from the Privacy Advisory Committee of the Information and Statistics Division, National Health Service, Scotland.

DEFINITIONS

For purposes of this study, SIDS was defined as the death of an infant during the first year of life with this diagnosis listed as the principal cause of death on the death certificate (code 798.0 in the *International Classification of Diseases, 9th Revision* [ICD-9] or code R95 in the *International Classification of Diseases, 10th Revision* [ICD-10]). During the period studied, a diagnosis of SIDS could be written on a death certificate in Scotland only after thorough investigation of the circumstances of the death. The minimal requirements are described by the Crown Office[10] (the government body that oversees the Procurator Fiscal, whose duties include the investigation of sudden deaths), and an autopsy is mandatory. In practice, the investigation of these deaths was frequently much more involved.[11] A previous, detailed study in which Scottish death certificates between 1992 and 1995 showed 201 deaths attributed to SIDS found that standard diagnostic criteria were fulfilled in all cases.[12] SIDS is a diagnosis of exclusion and is not made in the presence of a major congenital abnormality. The death certificate could contain up to three ICD-9 or ICD-10 di-

Table 1. (Continued.)

Characteristic	SIDS (N=114)	No SIDS (N=214,418)	P Value††
Serum alpha-fetoprotein quintiles — no. (%)			0.001
1	12 (10.5)	43,912 (20.5)	
2	20 (17.5)	42,185 (19.7)	
3	21 (18.4)	42,660 (19.9)	
4	29 (25.4)	43,193 (20.1)	
5	32 (28.1)	42,468 (19.8)	
Serum human chorionic gonadotropin multiple of the median			0.20
Median	0.95	1.00	
Interquartile range	0.60–1.44	0.71–1.40	
Infant			
Male sex — no. (%)	72 (63.2)	109,883 (51.2)	0.01
Birth-weight percentile			<0.001
Median	28	50	
Interquartile range	12–56	25–75	
Birth weight — g			<0.001
Median	3000	3410	
Interquartile range	2530–3310	3060–3750	
Gestational age — wk			<0.001
Median	39	40	
Interquartile range	37–40	39–41	

* Of the 114 cases of death attributed to SIDS, data were missing on the mother's height in 2 (1.8 percent), body-mass index in 9 (7.9 percent), and smoking status in 7 (6.1 percent). Of the remaining 214,418 records, data were missing on the mother's height in 2510 (1.2 percent), body-mass index in 15,877 (7.4 percent), parity in 24 (<0.1 percent), deprivation category in 355 (0.2 percent), and smoking status in 13,591 (6.3 percent) and were missing on the infant's sex in 9 (<0.1 percent), birth-weight percentile in 61 (<0.1 percent), and birth weight in 53 (<0.1 percent).

† P values were calculated by the Mann–Whitney U test, the chi-square test, or the chi-square test for trend, as appropriate.

‡ The mother's age is the age at the time of delivery, and the body-mass index and smoking status are those documented at her first visit for prenatal care. The Carstairs deprivation category is estimated on the basis of socioeconomic indicators in the area of residence; the method of calculation has been described in detail elsewhere.[13] The multiple of the median is the ratio of an individual value to the median value for the given week of gestation, corrected for maternal weight.[17]

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

agnostic codes. We ruled out coexisting congenital abnormalities by searching the second and third diagnostic codes (for ICD-9 codes 740.0 to 759.9 or ICD-10 codes beginning with "Q"); none of the cases in which death had been attributed to SIDS on the certificate also had these codes.

The mother's age and parity, the postal code of her residence, and all outcome data were obtained solely from the Scottish Morbidity Record. The mother's weight was obtained solely from the biochemical database. Her height and smoking status were obtained from the Scottish Morbidity Record or, in cases in which they were missing from the Scottish Morbidity Record, from the biochemical database. The smoking status (current, former, or never) was determined on the basis of information gathered at the time of the first prenatal visit or at the time of prenatal screening if this information was obtained from the biochemical database. The mother's age was defined as the age of the mother at the time of delivery. Her body-mass index was calculated as the weight in kilograms recorded at the time of sampling for the alpha-fetoprotein assay divided by the square of the height in meters. Socioeconomic status was estimated on the basis of the postal code of the mother's residence, according to Carstairs socioeconomic-deprivation categories[13] (based on 1991 Census data on car ownership, employment status, number of occupants per household room, and social class within postal-code sectors of residence that contain, on average, about 1600 residents).

The gestational age at birth was defined as the number of weeks of gestation completed, on the basis of the estimated date of delivery in each woman's clinical record; standard national criteria exist for estimation of the date of delivery with the use of menstrual and ultrasonographic data.[14] Since the early 1990s, the estimated gestational age has been confirmed by ultrasonography during the first half of pregnancy in more than 95 percent of pregnancies in the United Kingdom.[15] The birth weight was categorized into sex-specific and gestational-age–specific percentiles, as previously described in detail.[16] Maternal serum levels of alpha-fetoprotein and human chorionic gonadotropin were quantified as multiples of the median (the ratio of the individual value to the median value) for the given week of gestation, after correction for the mother's weight.[17]

STATISTICAL ANALYSIS

Univariate comparisons were performed with the Mann–Whitney U test, the chi-square test, and the chi-square test for trend, as appropriate. The P values for all hypothesis tests were two-sided. Crude and adjusted odds ratios for SIDS were obtained by means of logistic-regression analysis.[18] Biochemical data were categorized into deciles or quintiles. The mother's age, height, body-mass index, and parity were treated continuously in logistic-regression models, as were the birth-weight percentile and the gestational age (in weeks) at delivery. Nonlinearity of continuous variables in the logistic regression was tested and modeled with the use of fractional polynomials. The regression techniques involved the use of robust standard errors, as well as unique maternal identifiers, to account for dependence between births to the same mother.

The statistical significance of interaction terms was assessed by means of the Wald test, and results were considered significant when the P value was less than 0.01. Observations for which values were missing for variables that were more than 99.8 percent complete in the linked database were dropped from the multivariate analysis. For variables that were 99.8 percent or less complete in the linked database, missing values were estimated by multiple multivariate imputation.[19] The goodness of fit of the models was assessed with a Hosmer–Lemeshow test based on deciles of probability. All statistical analyses were performed with use of Stata software, version 8.2.

RESULTS

A total of 1,321,646 live singleton births at 24 to 43 weeks of gestation were recorded in the Scottish Morbidity Record between 1980 and 2001, and 1673 of the infants died from SIDS (12.7 per 10,000). Figure 1 shows the incidence of SIDS according to year of birth and indicates a sharp decline around 1990 and 1991, coincident with the public appreciation of the effects of a prone sleeping position and environmental tobacco smoke on the risk of SIDS. There were 216,563 linked records for singleton births for which the maternal serum alpha-fetoprotein level had been recorded. Of these, we excluded 867 (0.40 percent) with extreme levels of alpha-fetoprotein (defined as values at or below the 0.2nd percentile or at or above the 99.8th percentile), 1060 stillbirths (0.49 percent), and 131 births at a gestational age of less than 24 weeks or more than 43 weeks (0.06 percent); 2031 records listed one or more of these reasons for exclusion. Thus, the study cohort comprised 214,532 live births between November 15, 1991, and December 31, 2001.

There were 114 deaths attributed to SIDS in the cohort, yielding an incidence of 5.3 (95 percent confidence interval, 4.4 to 6.4) per 10,000 live births. The incidence in the whole of Scotland over the same period was 6.5 (95 percent confidence interval, 5.8 to 7.2) per 10,000 live births. There were 880 deaths during the first year of life in the cohort. In 311 of these deaths (35.3 percent), one or more of the three diagnostic codes included on the death certificate was the code for a congenital abnormality. There were no congenital abnormalities listed among the three diagnostic codes on the death certificate in the 114 cases of SIDS.

The assays for alpha-fetoprotein were performed between 15 and 21 weeks of gestation. The range of the maternal serum level of alpha-fetoprotein, expressed as multiples of the median, was 0.35 to 3.75; the 5th percentile was 0.59 and the 95th percentile 1.82. The quintiles of the maternal serum level of alpha-fetoprotein, expressed as multiples of the median for gestational age, were less than or equal to 0.77; greater than 0.77 but less than or equal to 0.93; greater than 0.93 but less than or equal to 1.10; greater than 1.10 but less than or equal to 1.35; and greater than 1.35. The demographic and obstetrical characteristics of the study cohort are shown in Table 1. Women whose infants

ultimately died of SIDS were younger, shorter, had a lower body-mass index, were of higher parity, were more likely to live in a very socioeconomically deprived area, were more likely to smoke, had higher second-trimester levels of alpha-fetoprotein, were more likely to have delivered a male infant, had offspring with lower birth-weight percentiles, and had delivered earlier than women whose infants did not die of SIDS (Table 1).

The risk of SIDS increased with increasing second-trimester maternal serum levels of alpha-fetoprotein (Fig. 2). The incidence of SIDS was 2.7 per 10,000 births among women with alpha-fetoprotein levels in the lowest quintile and 7.5 per 10,000 births among those with levels in the highest quintile, and there was a linear trend across the quintiles (Table 2). The risk of SIDS was inversely related to the birth-weight decile and the gestational age at birth (Fig. 3). Adjusting for these factors attenuated the strength of the association between alpha-fetoprotein levels and the risk of SIDS, but a significant relationship persisted: adjusted odds ratios for the second through fifth quintiles were 1.7 (95 percent confidence interval, 0.8 to 3.5), 1.7 (95 percent confidence interval, 0.8 to 3.5), 2.2 (95 percent confidence interval, 1.1 to 4.4), and 2.2 (95 percent confidence interval, 1.1 to 4.3), respectively (P for trend=0.01). In multivariate analysis, the risk of SIDS also varied according to the sex of the infant and the mother's age, parity, and smoking status (Table 2). Further adjustment for these factors did not materially affect the association between the alpha-fetoprotein level and the risk of SIDS (Table 2).

There were no significant interactions between the maternal serum alpha-fetoprotein level and any of the maternal or obstetrical characteristics in any of the models. The goodness of fit of all the models appeared to be adequate, as assessed by global tests of goodness of fit, which showed no significant difference between the observed and expected numbers of deaths attributed to SIDS when women were categorized according to the decile of probability predicted by the multivariate model. When maternal serum alpha-fetoprotein was treated as a continuous variable in logistic-regression models, the unadjusted odds ratio for SIDS associated with an increase of 1 in the multiple of the median was 2.0 (95 percent confidence interval, 1.4 to 3.0; P<0.001). The odds ratio adjusted for birth-weight percentile and gestational age was 1.6 (95 percent confidence interval, 1.1 to 2.3; P=0.02); the odds ratio adjusted for birth-weight percentile, gestational age, and all maternal characteristics was 1.5 (95 percent confidence interval, 1.0 to 2.2; P=0.03); and the odds ratio adjusted for birth weight as a continuous variable was 1.6 (95 percent confidence interval, 1.1 to 2.3; P=0.02). When all other continuous variables were categorized and missing values treated with the use of indicator variables, the adjusted odds ratio for an increase of 1 in the multiple of the median of maternal serum alpha-fetoprotein was 1.6 (95 percent confidence interval, 1.1 to 2.3; P=0.02).

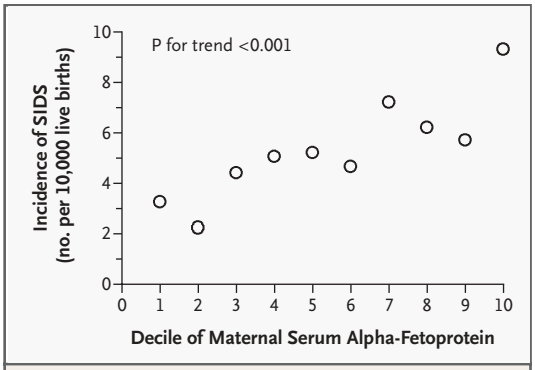

Figure 2. Incidence of SIDS, According to the Decile of Maternal Serum Alpha-Fetoprotein Level.

There was no significant association between the risk of SIDS and maternal serum levels of human chorionic gonadotropin, either expressed as a continuous variable (odds ratio for an increase of 1 in the multiple of the median for gestational age, 0.92; 95 percent confidence interval, 0.67 to 1.24; P=0.57) or categorized into quintiles (P for trend=0.19).

DISCUSSION

The present study shows that the risk of an infant's death from SIDS increased with increasing serum levels of alpha-fetoprotein in the mother during the second trimester of pregnancy. The risk of SIDS among the infants of women with alpha-fetoprotein levels in the highest quintile was 2.8 times that among infants whose mothers' levels was in the lowest quintile, although the absolute risk of SIDS remained low, even in the highest quintile (7.5 per 10,000 live births). We observed no significant association between serum levels of human chorionic gonadotropin and the risk of SIDS.

Both preterm birth and intrauterine growth re-

Table 2. Unadjusted and Adjusted Odds Ratios for SIDS in Relation to Characteristics of the Mother and Infant.*

Variable	Unadjusted Analysis		Analysis Adjusted for Characteristics of Mother and Infant†	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Mother				
Serum alpha-fetoprotein quintile				
1 (referent)	1.0		1.0	
2	1.7 (0.8–3.5)	0.13	1.7 (0.8–3.6)	0.13
3	1.8 (0.9–3.7)	0.10	1.8 (0.9–3.6)	0.12
4	2.5 (1.3–4.8)	0.009	2.2 (1.1–4.4)	0.02
5	2.8 (1.4–5.4)	0.003	2.2 (1.1–4.2)	0.02
		0.001 for trend		0.01 for trend
Age (yr)‡				
20 (referent)	1.0		1.0	
25	0.5 (0.4–0.6)	<0.001	0.5 (0.4–0.6)	<0.001
30	0.3 (0.2–0.5)	<0.001	0.3 (0.2–0.5)	<0.001
35	0.4 (0.2–0.6)	<0.001	0.3 (0.2–0.55)	<0.001
40	0.7 (0.4–1.3)	0.26	0.5 (0.2–1.1)	0.10
Height (per 10-cm increase)	0.6 (0.5–0.8)	0.001	0.8 (0.6–1.1)	0.24
Body-mass index (per 5-unit increase)	0.8 (0.6–1.0)	0.07	0.9 (0.7–1.2)	0.62
Parity (per one-birth increase)	1.4 (1.2–1.6)	<0.001	1.5 (1.3–1.7)	<0.001
Carstairs deprivation category				
1 (least deprived; referent)	1.0		1.0	
2	1.2 (0.2–5.9)	0.84	1.0 (0.2–4.8)	0.97
3	1.5 (0.3–6.7)	0.58	1.0 (0.2–4.4)	0.98
4	1.5 (0.4–6.6)	0.57	0.8 (0.2–3.7)	0.79
5	2.6 (0.6–11.1)	0.20	1.2 (0.3–5.1)	0.83
6	2.7 (0.6–11.6)	0.18	1.2 (0.3–5.2)	0.83
7 (most deprived)	6.8 (1.6–28.3)	0.008	2.2 (0.5–9.6)	0.28
Smoking status				
Never smoked (referent)	1.0		1.0	
Former smoker	1.3 (0.4–3.5)	0.67	1.1 (0.4–3.1)	0.90
Current smoker	4.9 (3.1–7.6)	<0.001	2.5 (1.5–4.1)	<0.001
Infant				
Male sex	1.6 (1.1–2.4)	0.01	1.6 (1.1–2.3)	0.02
Birth-weight percentile (per 10-percentile increase)	0.8 (0.8–0.9)	<0.001	0.9 (0.8–1.0)	0.003
Gestational age (per 1-wk increase)	0.8 (0.8–0.9)	<0.001	0.8 (0.8–0.9)	<0.001

* All data were treated as continuous except the quintile of serum alpha-fetoprotein, the Carstairs deprivation category, smoking status, and the infant's sex. CI denotes confidence interval.
† P=0.37 by the global test of goodness of fit (evaluated separately for each imputed data set and the lowest P value reported).
‡ The relationship between the mother's age (in years) and the risk of SIDS was nonlinear and was fitted with use of the following polynominals: the square of the age and the square of the age multiplied by the log of the age. Point estimates of the odds ratios and 95 percent confidence intervals (with reference to an age of 20 years) are given to illustrate the pattern of association. All other continuous variables were linear in the log odds scale.

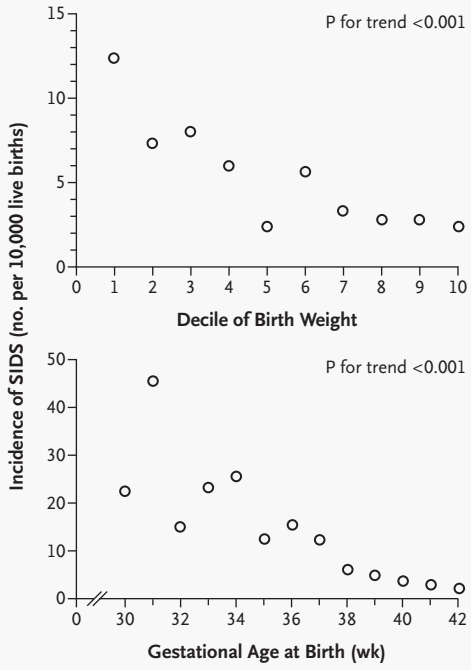

Figure 3. Incidence of SIDS According to Birth-Weight Decile (Top Panel) and Gestational Age at Birth (Bottom Panel).

In the graph shown in the bottom panel, all births at or before 30 weeks of gestation were pooled and plotted at 30 weeks because of the small number of these births.

striction are associated with an elevated maternal serum level of alpha-fetoprotein.[6] The association between the maternal serum alpha-fetoprotein level and the risk of SIDS appeared to be mediated in part by these factors. However, even after adjusting for gestational age at birth and birth-weight percentile, we found that the infants of mothers with alpha-fetoprotein levels in the upper two quintiles had a risk of SIDS that was more than twice the risk among infants of mothers with values in the lowest quintile.

Alpha-fetoprotein is the main protein contributing to oncotic pressure in the fetal circulation and is comparable to albumin in adults.[20] Elevated maternal serum levels of alpha-fetoprotein in the absence of fetal abnormality are thought to indicate increased placental permeability and therefore a defect in placental function.[6] Associations between elevated maternal serum levels of alpha-fetoprotein and both poor fetal growth and preterm birth[21] are believed to reflect the role of defective early placental function in these outcomes. Adjusting for gestational age and birth weight may thus result in an underestimation of the association between maternal serum alpha-fetoprotein levels and the risk of SIDS, since an adverse early intrauterine environment may mediate the subsequent risk of SIDS in part by its consequences on fetal growth and the timing of birth. In this study, a significant association remained after adjustment for these factors, however, suggesting that the intrauterine environment may influence the probability that a given postnatal environment will lead to SIDS. Experimental studies have shown that fetal hypoxemia induces a chemoreceptor-mediated redistribution of cardiac output, increasing flow to the cardiac and cerebral circulations.[22] Chronic, mild fetal hypoxemia leads to premature maturation of fetal cardiovascular control, manifested as a lower heart rate and a higher blood pressure early during gestation.[23] We speculate that a suboptimal intrauterine environment may lead to altered cardiorespiratory control, which could in turn predispose an infant toward SIDS, although this hypothesis requires further study.

The strengths of the present study include its large size, the availability of detailed information on the characteristics of the mothers, and the fact that all exposure data were collected independently of the ascertainment of events. Whereas previous studies have shown that the risk of SIDS varies according to both preterm birth and intrauterine growth restriction,[1] many studies have dichotomized gestational age at birth as term or preterm and have dichotomized birth weight as above or below a given percentile for gestational age. We found continuous relationships between gestational age at birth and the risk of SIDS as well as between birth-weight percentile and the risk of SIDS; this approach reduces the likelihood of residual confounding due to categorization of continuous variables. Nevertheless, some misclassification is possible. We relied on women's postal codes to classify their socioeconomic status, and for women who reported smoking, we did not have data on the number of cigarettes they smoked. However, after adjustment for gestational age and birth-weight percentile, further adjustment for characteristics of the mothers based on the available data had no material effect.

The sharp decline in the incidence of SIDS after the inception of public health programs aimed at improving infants' sleeping conditions has led to a search for factors that might explain the remaining cases. The observed association between elevated maternal serum alpha-fetoprotein levels during the second trimester and the incidence of SIDS suggests that an adverse intrauterine environment during the first half of pregnancy may be another important determinant of the risk of SIDS.

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ARTICLE

Predicting the Risk for Sudden Infant Death Syndrome From Obstetric Characteristics: A Retrospective Cohort Study of 505 011 Live Births

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ABSTRACT

OBJECTIVE. We sought to develop a simple robust method for assessing the risk for sudden infant death syndrome (SIDS) on the basis of obstetric characteristics.

METHODS. A population-based retrospective cohort study was conducted of data from the linked Scottish Morbidity Record, Stillbirth and Infant Death Enquiry and General Registrar's Office database of births and deaths, encompassing births in Scotland between 1992 and 2001. All women who had a singleton live birth between 24 and 43 weeks' gestation and for whom data were available (n = 505 011), divided into model development and validation samples, were studied. The main outcome measure was death of the infant in the first year of life as a result of SIDS.

RESULTS. The risk for SIDS was modeled in the development sample using logistic regression with the following predictors: maternal age, parity, marital status, smoking, and the birth weight and the gender of the infant. When the model was evaluated in the validation sample, the area under the receiver operating characteristic curve was 0.84 and the incidence of SIDS was 0.7 per 10 000 (95% confidence interval: 0.3–1.4) among 126 253 women in the lower 50% of predicted risk and 29.7 per 10 000 (95% confidence interval: 23.4–37.2) among the 25 250 women in the top 10% of predicted risk. A logistic-regression model then was developed for the whole population, and the output was converted into adjusted likelihood ratios. These are tabulated and provide a simple method for assessing the risk for SIDS associated with any combination of obstetric characteristics.

CONCLUSIONS. A model that uses maternal characteristics and outcome at birth is predictive of the risk for SIDS. This model is presented in a simple form that allows calculation of the individual risk for SIDS.

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Key Words
pregnancy outcome, sudden infant death, risk

Abbreviations
SIDS—sudden infant death syndrome
SMR2—Scottish Morbidity Record
GRO—General Registrar's Office
OR—odds ratio
ROC—receiver operating characteristic
CI—confidence interval

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THE FACTORS THAT determine the risk for sudden infant death syndrome (SIDS) have been the focus of studies for many years.[1] Identification of modifiable environmental exposures led to the "Back to Sleep" campaign and a dramatic fall in the incidence of SIDS. Despite this, SIDS remains the most common cause of death in infancy.[2,3] After an apparent SIDS death, there should be an analysis of all of the factors that may have contributed to the event. The procedures for this have been reviewed recently[4,5] and include detailed investigation of the scene of death and a thorough autopsy. Previous risks for SIDS are also taken into account in this process, including an assessment of whether there were any obstetric risk factors for SIDS. Many studies have addressed both prenatal and postnatal predictors of the risk for SIDS.[1] However, these analyses are presented in a manner that does not allow easy and accurate assessment of the absolute risk associated with a given combination of characteristics. Our aim was to (1) develop a valid model that relates the risk for SIDS accurately to obstetric characteristics and (2) present it in a format that is simple to understand and use.

METHODS

The study design was a retrospective cohort study of all singleton live births in Scotland who were between 24 and 43 weeks' gestation (inclusive) and documented in the Scottish Morbidity Record (SMR2) between 1992 and 2001. The outcome was death as a result of SIDS in the first year of life, ascertained through death certificate data from the General Registrar's Office (GRO).

Data Sources and Patient Selection

The SMR2 collects information on clinical and demographic characteristics and outcomes for all women who are discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been >99% complete since the late 1970s.[6] The Scottish Stillbirth and Infant Death Enquiry is a national register that routinely classifies all perinatal deaths in Scotland.[3] The GRO maintains computerized birth and death registration records. A probability-based matching approach[7] that used maternal identifiers to link the SMR2, the Scottish Stillbirth and Infant Death Enquiry, and the GRO database of birth certificates was used. The birth certificate contained offspring identifiers that then were used to link the pregnancy and perinatal death data to the death certificate register to identify deaths in infancy.

Definitions

SIDS was defined as death of an infant in whom the principal cause on the GRO death certificate was coded as 798.0 using the *International Classification of Diseases, Ninth Revision* or R95 using *International Classification of Diseases, 10th Revision*. During the period studied, a diagnosis of SIDS could be written on a death certificate in Scotland only after thorough investigation of the circumstances of the death. The minimum requirements are described by the Crown Office,[8] and an autopsy was mandatory. In practice, the investigation of these deaths was frequently much more involved.[9] A previous detailed study of deaths attributed to SIDS on Scottish death certificates between 1992 and 1995 found that standard diagnostic criteria were fulfilled in all cases.[10] Maternal age was defined as the age of the mother at the time of delivery. Smoking and marital status were defined as the status of the woman at the time of first attendance for prenatal care. Parity was defined as the total number of previous births, excluding abortions. Gestational age at birth was defined as completed weeks of gestation at the time of delivery. Gestational age has been confirmed by ultrasound scan in the first half of pregnancy in >95% of pregnancies in the United Kingdom from the early 1990s.[11]

Statistical Analysis

Univariate comparisons were performed using the Mann-Whitney U test, the χ^2 test, and the χ^2 test for trend, as appropriate. The P values for all hypothesis tests were 2-sided. Crude and adjusted odds ratios (ORs) were obtained by using logistic-regression analyses.[12] Parity, maternal age, and the infant's birth weight all were treated continuously in logistic-regression models. Treating these variables in this manner avoids loss of information as a result of categorization. We excluded cases with extremes of birth weight (<500 or >5000 g) to avoid overly influential effects of outliers. This improves the reliability of modeling of birth weight for the vast majority of the population. Because very small numbers of cases had values outside this range, estimates of probability for these extreme cases would be potentially unstable. Nonlinearity in the log odds scale was tested and modeled using fractional polynomials. Regression techniques used robust standard errors to allow for dependence of different births to the same mother using a maternal identifier. The statistical significance of interaction terms was assessed using the Wald test, and significance was assumed at $P < .01$. Observations with missing values were excluded. The population was randomly assigned to a model development and a model validation sample. Goodness of fit was assessed using the Hosmer-Lemeshow test based on deciles of probability. The discrimination of the model was assessed by the area under the receiver operating characteristic (ROC) curve. The final logistic-regression model fitted to the entire cohort was converted into adjusted likelihood ratios using a modification of our recently described method[13] (see Appendix for details). All statistical analyses were performed using the Stata 8.2 software package (Stata Corp, College Station, TX).

RESULTS

There were a total of 563 719 linked records of singleton births. Among these, there were 2955 (0.5%) stillbirths, 1043 (0.2%) births outside the range of 24 to 43 weeks' gestation, 270 (0.05%) births for which the weight was <500 g, and 1103 (0.2%) for which the weight was >5000 g. A total of 5099 (0.9%) had 1 or both of these characteristics, leaving 558 620 live-born infants who weighed between 500 and 5000 g and were delivered between 24 and 43 weeks' gestation. Among this group, there were 53 372 (9.6%) cases with missing data on smoking status, 263 (0.05%) with missing data on parity, 19 (<0.01%) with missing data on gender, and 15 (<0.01%) with missing data on maternal age. A total of 53 609 (9.6%) records had 1 or missing variables, leaving a study group of 505 011. The characteristics of the study group are tabulated in relation to whether the infant ultimately died from SIDS (Table 1). There were 317 SIDS deaths, giving an incidence of 6.3 (95% confidence interval [CI]: 5.6–7.0) per 10 000.

Univariate and multivariate logistic-regression analyses are tabulated for the model development group (n = 252 506; Table 2). There were significant associations between all of the factors studied and the risk for SIDS with the exception of being an ex-smoker. The relationships between the risk for SIDS and parity, maternal age, and birth weight were linear (in the log odds scale) in both univariate analysis and multivariate analysis. There were no statistically significant interactions between any of the variables.

The model then was used to assess the risk for SIDS in relation to the same characteristics in the validation group (n = 252 505, ie, out of sample). The area under the ROC curve was 0.84 when tested out of sample. The observed and predicted number of SIDS cases is plotted versus deciles of predicted probability (Fig 1). There were 9 SIDS deaths among the 126 253 women in the lower half of predicted risk, an incidence of 0.7 cases per 10 000 (95% CI: 0.3–1.4). There were 75 SIDS events among the 25 245 women in the top decile of predicted risk, an incidence of 29.7 cases per 10 000 (95% CI: 23.4–37.2). The model then was fitted for the whole population of 505 011. The area under the ROC curve for the model was 0.81 and the goodness of fit was adequate (P = .49). The fitted model then was converted into adjusted likelihood ratios (Table 3). The calculation of the risk for SIDS associated with any combination of characteristics is illustrated in Fig 2. Overall, 12 387 (2.4%) cases had a summary likelihood ratio >5. There were 55 SIDS cases among this group, giving an incidence of 44.4 per 10 000 (95% CI: 33.5–57.8).

Because >99% of missing data were on smoking

TABLE 1 **Comparison of Maternal, Demographic, and Obstetric Characteristics by Occurrence of SIDS (n = 505 011)**

	SIDS (n = 317)	Non-SIDS (n = 504 694)	P[a]
Maternal characteristics			
Maternal age, y	24 (20–28)	28 (24–32)	<.001
Parity			
Nulliparous	115 (36.3)	226 261 (44.8)	
1	100 (31.6)	176 603 (35.0)	
2	68 (21.5)	69 398 (13.8)	<.001
3	20 (6.3)	21 874 (4.3)	
4	10 (3.2)	6817 (1.4)	
>4	4 (1.3)	3741 (0.7)	
Smoking status			
Nonsmoker	73 (23.0)	305 663 (60.6)	
Smoker	230 (72.6)	155 535 (30.8)	<.001
Ex-smoker	14 (4.4)	43 496 (8.6)	
Marital status			
Other	221 (69.7)	195 444 (38.7)	
Married	96 (30.2)	309 250 (61.3)	<.001
Outcome			
Gender			
Female	125 (39.4)	246 419 (48.8)	
Male	192 (60.6)	258 275 (51.2)	.001
Gestational age	39 (38–40)	40 (39–41)	<.001
Preterm birth			
24–32	12 (3.8)	5098 (1.0)	
33–36	34 (10.7)	22 576 (4.5)	<.001
Term	271 (85.5)	477 020 (94.5)	
Birth weight, g	3030 (2625–3380)	3410 (3060–3745)	<.001

Data are expressed as n (%) or median (interquartile range), as appropriate.

[a] P value is from the Mann Whitney U test, the χ^2 test, or the χ^2 test for trend, as appropriate.

TABLE 2 **Unadjusted and Adjusted OR for Risk for SIDS in Relation to Obstetric Characteristics Among Model Development Group ($n = 252\,506$)**

Variables	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)[a]	*P*
Maternal characteristics				
Age (per 5-y increase)	0.59 (0.50–0.69)	<.001	0.65 (0.53–0.79)	<.001
Parity (per birth)	1.18 (1.06–1.33)	.004	1.39 (1.23–1.58)	<.001
Married	0.28 (0.20–0.38)	<.001	0.54 (0.38–0.78)	.001
Ex-smoker	1.52 (0.77–3.02)	.23	1.19 (0.60–2.39)	.62
Smoker	4.90 (3.48–6.90)	<.001	2.49 (1.73–3.60)	<.001
Pregnancy outcome				
Male	1.44 (1.06–1.96)	.02	1.53 (1.13–2.07)	.007
Birth weight (per 500-g increase)	0.65 (0.59–0.72)	<.001	0.72 (0.64–0.81)	<.001

All data were treated as continuous variables except for smoking, marital status, and gender. The referent categories for the 3 categorical variables were nonsmokers, unmarried women, and female infants, respectively.

[a] Global test of goodness of fit (within sample): $P = .48$.

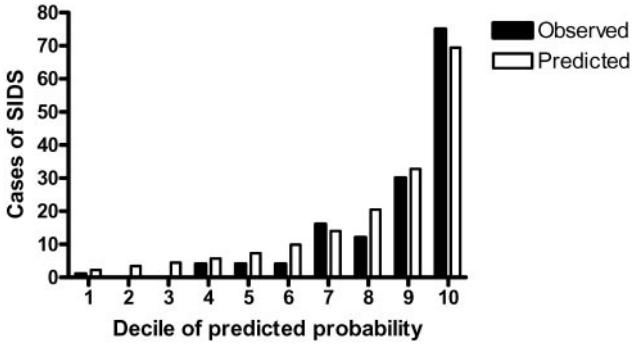

FIGURE 1
Observed and expected number of cases of SIDS in validation sample ($n = 252\,505$) in relation to deciles of predicted probability from the model generated from the development sample ($n = 252\,506$). Distribution of cases comparing observed and expected (Hosmer-Lemeshow test of goodness of fit): $P = .05$.

status, we fitted a model for the 53 372 women with missing data on this characteristic. The constant and coefficients were very similar to the other women (data not shown).

DISCUSSION

The investigation of a sudden infant death requires a detailed analysis of all of the factors that may have contributed to the event, and the procedures for this have been reviewed recently.[4,5] This includes detailed investigation of the scene of death and thorough postmortem investigations. It is recognized, however, that a number of characteristics of the pregnancy contribute to the risk for SIDS.[1] It is self-evident that a thorough examination of the likely cause of death involves an assessment of the previous risk relating to the outcome of the pregnancy. Many previous studies have developed statistical models to characterize obstetric predictors of SIDS. However, none of these is presented in a way that allows the simple and intuitive assessment of the absolute risk for this event associated with a given combination of birth characteristics. The aim of the present study was to develop a method that was valid, had discriminative power, and was simple to use.

We developed a logistic-regression model and related the risk for SIDS to marital and smoking status, maternal age and parity, and the birth weight and the gender of the infant. Birth weight is a reflection of both fetal growth and gestational age at birth. We previously demonstrated log linear relationships between the risk for SIDS and both week of gestation of birth and birth weight percentile.[14] In the present study, we used birth weight. Performance of the model was virtually identical to a model using week of gestation at birth and birth weight percentile (data not shown). Birth weight has the advantage of being less dependent on definition than gestational age and is more likely to be known than the exact birth weight percentile. We assessed the calibration and discrimination of the model in the validation sample. This demonstrated that the model fit the out-of-sample data well and had good discriminative power. A previous study had performed out-of-sample validation of 4 risk scoring systems for SIDS and found sensitivities of 41%, 53%, 62%, and 71% when the top 20% of predicted risk were classified as high risk; the best performing model included 17 predictors.[15] In our own study using a model that had just 6 predictors, 72% of cases in the validation sample were in the top 20% of predicted risk.

A number of studies have shown that women with a previous SIDS event have an approximately fivefold risk for recurrence compared with the general population.[16–19] In the United Kingdom, these women are offered a structured scheme for the care of the next infant, which involves symptom diaries, apnea monitors, scales, and weekly home visits by the family health visitor.[20] Logically, the 2.4% of women with a summary likelihood ratio of ≥5 on the basis of the model might be offered a similar intervention, although this would require additional evaluation of efficacy and economic justification. However, application of this model assumes

TABLE 3 **Adjusted Likelihood Ratios for Maternal and Obstetric Characteristics and the Risk for SIDS**

Characteristic	Adjusted Likelihood Ratios
Age, y	
15	2.84
16	2.60
17	2.38
18	2.18
19	1.99
20	1.83
21	1.67
22	1.53
23	1.40
24	1.28
25	1.18
26	1.08
27	0.99
28	0.90
29	0.83
30	0.76
31	0.69
32	0.63
33	0.58
34	0.53
35	0.49
36	0.45
37	0.41
38	0.37
39	0.34
40	0.31
41	0.29
42	0.26
43	0.24
44	0.22
45	0.20
Birth weight, g	
500	7.73
550	7.44
600	7.17
650	6.90
700	6.64
750	6.40
800	6.16
850	5.93
900	5.71
950	5.50
1000	5.29
1050	5.10
1100	4.91
1150	4.73
1200	4.55
1250	4.38
1300	4.22
1350	4.06
1400	3.91
1450	3.77
1500	3.63
1550	3.49
1600	3.36
1650	3.24
1700	3.12
1750	3.00
1800	2.89
1850	2.78
1900	2.68
1950	2.58
2000	2.48
2050	2.39
2100	2.30
2150	2.22
2200	2.13
2250	2.05
2300	1.98
2350	1.90
2400	1.83
2450	1.77
2500	1.70
2550	1.64
2600	1.58
2650	1.52
2700	1.46
2750	1.41
2800	1.35
2850	1.30
2900	1.26
2950	1.21
3000	1.16
3050	1.12
3100	1.08
3150	1.04
3200	1.00
3250	0.96
3300	0.93
3350	0.89
3400	0.86
3450	0.83
3500	0.80
3550	0.77
3600	0.74
3650	0.71
3700	0.69
3750	0.66
3800	0.64
3850	0.61
3900	0.59
3950	0.57
4000	0.55
4050	0.53
4100	0.51
4150	0.49
4200	0.47
4250	0.45
4300	0.44
4350	0.42
4400	0.40
4450	0.39
4500	0.37
Smoking status	
Nonsmoker	0.52
Smoker	1.59
Marital status	
Unmarried	1.23
Married	0.71
Parity	
0	0.73
1	1.06

TABLE 3 **Continued**

Characteristic	Adjusted Likelihood Ratios
2	1.54
3	2.23
4	3.23
5	4.69
Gender	
Female	0.78
Male	1.23

The logistic-regression equation was as follows: log odds = −3.583 + age(−0.440) + parity(0.372) + birth weight (−0.379) + male(0.454) + married(−0.551) + smoker(1.116), where male, married, and smoker are indicator variables = 1 if true or 0 if other and all continuous variables are expressed as the same units listed in Table 2.

Consider a mother who is unmarried (LR = 1.23), 20 years old (LR = 1.83), parity 1 (LR = 1.06), who smoked during pregnancy (LR = 1.59), delivering a male infant (LR = 1.23) weighing 2600g (1.58).

Summary likelihood ratio = 1.23 x 1.83 x 1.06 x 1.59 x 1.23 x 1.58 = 7.37

Pre-test odds = 317/504,694 = 0.000628

Post-test odds = 0.000628 x 7.37 = 0.0046

Risk of SIDS approximately 1 in 200 (1/0.0046)

Note: for more common outcomes, the post-test odds would have to be converted back to a post-test probability = odds/odds+1.

FIGURE 2
Sample calculation using adjusted likelihood ratios.

that the relationships between the variables studied and the risk for SIDS are similar in other populations.

The absolute risk for an outcome associated with a given combination of characteristics can be estimated from a logistic-regression equation using the constant and the coefficients. The constant reflects the baseline risk, and the sum of the coefficients reflects the modification of the baseline risk associated with the given combination of characteristics. However, typically, medical publications do not report the constant; therefore, this calculation cannot be performed. Moreover, even if provided with the constant and the coefficients, only a tiny minority of doctors would have the knowledge to perform this calculation. We sought to simplify estimation of the absolute risk from a logistic-regression model by expressing the output as adjusted likelihood ratios rather than as ORs. In fact, a likelihood ratio is merely a special type of OR. Taking the example of expressing the risk for a given outcome among male individuals, the OR associated with being male is the odds of the disease in male individuals divided by the odds of the disease among female individuals. The likelihood ratio associated with being male is the odds of the disease in male individuals divided by the odds of the disease in the whole population. Therefore, the OR expresses the risk relative to another category of the given characteristic (eg, male relative to female), whereas the likelihood ratio expresses the risk relative to the whole population. Using the example of gender, 2 likelihood ratios are generated: 1 expresses the risk for male individuals, and 1 expresses the risk for female individuals.

Estimating the absolute risk of a given event associated with any combination of characteristics is relatively simple using adjusted likelihood ratios (see Fig 2). The prior risk of disease is the odds in the population. The risk associated with any combination of variables is calculated by multiplying the prior risk by the appropriate likelihood ratios (Table 3). Therefore, estimating the absolute risk requires relatively little statistical expertise. Because the output of the model is in the form of an individual estimated probability, our approach avoids the loss of information involved in dichotomizing infants as "high" or "low" risk on the basis of an arbitrary threshold on an abstract numerical scale. Informing parents that their infant is at high risk of SIDS may cause unjustified anxiety, because the risk may be small in absolute terms. The likelihood ratio based approach has the key advantage that the output of the model is expressed in terms of the absolute risk associated with the given individual's combination of characteristics.

Expressing logistic-regression models in the form of adjusted likelihood ratios has several other advantages. First, if a predictor variable is unknown, then it may simply be ignored: omitting a variable in a likelihood ratio–based model makes the plausible assumption that the individual has the background risk for the population in relation to the given characteristic. Second, the use of adjusted likelihood ratios removes the need to select a reference category. In contrast, in logistic-regression analysis, a category of risk has to be regarded as referent. By choosing an extreme category as referent, ORs for all of the other categories will tend to be farther from unity. Therefore, the OR for a given characteristic may reflect the deviation in risk from the rest of the population in the referent category as well as the category in question. In contrast, by expressing the output of logistic-regression models as likelihood ratios, the odds of disease associated with any given feature are expressed relative to the odds in the whole population. Finally, because the model uses the previous odds as the starting point, there is the potential for using the adjusted likelihood ratios in other populations in which the incidence of the disease is higher or lower and accounting for this by using the local incidence to estimate the previous odds. This should be done carefully, however, as it assumes that variation in the incidence between populations does not depend on variation in the prevalence of the risk factors included in the model.

Other multivariate methods can be used to generate adjusted likelihood ratios, such as distribution modeling, which is used widely in Down syndrome screening.[21] However, these methods do not directly incorporate binary variables, such as gender. Moreover, logistic-re-

gression modeling is much more widely used in the analysis of risk, and many model-building tools have been developed for this method. A previous attempt was made to express logistic regression in the form of likelihood ratios.[22] However, the previous method of calculation does not agree with the multivariate logistic-regression output if the model contains categorical variables with >2 levels or if the transformation of a continuous variable changed between the univariate and the multivariate model.

CONCLUSIONS

We present a novel method for estimating the risk for SIDS in relation to a given combination of maternal and obstetric characteristics. This is simple to use and gives arithmetically identical results to much more complex statistical models.

APPENDIX: ESTIMATING LIKELIHOOD RATIOS

The logistic-regression model is $\log(\text{odds}) = a + b_1x_1 + b_2x_2 + \ldots + b_nx_n$. The adjusted likelihood ratios are calculated as multiples of $\exp(b_1x_1)$, $\exp(b_2x_2)$, etc, in 2 stages.

In the first stage, we fit the above model with the term b_1x_1 replaced with an unknown constant d_1 and with all other terms (including the constant) fixed at their previous estimated values. The estimated value of d_1 captures the risk before x_1 is known, so the likelihood ratio is $\exp(b_1x_1 - d_1)$. This is repeated for each term $b_2x_2, \ldots, b_nx_n$, and the constant is replaced by $a' = (a + d_1 + d_2 + \ldots + d_n)$.

Because of the nonlinearity of the log odds function, a′ may not exactly equal the overall log odds of the outcome, a_0, if the x variables are correlated. In the second stage, we therefore compute a correction factor $c_j(a_0 - a')$, where $c_1 + \ldots + c_n = 1$, and we report likelihood ratios $\exp[b_jx_j - d_j + c_j(a_0 - a')]$. In this article, c_j is calculated as $m_j/(m_1 + \ldots + m_n)$, where m_j is the sample minimum or maximum (depending on whether $a_0 - a'$ is positive or negative) of $b_jx_j - d_j$: this procedure ensures that the range of adjusted likelihood ratios spans 1.

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ORIGINAL ARTICLE

Neonatal respiratory morbidity at term and the risk of childhood asthma

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Objective: To determine whether neonatal respiratory morbidity at term is associated with an increased risk of later asthma and whether this may explain previously described associations between caesarean delivery and asthma.
Design: Retrospective cohort study using Scottish Morbidity Record (SMR) data of maternity (SMR02), neonatal (SMR11), and acute hospital (SMR01) discharges.
Setting: Scotland.
Participants: All singleton births at term between 1992–1995 in 23 Scottish maternity hospitals.
Main outcome measures: Hospital admission with a diagnosis of asthma in the principal position between 1992 and 2000.
Results: Children who had a diagnosis of transient tachypnoea of the newborn or respiratory distress syndrome were at increased risk of being admitted to hospital with a diagnosis of asthma (hazard ratio (HR) 1.7, 95% confidence interval (95% CI) 1.4 to 2.2, $p<0.001$). This association was observed both among children delivered vaginally (HR 1.5, 95% CI 1.1 to 2.0, $p=0.007$) and among those delivered by caesarean section (HR 2.2, 95% CI 1.6 to 3.0, $p<0.001$). In the absence of neonatal respiratory morbidity, delivery by caesarean section was weakly associated with the risk of asthma in childhood (HR 1.1, 95% CI 1.0 to 1.2, $p=0.004$). The strengths of the associations were similar whether the caesarean delivery was planned or emergency and were not significantly altered by adjustment for maternal, obstetric, and other neonatal characteristics.
Conclusions: Neonatal respiratory morbidity at term is associated with an increased risk of asthma in childhood which may explain previously described associations between caesarean delivery and later asthma.

Recent studies have demonstrated that children delivered by caesarean section have an increased risk of hospital admission for asthma in childhood.[1 2] It has been hypothesised that this may be explained by effects of mode of delivery on the gut and susceptibility to atopy. However, caesarean delivery is a well recognised cause of neonatal respiratory morbidity at term, specifically, transient tachypnoea of the newborn and respiratory distress syndrome.[3 4] A number of previous studies have demonstrated that neonatal respiratory morbidity secondary to preterm delivery is associated with an increased risk of later asthma.[5–8] However, there are no studies, to our knowledge, which have examined the risk of later asthma in relation to neonatal respiratory morbidity confined to term births. The aims of the present study were to determine whether neonatal respiratory morbidity at term was associated with an increased risk of later asthma and to determine whether any observed association varied in relation to mode of delivery.

METHODS

Patient selection

The Scottish Morbidity Record 2 (SMR02) collects information on clinical and demographic characteristics and outcomes for all women discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been greater than 99% complete since the late 1970s.[9] Data were extracted on all singleton liveborn infants delivered between 37 and 43 weeks gestation inclusive in Scotland between 1992 and 1995 (inclusive). SMR02 records were linked to the SMR11 (1992–1995) database, which collects discharge data on all neonates delivered in Scottish hospitals, and to the SMR01, which collects discharge data on all acute hospital admissions in Scotland. SMR01 admissions were analysed from 1st January 1992 to 31st December 2000, providing between 5 and 9 years of follow up on the cohort. All linkages were performed using a probability based matching approach which has been described in detail elsewhere.[10] Therefore, the final linked file contained demographic, obstetric, and neonatal characteristics and dates of hospital admission of the child. Ethical approval for the linkage was obtained from the Privacy Advisory Committee of the Information and Statistics Division of the National Health Service in Scotland. The data sources employed are given in table 1.

Exclusion criteria

Multiple pregnancies, stillbirths, births outside the range 37–43 weeks gestation, births in hospitals that performed less than 100 planned caesarean deliveries over the study period, and vaginal breech births were all excluded. Records were also excluded where there were missing values for any of the covariates.

Obstetric definitions

Gestational age at birth was defined as completed weeks of gestation on the basis of the estimated date of delivery in each woman's clinical record. Gestational age has been confirmed by ultrasound scan in the first half of pregnancy in more than 95% of pregnancies in the UK since the early

Abbreviations: HR, hazard ratio; ICD, International Classification of Disease; IQR, inter-quartile range; RDS, respiratory distress syndrome; SMR, Scottish Morbidity Record; TTN, transient tachypnoea of the newborn

Table 1 Data sources

Database	Data type	Years*	Data extracted
SMR02	Maternal hospital discharge	1992–1995	Obstetric, maternal (including ICD9 diagnoses), and neonatal characteristics
SMR11	Neonatal discharge	1992–1995	Neonatal diagnoses (ICD9)
GRO	Death certificate	1992–2000	Deaths
SMR01	General and paediatric hospital discharge	1992–2000	Hospital discharges with diagnosis of asthma (ICD9 and ICD10)

GRO, General Registrar's Office; ICD, International Classification of Disease; SMR, Scottish Morbidity Record.
*All dates are inclusive.

1990s[11] and standard national criteria exist for the estimation of date of delivery using menstrual and ultrasound data.[12] Smoking was defined as the smoking status of the woman at the time of first attendance for antenatal care. Maternal age was defined as the age of the mother at the time of delivery. Postcode of residence was used to derive Carstairs socio-economic deprivation categories.[13] These are based on 1991 Census data on car ownership, unemployment, overcrowding, and social class within postcode sectors of residence which contain, on average, around 1600 residents. Emergency caesarean section was defined as any non-planned caesarean delivery. Mothers with asthma were diagnosed by ICD9 diagnostic code 493 in any position.

Paediatric definitions

Neonatal respiratory morbidity was documented in the SMR11 record using ICD9 diagnostic codes. Neonatal respiratory morbidity was defined as respiratory distress syndrome (769.9) or transient tachypnoea of the newborn (770.6) in any position. Infants who had neither of these diagnoses formed the reference category. Infants with other perinatal respiratory diagnoses were excluded (770.2–770.5 and 770.7–770.9) since these diagnoses were either rare or non-specific and therefore difficult to analyse and interpret. Infants with aspiration documented were also excluded (770.1). Hospital admissions in childhood for asthma were classified by ICD9 or ICD10 codes from the SMR01 registry and admission for asthma was defined as 493 (ICD9) or J45–J46 (ICD10) in the principal position. We also obtained data on hospital discharge for a condition which should be independent of mode of delivery in order to detect bias towards hospital admission in relation to mode of delivery due to selective migration. The outcome studied was fracture of an upper limb long bone, defined as 812–813 (ICD9) or S422–S424, S52 (ICD10) in the principal position.

Statistical analyses

Continuous variables were summarised by the median and inter-quartile range (IQR) and comparisons between groups were performed using the Mann-Whitney U test. Univariate comparisons of categorical data were performed using the χ^2 test. The p values for all hypothesis tests were two sided and statistical significance was assumed at $p<0.05$. The risk of asthma and fractured long bone was assessed using a proportional hazards model of the time to first hospital admission. All categorical covariates were modelled by dummy variables. Birth weight was converted to a z score relative to the mean birth weight for the week of gestation of delivery and sex. The proportional hazards assumption was tested using the test of Grambsch and Therneau.[14] If the proportional hazards assumption was violated by a covariate, multivariate analysis was stratified by categories of the given factor. Otherwise, all numerical variables (gestational age, maternal age, height, and normalised birth weight) were treated as continuous in the statistical models. Assessment of linearity in the log hazard scale and selection of polynomials was performed using fractional polynomials.[15] All models employed robust standard errors and the analysis clustered on a maternal identifier to allow for dependence within siblings. The statistical significance of interaction terms was assessed using the Wald test (accounting for clustering) and statistical significance of interactions was assumed at $p<0.01$. The goodness of fit of models was assessed using the May and Hosmer test.[16] All statistical analyses were performed using the Stata software package (Stata, TX, USA), version 8.2.

RESULTS

There were records for 241 846 singleton live births in Scotland over the period 1992–1995. We excluded 27 604 (11.4%) records where the hospital of delivery performed less than 100 planned caesarean deliveries or the gestational age was outside the range 37–43 weeks. Among the remaining 214 242 births, there were missing values for maternal height in 16 572 (7.7%), for smoking in 21 880 (10.2%), for sex in four (<0.1%), for deprivation category in 727 (0.3%), for birth weight in 38 (<0.1%), for mode of delivery in 66 (<0.1%), for parity in 151 (0.1%), induced labour in 13 (<0.1%), and neonatal respiratory diagnosis in 2929 (1.4%). In total 37 454 records (17.5%) had one or more of these missing values. Of the remaining 176 788 records, there was a perinatal respiratory diagnosis other than transient tachypnoea or respiratory distress syndrome in 3050 (1.7%) and 615 (0.3%) were vaginal breech births. There was overlap between these categories and the final study group was 173 319.

The demographic, obstetric, and neonatal characteristics of the study group are tabulated by neonatal respiratory morbidity (table 2). With the exceptions of deprivation category and whether labour was induced, all the characteristics of the group varied according to neonatal respiratory morbidity. Infants who experienced neonatal respiratory morbidity were at increased risk of hospital admission with a diagnosis of asthma in later childhood (fig 1). A test for interaction between caesarean delivery and neonatal respiratory morbidity demonstrated a trend for a stronger association between neonatal respiratory morbidity among babies delivered by caesarean section: the hazard ratio (HR) for the interaction was 1.4 (95% confidence interval (CI) 0.9 to 2.2, $p = 0.1$). Further analysis was performed following separation into those delivered vaginally and those delivered by caesarean section.

The crude number of events, years of follow up, and expected number of admissions are given in table 3. Among those delivered by caesarean section, the association between neonatal respiratory morbidity and later asthma did not significantly differ according to whether the procedure was planned or emergency ($p = 0.9$). The associations were minimally affected by adjusting for maternal, other obstetric, and neonatal characteristics (table 3). There were no significant interactions between mode of delivery or neonatal respiratory morbidity and any of these other factors in the multivariate model.

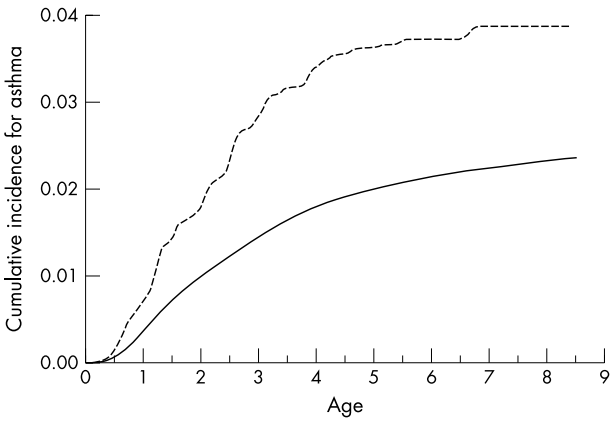

Figure 1 Cumulative incidence of hospital admission for asthma over the first 8–9 years of life for children born at term with neonatal respiratory morbidity (broken line, defined as respiratory distress syndrome or transient tachypnoea of the newborn) and those with no neonatal respiratory morbidity (solid line). Comparison of curves (log rank test): $p<0.001$. HR for neonatal respiratory morbidity = 1.7, 95% CI 1.4 to 2.2.

Including the 3050 cases with a non-infective perinatal respiratory diagnosis other than transient tachypnoea or respiratory distress syndrome had virtually no effect on the HRs in table 3. We examined the risk of hospital admission for fractured long bone after 3 months of age to test for bias in hospital admission in relation to mode of delivery or neonatal morbidity, for example due to selective migration. There were 2218 hospital admissions with a fractured upper limb long bone. There was no statistically significant association between admission for long bone fracture and neonatal respiratory morbidity (adjusted HR 0.8, 95% CI 0.5 to 1.2, $p = 0.2$).

DISCUSSION

This is the first study to our knowledge to examine the risk of later asthma among children who experience neonatal respiratory morbidity confined to births at term. The main finding of this paper is that neonates who experience respiratory distress syndrome or transient tachypnoea of the newborn at term are at increased risk of asthma in childhood. The relationship was unaltered by adjusting for hospital of birth, maternal age, height, deprivation category, parity and smoking, induction of labour, week of gestation of delivery, and the child's birth weight, sex, and Apgar score. The association is plausible since previous studies have shown increased risks of later asthma associated with neonatal respiratory morbidity secondary to preterm delivery.[5–8]

It is possible that the association between neonatal respiratory morbidity is explained by some unmeasured confounder. For instance, it has been shown that the offspring of asthmatic women are more likely to experience neonatal respiratory morbidity in neonatal life.[17] However, we found no effect of adjusting for a maternal diagnosis of asthma. Moreover, caesarean section is a well recognised cause of neonatal respiratory morbidity[3 4] and in our own study we estimated that two thirds of neonatal respiratory morbidity in the caesarean delivery group could be attributed to the mode of delivery. If the relationship between neonatal respiratory morbidity and later asthma was due to the effect of an unmeasured confounder, we would have anticipated a weaker association between neonatal respiratory morbidity and asthma in the caesarean delivery group, since most neonatal respiratory morbidity was determined by the mode of delivery. However, the interaction term between neonatal respiratory morbidity and caesarean delivery was 1.4 and had confidence intervals of 0.9 to 2.2. This indicates that the relationship between neonatal respiratory morbidity and later asthma is at least as strong in the caesarean delivery group

Table 2 Demographic, obstetric, and neonatal characteristics of cohort by neonatal respiratory morbidity

			No RDS/TTN, n = 170 909	RDS/TTN, n = 2230	p*
Maternal characteristics	Age (years)	Median (IQR)	28 (24–31)	28 (24–31)	0.007†
	Parity	Nulliparous	75 960 (44.4)	1066 (47.8)	0.002
		Multiparous	94 949 (55.6)	1164 (52.2)	
	Deprivation category, n (%)	1 (least deprived)	9113 (5.3)	112 (5.0)	0.47
		2	22 797 (13.3)	280 (12.6)	
		3	34 091 (10.0)	456 (20.5)	
		4	41 606 (24.3)	547 (24.5)	
		5	27 895 (16.3)	382 (17.1)	
		6	21 685 (12.7)	258 (11.6)	
		7 (most deprived)	13 722 (8.0)	195 (8.7)	
	Height (cm)	Median (IQR)	162 (157–166)	162 (157–166)	<0.001†
	Smoking	Non-smoker	103 259 (60.4)	1421 (63.7)	0.001
	Status, n (%)	Ex-smoker	14 140 (8.3)	192 (8.6)	
		Smoker	53 510 (31.3)	617 (27.7)	
	Maternal asthma		385 (0.2)	9 (0.4)	0.08
Obstetric characteristics	Mode of delivery, n (%)	Vaginal birth	146 404 (85.7)	1366 (61.3)	<0.001
		Emergency caesarean	14 718 (8.6)	411 (18.4)	<0.001
		Elective caesarean	9787 (5.7)	453 (20.3)	<0.001
	Gestational age at delivery (weeks)	Median (IQR)	40 (39–41)	40 (38–41)	<0.001
	Onset of labour, n (%)	Spontaneous	129 064 (75.5)	1686 (75.6)	0.92
		Induced	41 845 (24.5)	544 (24.4)	
Neonatal characteristics	Sex, n (%)	Female	84 536 (49.5)	757 (34.0)	<0.001
		Male	86 373 (50.5)	1473 (66.1)	
	Birth weight (g)	Median (IQR)	3440 (3120–3760)	3489 (3100–3860)	<0.001
	5 min	<7	2340 (1.4)	114 (5.1)	<0.001
	Apgar, n (%)	7–10	168 569 (98.6)	2116 (94.9)	

*χ^2 test or Mann-Whitney U test, as appropriate.
†Although the medians and IQR do not differ, the groups were different due to less than 1 unit differences in these variables between the two groups.
IQR, inter-quartile range; RDS, respiratory distress syndrome; TTN, transient tachypnoea of the newborn.

Table 3 Number of events, follow up, and incidence of first hospital admission for asthma in relation to mode of delivery and neonatal respiratory morbidity

	Mode of delivery and neonatal characteristics	n	Number of asthma admissions	Total years of follow up	Expected asthma admissions	Crude HR (95% CI)	p	†Adjusted HR (95% CI)	p
Vaginal birth	No TTN/RDS*	146 404	3171	1 002 961	3264	(1.0)		(1.0)	
	With TTN/RDS	1366	44	9218	30	1.5 (1.1 to 2.0)	0.007	1.4 (1.0 to 1.8)	0.04
All caesarean sections	No TTN/RDS	24 505	601	166 397	544	1.1 (1.0 to 1.2)	0.004	1.1 (1.0 to 1.2)	0.006
	With TTN/RDS	864	40	5767	19	2.2 (1.6 to 3.0)	<0.001	2.2 (1.6 to 3.0)	<0.001
Emergency caesarean section	No TTN/RDS*	14718	357	99 848	326	1.1 (1.0 to 1.3)	0.034	1.1 (1.0 to 1.3)	0.04
	With TTN/RDS	411	18	2775	9	2.1 (1.3 to 3.3)	0.002	2.2 (1.4 to 3.6)	0.001
Elective caesarean section	No TTN/RDS	9787	244	66 549	217	1.2 (1.0 to 1.3)	0.031	1.1 (1.0 to 1.3)	0.06
	With TTN/RDS	453	22	2992	10	2.3 (1.5 to 3.5)	<0.001	2.2 (1.4 to 3.4)	<0.001

*Reference category.
†Hazards were non-proportional for hospital, maternal age, birth weight for gestation, parity, and smoking. Therefore, multivariate analysis was stratified by these variables and adjusted for induction, maternal height, week of gestation, male sex, Apgar, deprivation category, and maternal asthma. Goodness of fit: p = 0.4.
RDS, denotes respiratory distress syndrome; TTN, transient tachypnoea of the newborn.

and, indeed, there was a trend towards a stronger association among women delivered by caesarean section than those delivered vaginally.

Previous studies had demonstrated increased risks of asthma among children delivered by caesarean section.[1 2] However, these studies lacked data on neonatal complications and hypothesised that the relationship may be explained by effects of caesarean section on intestinal microbial flora leading to susceptibility to atopic conditions. Both studies described relatively weak associations with odds ratios for asthma among children delivered by caesarean section of 1.2 to 1.4. Our data suggest that the association between caesarean delivery and later asthma may be mediated by neonatal respiratory morbidity. This would explain why the overall association between caesarean birth and asthma is weak since the majority of infants delivered by caesarean section do not experience neonatal respiratory morbidity. Serial population prevalence studies have suggested that rates of wheezing disorders in children are increasing.[18] Given that this has occurred over a period where caesarean delivery rates have increased, further research is required to determine the possible contribution of increasing rates of caesarean delivery to the increased prevalence of childhood wheezing.

The strengths of the present study are the scale and the fact that exposure data were collected prospectively and independently of outcome data. As with other large scale registry based studies, however, the amount of information on each individual case was relatively limited. We lacked data on breast feeding. However, recent large scale longitudinal studies have cast doubt on the protective effect of breastfeeding on asthma risk[19] and studies which have shown an increased risk of asthma among bottle fed infants describe a relative risk of asthma in the region of 1.4[20] which could clearly not cause a relative risk of 2.2 by confounding. It is likely that the indication for caesarean section may lead to systematic differences in treatment in neonatal life compared with infants delivered vaginally. It is theoretically possible, for example, that the association with later asthma might be explained by a confounding effect of early antibiotic treatment. However, the incidence of suspected or proven sepsis among infants delivered by emergency caesarean section is 14% compared with 2% among infants delivered by planned caesarean section.[21] Since we saw virtually identical relationships between planned and emergency caesarean section and later asthma, the association is unlikely to be explained by confounding effects of either the indication for caesarean delivery or post-natal treatment of the child.

The outcome measured was hospital admission for asthma which will necessarily involve the severe end of the disease spectrum. Further studies should address the relationship between neonatal respiratory morbidity and asthma managed in the community. The follow up period in our study was limited to childhood. Recent studies have reported a greater than threefold risk of asthma in adulthood and caesarean delivery.[22] The possible role of neonatal respiratory morbidity in the aetiology of adult asthma remains to be determined.

CONTRIBUTORS

GS had the original idea and formulated the hypothesis. RD performed the record linkage and prepared the data for analysis. AW and IW performed the statistical analysis. GS, JP, AW, and IW interpreted the results. GS drafted the manuscript and all authors edited and approved the final version.

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Conflict of interest: none declared.

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Section 6. Obstetric outcome and the risk of subsequent maternal disease

Smith GCS, Wood A, Pell JP, Dobbie R. First cesarean birth and subsequent fertility. Fertil Steril 2006;85:90-95.

Smith GCS, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001;357: 2002–06.

Distribution of asthma and lung function in participants aged 42 according to severity of asthma at age 7 or 10

	No (%) at age 42					Lung function at age 42		
Symptoms age 7	No recent asthma (n=199)	Infrequent asthma (n=58)	Frequent asthma (n=76)	Persistent asthma (n=70)	Total (n=403)	No measured (n=267)	FEV_1/FVC (95% CI)	Mean % of predicted FEV_1 (95% CI)
Mild wheezy bronchitis	40 (66)	12 (20)	9 (15)	0	61	40	80 (79 to 82)	109 (103 to 114)
Wheezy bronchitis	50 (57)	13 (15)	16 (18)	9 (10)	88	62	79 (76 to 81)	102 (98 to 106)
Asthma	28 (29)	19 (19)	27 (28)	24 (24)	98	70	75* (73 to 77)	95* (92 to 99)
Severe asthma	8 (11)	9 (13)	20 (29)	33 (47)	70	42	70* (67 to 74)	85* (78 to 91)
Control	73 (85)	5 (6)	4 (5)	4 (5)	86	53	80 (78 to 82)	104 (101 to 108)

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.
*P<0.001 compared with controls.

Fifteen of the original cohort had died at follow up, one from asthma. Of the remaining 464, 403 participated in the current review, giving a continuing participation rate of 87%. In all, 267 participants attended the laboratory for measurement of lung function. We calculated mean values of lung function using standard two sample *t* tests and confidence intervals of the mean by standard methods.

The table shows the clinical expression of asthma at age 42 according to severity of disease at recruitment. The distribution of severity at age 42 has not changed from that at age 35.[5] The proportion of cases with no recent asthma has increased steadily from 20% at age 14 years to 40% (126/317) at age 42.

Lung function was similar to that of controls in participants who had had wheezy bronchitis in childhood (table). Participants who had had asthma aged 7 had reduced lung function at age 42.

Comment

Our study shows that the pattern of asthma during childhood predicts outcome. Most children with persistent asthma had continuing symptoms into adult life and reduced lung function. However, children who had intermittent symptoms associated with respiratory tract infections generally had complete resolution of symptoms in adult life. The small number of participants who still had mild, intermittent symptoms at age 42 had normal lung function. This good outcome was achieved despite the fact that anti-inflammatory treatments were not available for most of their childhood.

Contributors: CFR, AO, and JW initiated the project and, together with EH, AL, MR and LW, developed the protocol. EH, AL, MR, and LW were responsible for recruitment, data collection, and data analysis. JBC was the statistician. The manuscript was jointly written and reviewed by all of the authors. CFR is the guarantor.

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Spontaneous loss of early pregnancy and risk of ischaemic heart disease in later life: retrospective cohort study

Gordon C S Smith, Jill P Pell, David Walsh

We recently showed that complications in late pregnancy are associated with an increased risk of maternal ischaemic heart disease (IHD) in later life.[1] We hypothesised that this may reflect common determinants, such as thrombophilic genetic defects and anticardiolipin antibodies. Spontaneous losses of pregnancy are also associated with inherited and acquired thrombophilias in the mother.[2] We examined whether spontaneous losses of early pregnancy are associated with maternal risk of IHD.

Participants, methods, and results

We used routine national maternity data (SMR2) to identify all 129 290 eligible women who delivered their first liveborn infant in Scotland during 1981-5. The exclusion and inclusion criteria, definitions, and demographic characteristics were as previously described.[1] We used national death (GRO) and discharge (SMR1) data to determine the risk of death or hospital admission due to IHD during 1981-99. The cumulative probabilities of survival free from IHD events were assessed with Cox's proportional hazards models with age as the time scale (Stata version 7.0, StataCorp, College Station, TX,USA).

A history of any spontaneous loss of early pregnancy before the first live birth was associated with an increased risk of IHD (table). The association was independent of maternal age at the time of first birth, height, socioeconomic deprivation, essential hypertension, and complications during the first pregnancy. The magnitude of the risk increased with the number of previous losses. By contrast, there was no association between therapeutic abortion and subsequent risk of IHD (adjusted hazard ratio 0.93, 95% confidence interval 0.59 to 1.46). Only 0.1% (162) of women had had a hernia repair, and there was no significant association

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Maternal ischaemic heart disease events and number of previous spontaneous losses of early pregnancy losses. Figures are hazard ratios (95% confidence interval)*

	No of losses of early pregnancy			
	0†(n=117 538)	1-2(n=11 371)	≥3(n=381)	≥1(n=11 752)
No (%) of events	261 (0.2)	48 (0.4)	4 (1.0)	52 (0.4)
Crude	1.0	1.44 (1.06 to 1.97), P=0.02	2.34 (0.87 to 6.32), P=0.09	1.49 (1.10 to 2.01), P=0.009
Adjusted for case mix‡	1.0	1.47 (1.08 to 2.00), P=0.02	2.32 (0.86 to 6.27), P=0.10	1.51 (1.12 to 2.04), P=0.007
Adjusted for case mix‡ and obstetric complications§	1.0	1.48 (1.09 to 2.02), P=0.01	2.35 (0.87 to 6.36), P=0.09	1.52 (1.13 to 2.06), P=0.006

*All covariates in multivariate models were significantly associated with ischaemic heart disease. Proportional hazard assumption tested with Stata "stphtest" command with Schoenfeld residuals. There was no evidence for violation of assumption in any model (all P>0.5).
†Reference category.
‡Age, height, deprivation, and essential hypertension in first pregnancy.
§Lowest fifth of birthweight distribution, preterm delivery, pre-eclampsia.

with spontaneous early pregnancy loss (0.93, 0.55 to 1.59), suggesting that there was no bias due to selective migration. We did not have data on the smoking status of women in the 1981-5 cohort. However, we had data on 181 636 women who had a first livebirth from 1992 to 1998, inclusive. The proportion of women who were current smokers at the first attendance for prenatal care was only marginally higher among women with a history of spontaneous loss of early pregnancy (28.4%) than among those with no such history (26.8%).

Comment

To our knowledge, this is the first study to show a specific association between spontaneous abortion and maternal risk of IHD. Our findings may explain the results of previous studies that have found an association between the total number of pregnancies and maternal risk of IHD as women who suffer recurrent losses of early pregnancy must have more pregnancies to achieve their target family size.[3] However, it is unlikely that the association between spontaneous abortion and maternal IHD is simply an effect of parity as there was no association with therapeutic abortion.

The strengths of our study are that prospective data collection precluded bias and, in contrast with a case-control study, we were able to include women who subsequently died. However, further studies are required to corroborate our findings and to confirm that the association is independent of smoking and other confounding factors, such as maternal disease (for example, diabetes and polycystic ovarian syndrome).

Several studies have shown associations between acquired and inherited thrombophilias and both spontaneous loss of early pregnancy [2] and IHD.[4 5] Implantation of the embryo and development of the placenta involve complex adaptations of the mother's cardiovascular and microvascular systems. We hypothesise that occult cardiovascular, microvascular, or haemostatic dysfunction result in pregnancy complications during reproductive years and in overt cardiovascular disease in later life. A woman's reproductive history may, therefore, inform future cardiovascular risk.

Contributors: GCSS had the original concept, reviewed previous publications, undertook the statistical analyses, and is guarantor. GCSS and JPP wrote the initial draft. DW performed the record linkage. GCSS, JPP, and DW agreed the study design, interpreted the results, revised the original draft, and approved the final version.

Competing interests: None declared.

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Incidence of erectile dysfunction and characteristics of patients before and after the introduction of sildenafil in the United Kingdom: cross sectional study with comparison patients

continued over

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James A Kaye, Hershel Jick

P+

Two tables comparing prevalences of medical conditions appear on bmj.com

Erectile dysfunction, the consistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance, is reported to occur in association with cardiovascular disease, diabetes, hypertension, hypercholesterolaemia, smoking, spinal cord injury, prostate cancer, genitourinary surgery, psychiatric disorders, and the use of many drugs, including alcohol.[1] Sildenafil (Viagra), an oral treatment for erec-

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Original Contribution

Birth Weight and the Risk of Cardiovascular Disease in the Maternal Grandparents

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Pregnancy complications and cardiovascular disease share some common determinants. It has previously been hypothesized that family history of cardiovascular disease would be associated with low birth weight. Records from 120,317 Scottish births, 1992–2006, were linked to hospital admission and death certificate data for 71,681 pairs of maternal grandparents. There was a negative relation between the birth weight of the baby and the risk of either grandparent's experiencing ischemic heart disease (for a 1-kg increase in birth weight, hazard ratio = 0.86, 95% confidence interval: 0.83, 0.89) or cerebrovascular disease (hazard ratio = 0.82, 95% confidence interval: 0.77, 0.87). Further analysis demonstrated that the associations were explained by increased risks of both delivering a small-for-gestational-age infant and delivering preterm among women whose parents had experienced cardiovascular disease. Adjustment for the mother's characteristics at the time of the birth attenuated the relation, but significant associations persisted: With a 1-kg increase in birth weight, the adjusted hazard ratio for ischemic heart disease = 0.93 (95% confidence interval: 0.89, 0.96) and for cerebrovascular disease = 0.93 (95% confidence interval: 0.89, 0.96). Familial aggregation of common determinants of pregnancy complications and cardiovascular disease is the likely explanation for the relation between an infant's birth weight and the risk of cardiovascular disease in other family members.

birth weight; family health; fetal growth retardation; myocardial ischemia; pregnancy; premature birth; stroke; venous thromboembolism

Abbreviations: ICD, *International Classification of Diseases*; SMR01, a registry of all general hospital admissions; SMR02, Scottish Morbidity Record.

It has previously been shown that there is a strong relation between the birth weight of an infant and the mother's subsequent risk of ischemic heart disease (1–3). Others, as well as ourselves, have speculated that this may reflect common determinants of pregnancy complications and ischemic heart disease, which could be genetic, physiologic, environmental, or socioeconomic. Both genetic and nongenetic determinants of heart disease tend to persist within a family, a phenomenon known as familial aggregation (4). Hence, if low birth weight and ischemic heart disease share common determinants, it would be predicted that the risk of cardiovascular disease would be increased in the grandparents of the low-birth-weight infant. We have previously analyzed self-reported family history of ischemic heart disease among 3,320 women with known outcome of a singleton pregnancy and found a trend toward increased risk of a family history among women with a history of a low-birthweight infant (5). In the present study, we report the risk of death or hospital admission for ischemic heart disease, cerebrovascular disease, and venous thromboembolism in 71,681 pairs of maternal grandparents in relation to the birth weight of 120,317 singleton, liveborn grandchildren.

MATERIALS AND METHODS

The Information Services Division of the National Health Service in Scotland and the General Registrar's Office maintain a series of registries that provided the data sources for the present study. The Information Services Division maintains a registry of maternal, obstetric, and offspring

characteristics relating to all births in Scotland, the Scottish Morbidity Record (SMR02), and a registry of all general hospital admissions (SMR01). The General Registrar's Office maintains a computerized registry of all births and deaths. Since 1967, the registry of births contained computerized records of the names and dates of birth of the infant and both parents. We linked the pregnancy record of the mother to the death and hospital admissions records of her parents (i.e., the grandparents of the infant) using the pregnant woman's own birth certificate as the common source of identifiers. Approval of the study was provided by the Privacy Advisory Committee of the Information Services Division. Analysis was performed in 2 ways, reflecting the fact that, in familial studies, the same event may be regarded as an event in one analysis and an exposure in another (4). The primary analysis was the risk of cardiovascular disease in the maternal grandparents in relation to the birth weight of the infant. The secondary analysis was designed to explore the basis for any such association, as low birth weight can be a reflection of a reduced rate of fetal growth, earlier delivery, or a combination of both. Hence, in the secondary analysis, the outcomes were taken to be delivery of a small-for-gestational-age infant or preterm birth, with the experience of disease in the grandparents as an exposure. In both analyses, we excluded maternity records where the pregnancy was a multiple birth, where the birth weight was less than 400 g, or where the gestational age at delivery was less than 24 weeks.

Record linkage

All records were linked by using the combination of full name and date of birth. Previous experience has indicated approximately 98% accuracy of linkage of records in Scotland with a probabilistic approach (6). The Scottish Morbidity Record (SMR02) database yielded the maternal characteristics and the outcome of the pregnancy. Pregnancy records were obtained between 1992 and 2006. We confined analysis to records collected from 1992 onward, as smoking data began to be collected at this date. The SMR02 record included the mother's maiden name (i.e., her family name when she was born) and her own date of birth. This was used to link her pregnancy record to her own birth certificate. This linkage was, therefore, only possible for women who had been born in Scotland and where the mother's maiden name was documented in the SMR02 (this is not a compulsory field in the registry). The birth certificate was then used to obtain the names and dates of birth of the woman's mother and father. These details were then used to identify hospital admissions (SMR01) or deaths (General Registrar's Office death certificate database) for the woman's parents between 1981 and 2006 (inclusive). In order to maintain confidentiality, this part of the process was conducted by using a process of pseudorandomization (Web Figure 1). (This information is described in the first of 2 supplementary figures; each is referred to as ''Web figure'' in the text and is posted on the *Journal*'s website (http://aje.oxfordjournals.org/).) The final data set consisted, therefore, of the characteristics of the mother at the time of pregnancy, the outcome of the pregnancy, and the experience of hospital admission or death of the mother's parents. Throughout the paper, the mother's parents are referred to as the ''maternal grandparents.''

Definitions

The postal code of residence at the time of the pregnancy was used to derive Carstairs socioeconomic deprivation scores (7). Parity was defined as the number of previous livebirths or stillbirths. Smoking was defined as the smoking status of the woman at the time of first attendance for antenatal care. Maternal height was measured in centimeters, and the value used was that documented in each woman's clinical record. Maternal age was defined as the age of the mother at the time of birth. Marital status was defined as married or unmarried. Gestational age at birth was defined as completed weeks of gestation on the basis of the estimated date of delivery in each woman's clinical record. Gestational age has been confirmed by ultrasound in the first half of pregnancy in more than 95% of women in the United Kingdom since the early 1990s (8). Preterm birth was defined as birth before 37 weeks' gestation. Birth weight was classified into sex- and gestational age-specific percentiles derived from the study cohort. Small-for-gestational-age birth weight was defined as a birth weight in the smallest 5% for sex and week of gestational age at delivery. Preeclampsia was defined as the presence of an appropriate *International Classification of Diseases* (ICD), Ninth Revision, code 642.4 or 642.5 or ICD, Tenth Revision, diagnostic codes O140, O141, and O149 in the delivery record. Events in the maternal grandparents were defined on the basis of ICD codes listed in the principal position of the hospital record or death certificate. Ischemic heart disease was defined as either ICD, Ninth Revision, codes 410–414 or ICD, Tenth Revision, codes I20–25; cerebrovascular disease was defined as either ICD, Ninth Revision, codes 430–438 or ICD, Tenth Revision, codes I60–I69 or G45; and venous thromboembolism was defined as either ICD, Ninth Revision, code 453.8, 453.9, or 415.1 or ICD, Tenth Revision, code I82.8, I82.9, or I26.

Statistical analysis

Continuous variables were summarized by the median and interquartile range, and comparisons between groups were performed by using the Kruskal-Wallis test. Unadjusted comparisons of categorical data were performed by using the chi-square test and the test for trend, as appropriate. The P values for all hypothesis tests were 2 sided, and statistical significance was assumed at $P < 0.05$. Covariables with >5% missing values (height and smoking status) were imputed by using multiple imputation by chain equations (9). Five imputations were created with a set of appropriate imputation models constructed from all covariables and all outcome variables (time-to-event outcome variables were log transformed). Almost identical results were obtained from analyses of the complete cases and using missing indicator variables for height and smoking status.

The risk of cardiovascular disease in each maternal grandparent was estimated by using a Cox proportional hazards model, with grandparental age as the time scale. The

Table 1. Summary of Maternal Characteristics at the Time of First Eligible Pregnancy ($n = 78{,}294$), Scotland, 1992–2006[a]

	No History of Disease ($n = 67{,}727$)		At Least 1 Grandparent With a History of Disease[b]								
			Ischemic Heart Disease ($n = 7{,}983$)			Cerebrovascular Disease ($n = 2{,}828$)			Venous Thromboembolism ($n = 715$)		
	No.	%	No.	%	*P* Value	No.	%	*P* Value	No.	%	*P* Value
Maternal characteristics											
Age, years (median (IQR))	20 (18–23)[c]		20 (18–23)[c]		<0.001	20 (18–23)[c]		0.33	20 (18–23)[c]		0.09
Marital status											
Unmarried	61,297	90.5	7,180	89.9	0.10	2,561	90.6	0.93	644	90.1	0.69
Married	6,430	9.5	803	10.1		267	9.4		71	9.9	
Deprivation											
1 (least deprived)	1,424	2.1	137	1.7	<0.001	40	1.4	<0.001	5	0.7	<0.001
2	5,533	8.2	479	6.0		177	6.3		34	4.8	
3	11,701	17.3	1,213	15.2		399	14.1		122	17.1	
4	18,277	27.0	2,057	25.8		706	25.0		187	26.2	
5	13,779	20.3	1,735	21.7		590	20.9		140	19.6	
6	9,741	14.4	1,291	16.2		501	17.7		126	17.6	
7 (most deprived)	7,282	10.8	1,071	13.4		415	14.7		101	14.1	
Height, cm											
Median (IQR)	163 (159–167)		163 (158–167)		<0.001	162 (158–167)		<0.001	163 (158–167)		0.76
Missing	13,898	20.5	1,574	19.7		564	19.9		145	20.3	
Smoking status											
Nonsmoker	29,834	44.1	3,251	40.7	<0.001	1,135	40.1	<0.001	287	40.1	0.18
Smoker	24,566	36.3	3,324	41.6		1,165	41.2		281	39.3	
Former smoker	8,286	12.2	829	10.4		296	10.5		95	13.3	
Missing	5,041	7.4	579	7.3		232	8.2		52	7.3	
Parity											
0	64,631	95.4	7,627	95.5	0.8	2,690	95.1	0.83	679	95.0	0.16
1	3,052	4.5	350	4.4		136	4.8		35	4.9	
2	20	0.04	5	0.06		1	0.04		0	0.0	
≥3	14	0.02	1	0.01		1	0.04		1	0.14	
Infant characteristics											
Sex											
Male	35,072	51.8	4,153	52.0	0.7	1,462	51.7	0.93	386	54	0.24
Female	32,653	48.2	3,830	48.0		1,366	48.3		329	46.0	
Gestational age, weeks											
Median (IQR)	40 (39–41)		40 (39–41)		<0.001	40 (39–41)		0.04	40 (39–41)		0.15
Preterm	4,577	6.7	597	7.5	0.02	217	7.7	0.06	57	8.0	0.20
Birth weight, g (median (IQR))	3,340 (2,990–3,660)		3,290 (2,940–3,620)		<0.001	3,290 (2,950–3,620)		<0.001	3,320 (2,980–3,640)		0.23

Abbreviations: IQR, interquartile range; SD, standard deviation.

[a] *P* value for comparison with no history of disease using the Mann-Whitney *U* test, the chi-square test, or the chi-square test for trend, as appropriate.

[b] Diagnoses are not mutually exclusive.

[c] The mean ages of women in columns from left to right: 20.73 (SD, 3.42), 20.94 (SD, 3.51), 20.81 (SD, 3.47), and 20.64 (SD, 3.30) years.

unit of analysis was the grandparent, and the birth weight of the grandchild was the exposure. Because the same grandparent entered the model multiple times, corresponding to the number of grandchildren in the data set, the analyses were clustered on the grandparental identifier to allow dependence between grandchildren for each grandparent (a pair of grandparents were assumed independent). This approach allowed for any pattern of dependence within the grandparent cluster. The risk of pregnancy ending in delivery of a small-for-gestational-age infant, preterm birth, or

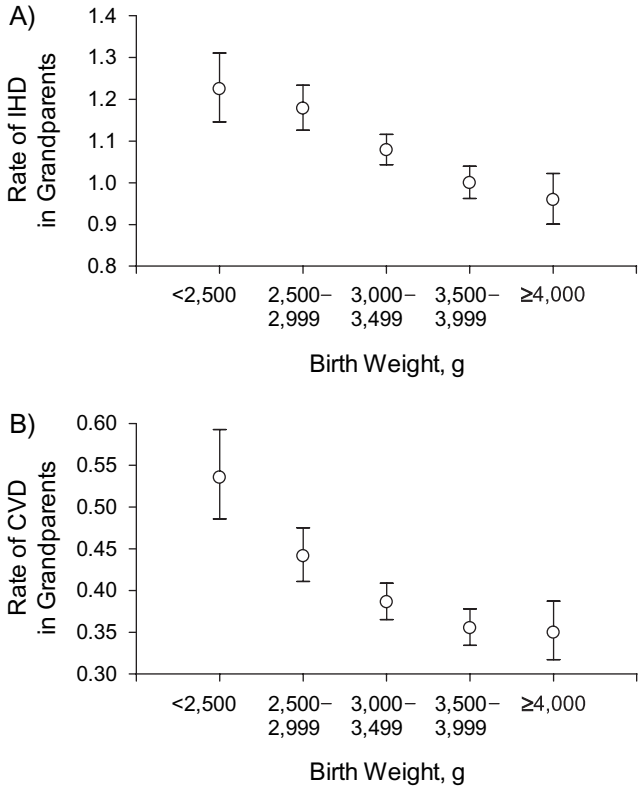

Figure 1. Rates of ischemic heart disease (IHD) (A) and cerebrovascular disease (CVD) (B) in either maternal grandparent (expressed per 1,000 person-years) in relation to the birth weight of the infant, Scotland, 1992–2006. Bars are confidence intervals and are adjusted for clustering (refer to Materials and Methods).

preeclampsia was assessed by using multivariable logistic regression analysis. The unit of analysis was the grandchild, and the exposure was history of disease in either grandparent up to the end of 2006. Analyses were clustered on the pairs of grandparents to allow dependence between grandchildren with the same set of grandparents. All analyses of pregnancy outcome were adjusted for both grandparents' age at censoring, as the design of the study is such that the length of available follow-up on the grandparent varies, and this is clearly a major determinant of the risk of an event. The statistical significance of interaction terms was assessed by using the Wald test. In the multiple imputation and logistic regression models, all categorical covariables were modeled by dummy variables. Maternal age, height, and birth weight percentile were all treated continuously in the regression models. All available maternal characteristics were included in multivariable analyses. Assessment of linearity was performed by using fractional polynomials in the observed data (i.e., not the imputed data for height). All statistical analyses were performed by using STATA, version 10.1, software (StataCorp LP, College Station, Texas).

RESULTS

We were able to link 130,904 SMR02 records to the mother's birth certificate. A total of 8,413 records had missing name and/or date of birth of 1 or both parents in the birth certificate, leaving 122,491 pregnancy records with complete data on grandparental identifiers. A total of 2,174 records were excluded as they included 1 or more of the following: multiple births ($n = 1{,}043$, 0.85%); antepartum or intrapartum stillbirth ($n = 573$, 0.5%); birth weight less than 400 g ($n = 47$, <0.01%); gestational age outside the range 24–43 weeks ($n = 75$, <0.01%); or missing maternal age, deprivation category, birth weight, gestational age, or sex ($n = 519$, 0.5%). The final linked data set consisted of 120,317 pregnancy records from a total of 78,294 women, with hospital admission and death data on 71,681 pairs of maternal grandparents.

When tabulated by the maternal characteristics at the time of the first eligible recorded pregnancy, grandparental history of both ischemic heart disease and cerebrovascular disease was positively associated with the mother's age at the time of delivery, her being married, her Carstairs category of socioeconomic deprivation, smoking and parity, and preterm birth (Table 1). Grandparental history of both ischemic heart disease and cerebrovascular disease was negatively associated with the mother's height, the gestational age at delivery, and the birth weight of the infant. The unadjusted grandparental rates of ischemic heart disease and cerebrovascular disease are plotted against birth weight category (Figure 1). The median age of grandparents at censoring who had no history of disease was 53 years, the interquartile range was 49–57, and the 90th percentile was 61. As they were followed up for 26 years, 90% of the group were aged 35 years or less at the time when their cardiovascular events started to be identified. Hence, only a small number of events would have been missed because of left truncation.

A 1-kg increase in the birth weight of the infant was associated with a 14% decrease in the grandparental risk of ischemic heart disease (Table 2) and an 18% decrease in the grandparental risk of cerebrovascular disease (Table 3). Adjustment for the maternal characteristics at the time of birth reduced the associations to 7% and 11%, respectively. Other maternal characteristics at the time of birth were also associated with grandparental risk of disease in multivariable analysis. Grandparental risk of both ischemic heart disease and cerebrovascular disease was positively associated with the mother's Carstairs socioeconomic deprivation category, smoking, and parity, and it was negatively associated with the mother's age and height at the time of the delivery. There was no association between the birth weight of the infant and the grandparental risk of venous thromboembolism (Table 4), although this outcome was positively associated with the mother's Carstairs socioeconomic deprivation category and parity at the time of the birth. There was no evidence that the association between birth weight and either ischemic heart disease or cerebrovascular disease significantly varied according to maternal age, marital status, deprivation category, height, smoking status, or parity (Web Figure 2).

The risk of delivery of a small-for-gestational-age infant, preterm delivery, and preeclampsia was then analyzed in relation to the maternal grandparents' experience of cardiovascular disease. The odds of delivering a small-for-gestational-age infant were increased by 19% where either

Table 2. Birth Weight, Other Maternal Characteristics, and the Grandparental Risk of Hospital Admission for Ischemic Heart Disease, Scotland, 1992–2006

	Death or Hospital Admission of Either Maternal Grandparent With Ischemic Heart Disease					
	Unadjusted Analysis			Adjusted Analysis		
	Hazard Ratio	95% Confidence Interval	*P* Value	Hazard Ratio	95% Confidence Interval	*P* Value
Birth weight (per kg)	0.86	0.83, 0.89	<0.001	0.93	0.89, 0.96	<0.001
Age, years (per 5 years)	0.87	0.85, 0.89	<0.001	0.89	0.86, 0.92	<0.001
Marital status						
Unmarried	1.0			1.0		
Married	0.83	0.79, 0.88	<0.001	0.98	0.92, 1.05	0.64
Deprivation						
1 (least deprived)	0.76	0.64, 0.89	<0.001	0.83	0.70, 0.98	<0.001
2	0.68	0.62, 0.75		0.72	0.65, 0.80	
3	0.88	0.82, 0.94		0.90	0.84, 0.97	
4	1.0			1.0		
5	1.16	1.09, 1.23		1.13	1.06, 1.20	
6	1.19	1.12, 1.28		1.15	1.07, 1.24	
7 (most deprived)	1.44	1.33, 1.55		1.35	1.26, 1.47	
Height (per 5 cm)	0.93	0.91, 0.95	<0.001	0.96	0.93, 0.98	<0.001
Smoking status						
Nonsmoker	1.0		<0.001	1.0		<0.001
Former smoker	0.94	0.88, 1.01		0.94	0.92, 1.05	
Smoker	1.31	1.25, 1.37		1.19	1.13, 1.25	
Parity						
0	1.0		<0.001	1.0		<0.001
1	1.05	1.03, 1.08		1.11	1.08, 1.15	
2	1.25	1.11, 1.41		1.32	1.16, 1.50	
≥3	1.54	0.91, 2.60		1.66	0.99, 2.76	

maternal grandparent had experienced ischemic heart disease and by 33% where either had experienced cerebrovascular disease (Table 5). These associations were attenuated by about one-half and one-third, respectively, following adjustment for the maternal characteristics at the time of birth. The odds of delivering preterm were increased by 12% where either maternal grandparent had experienced ischemic heart disease and by 23% where either had experienced cerebrovascular disease (Table 5). These associations were attenuated by about one-third and one-fifth, respectively, following adjustment for the maternal characteristics at the time of birth. The odds of preeclampsia were increased only in multivariable analysis in association with grandparental ischemic heart disease (Table 5). This association may have been masked in unadjusted analysis by negative confounding by smoking, given the protective effect of smoking on the risk of preeclampsia (10) and its positive association with the risk of ischemic heart disease (11). There was no association between grandparental experience of venous thromboembolism and any of the obstetric outcomes.

DISCUSSION

The main finding of the current analysis is that increased birth weight of the infant was associated with a decreased risk of death or hospital admission from cardiovascular disease in the maternal grandparents. For each 1-kg increase in birth weight, the grandparental risk of ischemic heart disease declined by 14%, and the risk of cerebrovascular disease declined by 18%. Adjustment for the maternal characteristics at the time of birth reduced the associations to 7% and 11%, respectively. Previous studies have also demonstrated associations between an individual's birth weight and his/her personal risk of ischemic heart disease in later life, estimated as a 16% reduction in the odds of ischemic heart disease for each 1-kg increase in birth weight (12). In a previous analysis using record linkage of routinely collected data from Scotland, we also demonstrated a strong association between the birth weight of the infant and the mother's risk of ischemic heart disease in the next 15–20 years (2), and this has also been observed in other populations (1, 13). Hence, low birth weight is associated with an increased risk of cardiovascular disease for the individual,

Table 3. Birth Weight, Other Maternal Characteristics, and the Grandparental Risk of Hospital Admission for Cerebrovascular Disease, Scotland, 1992–2006

	Death or Hospital Admission of Either Maternal Grandparent With Cerebrovascular Disease					
	Unadjusted Analysis			Adjusted Analysis		
	Hazard Ratio	95% Confidence Interval	*P* Value	Hazard Ratio	95% Confidence Interval	*P* Value
Birth weight (per kg)	0.82	0.77, 0.87	<0.001	0.89	0.84, 0.95	<0.001
Age, years (per 5 years)	0.84	0.80, 0.87	<0.001	0.86	0.81, 0.90	<0.001
Marital status						
Unmarried	1.0			1.0		0.17
Married	0.76	0.68, 0.84	<0.001	0.92	0.82, 1.03	
Deprivation						
1 (least deprived)	0.56	0.41, 0.77	<0.001	0.64	0.46, 0.87	<0.001
2	0.76	0.64, 0.90		0.82	0.69, 0.96	
3	0.84	0.74, 0.96		0.87	0.77, 0.99	
4	1.0			1.0		
5	1.11	0.99, 1.24		1.08	0.96, 1.20	
6	1.35	1.19, 1.53		1.28	1.13, 1.46	
7 (most deprived)	1.49	1.30, 1.71		1.38	1.20, 1.58	
Height (per 5 cm)	0.91	0.88, 0.94	<0.001	0.94	0.91, 0.97	<0.001
Smoking status						
Nonsmoker	1.0		<0.001	1.0		<0.001
Former smoker	0.91	0.81, 1.02		0.91	0.81, 1.03	
Smoker	1.36	1.25, 1.47		1.20	1.11, 1.31	
Parity						
0	1.0		0.01	1.0		<0.001
1	1.06	1.02, 1.11		1.15	1.08, 1.22	
2	1.29	1.05, 1.57		1.39	1.12, 1.72	
≥3	0.88	0.36, 2.13		0.97	0.40, 2.37	

his/her parents, and his/her maternal grandparents. The findings are analogous with the relation between family history of type 2 diabetes mellitus and gestational diabetes. The latter association does not reflect a direct effect of a diagnosis of diabetes mellitus in a relative on the risk of gestational diabetes in a pregnant woman. Rather, it reflects a common dependence of both outcomes on insulin resistance. Similarly, we infer that factors leading to ischemic heart disease and cerebrovascular disease also lead to pregnancy complications resulting in low birth weight. We speculate that familial aggregation of these factors leads to associations between birth weight and the risk of cardiovascular disease in all members of a family.

Analysis of the association by birth weight allowed direct comparison with other related studies, but this did not resolve which of the 2 main determinants of birth weight (the rate of fetal growth during pregnancy and the gestational age at birth) accounted for the association. We observed that grandparental experience of cardiovascular disease was associated with both an increased risk of delivery of a small-for-gestational-age infant and an increased risk of preterm birth. These associations were variably explained by other maternal characteristics. The persistence of associations between pregnancy outcome and grandparental experience of disease in multivariable analysis could simply reflect the effect of unmeasured socioeconomic and environmental factors. It could also reflect the effect of common genetic risk factors for pregnancy complications and ischemic heart disease. For example, previous studies have demonstrated an inverse relation between parental blood pressure and the birth weight of the infant (14, 15). It is possible that grandparental carriage of a genetic predisposition toward hypertension could lead to an increased risk of cardiovascular disease in the individual and that passing the allele on to the daughter could lead to an increased risk of her delivering a low-birth-weight infant. Thrombophilic mutations are another candidate genetic link, as these are associated with both cardiovascular disease (16, 17) and pregnancy complications (18). However, we observed no relation between the birth weight of the infant and the grandparental incidence of venous thromboembolism despite the fact that these mutations are strongly associated with the risk of venous thromboembolism (18).

We had previously analyzed data from over 3,000 women, relating pregnancy complications ascertained through the SMR02 and the woman's self-reported family

Table 4. Birth Weight, Other Maternal Characteristics, and the Grandparental Risk of Hospital Admission for Venous Thromboembolism, Scotland, 1992–2006

	Death or Hospital Admission of Either Maternal Grandparent With Venous Thromboembolism					
	Unadjusted Analysis			Adjusted Analysis		
	Hazard Ratio	95% Confidence Interval	*P* Value	Hazard Ratio	95% Confidence Interval	*P* Value
Birth weight (per kg)	0.93	0.83, 1.05	0.27	0.96	0.85, 1.09	0.56
Age, years (per 5 years)	0.82	0.75, 0.89	<0.001	0.81	0.73, 0.90	<0.001
Marital status						
Unmarried	1.0			1.0		
Married	0.85	0.69, 1.06	0.24	1.04	0.83, 1.30	0.73
Deprivation						
1 (least deprived)	0.26	0.10, 0.67	<0.001	0.28	0.11, 0.73	0.006
2	0.73	0.52, 1.03		0.76	0.54, 1.07	
3	1.00	0.79, 1.26		1.01	0.80, 1.28	
4	1.0			1.0		
5	1.09	0.86, 1.37		1.07	0.85, 1.35	
6	1.21	0.94, 1.55		1.18	0.92, 1.52	
7 (most deprived)	1.44	1.10, 1.88		1.39	1.06, 1.83	
Height (per 5 cm)	1.01	0.94, 1.09	0.73	1.04	0.96, 1.12	0.36
Smoking status						
Nonsmoker	1.0		0.10	1.0		0.54
Former smoker	1.09	0.87, 1.36		1.07	0.85, 1.34	
Smoker	1.21	1.02, 1.42		1.10	0.92, 1.32	
Parity						
0	1.0		0.10	1.0		0.02
1	1.05	0.95, 1.15		1.16	1.02, 1.32	
2	0.95	0.57, 1.59		1.12	0.65, 1.94	
≥3	2.88	1.08, 7.67		3.44	1.25, 9.47	

history of ischemic heart disease using data from a cohort study (5). We described a similar association between low birth weight and family history of ischemic heart disease, although this was of borderline statistical significance, given the small numbers. The present study has a number of strengths over the previous study. First, we had similarly detailed information on pregnancy complications but had data available from more than 100,000 births. Second, ascertainment of grandparental history of disease was performed by record linkage to national registries. This precluded the possibility of recall bias. Moreover, we were able also to study the relation between birth weight and the risk of other cardiovascular conditions in the maternal grandparents, such as cerebrovascular disease and venous

Table 5. Experience of Disease in Either Maternal Grandparent and the Risk of Pregnancy Complications, Scotland, 1992–2006

Outcome	Ischemic Heart Disease						Cerebrovascular Disease					
	Unadjusted[a]			Adjusted[a,b]			Unadjusted[a]			Adjusted[a,b]		
	Odds Ratio	95% Confidence interval	*P* Value	Odds Ratio	95% Confidence interval	*P* Value	Odds Ratio	95% Confidence interval	*P* Value	Odds Ratio	95% Confidence interval	*P* Value
Small for gestational age	1.19	1.10, 1.30	<0.001	1.09	1.00, 1.19	0.06	1.33	1.16, 1.51	<0.001	1.21	1.06, 1.38	0.005
Preterm birth	1.12	1.04, 1.21	0.005	1.07	0.99, 1.16	0.08	1.23	1.09, 1.40	0.001	1.18	1.04, 1.33	0.01
Preeclampsia	1.08	0.95, 1.23	0.24	1.16	1.02, 1.33	0.02	0.87	0.70, 1.09	0.23	0.95	0.76, 1.18	0.64

[a] All odds ratios are adjusted for grandparents' age at censoring.
[b] Also adjusted for maternal age, marital status, smoking status, Carstairs socioeconomic category, height, and parity.

thromboembolism. Finally, the likelihood of a positive family history of disease also depends on the age of the relatives. Use of the Cox model to quantify the risk of events in the grandparents allowed us to account directly for variation in the age of the maternal grandparents.

The current study also had a number of weaknesses. First, we relied on registry-based classification of both exposures and events. Hence, smoking status is self-reported and not validated by cotinine assay. Moreover, definition of both grandparental disease and pregnancy complications may be prone to error. For example, preeclampsia is ascertained only by ICD codes, and we have no information on the criteria for the diagnosis. Similarly, we do not have access to the results of tests used to diagnose cardiovascular disease, such as troponin or electrocardiogram for ischemic heart disease, neuroimaging for cerebrovascular disease, and venography and angiography for venous thromboembolism. Furthermore, record linkage could only be performed for women who had been born in Scotland and where the maiden name was recorded in the SMR02. As this was not a mandatory field in the SMR02, the linkage systematically favored unmarried women. Moreover, the computerized registry of births was available only for births since 1967. Therefore, the linkage design was constrained to a maximum maternal age of 39 years (i.e., a woman born in 1967 who had a birth in 2006). Hence, the linkage also favored inclusion of younger women. Consequently, the cohort is not a random or, indeed, a representative sample of the Scottish population. At the time of the first eligible pregnancy, the median age was 20 years, and approximately 90% of the women were unmarried. Compared with another cohort of livebirths in Scotland in 1992–2001 (19), the current cohort also had higher proportions of smoking and preterm birth and lower median birth weights. In order to address the possibility that the association may vary according to the nature of the population studied, the repeated analysis was stratifying by the mother's characteristics at the time of birth (Web Figure 2). This demonstrated that the association between birth weight and the risk of cardiovascular disease in the maternal grandparents was similar across strata of maternal age, marital status, socioeconomic deprivation, height, smoking status, and parity. Nevertheless, the selected nature of the current cohort may mean that the experience of cardiovascular disease in their family members may differ compared with other populations. However, our findings are also consistent with other analyses. A number of studies have also reported associations between a family history of cardiovascular disease and the risk of preeclampsia (20–23), and the present analysis also demonstrated an association between preeclampsia and grandparental ischemic heart disease. Furthermore, a previous study examined a cohort of parents of women who experienced preeclampsia and intrauterine growth restriction, and they were found to exhibit abnormalities of glycemic control, anthropometry, blood pressure, and low density lipoprotein (24).

The analysis also revealed associations between the mother's other characteristics and her parents' experience of disease, although interpretation of these findings should be cautious as these were secondary analyses. There were striking associations between the Carstairs socioeconomic category of the woman's area of residence at the time of the pregnancy and the risk of cardiovascular disease in her parents, with the difference in the risk of the 3 outcomes studied varying up to 5-fold across the range of deprivation category. Similarly, maternal smoking and short stature were associated with an increased risk of ischemic heart disease and cerebrovascular disease in her parents. Socioeconomic deprivation, smoking, and short stature are all risk factors for ischemic heart disease in women (11, 25, 26). These observations support the concept that familial aggregation of demographic and environmental risk factors may explain a proportion of the familial aggregation of cardiovascular disease. Interestingly, there was a positive association between a woman's parity and her parents' risk of cardiovascular disease. Previous studies have indicated a positive association between number of pregnancies and personal risk of ischemic heart disease (27), and it has been speculated that this could be a direct effect of pregnancy. However, the association between higher parity and parental risk of disease could not plausibly be explained by a direct effect of the pregnancy. Hence, the present observation is supportive of the view that high parity may be associated with the risk of ischemic heart disease by a noncausal mechanism (28).

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Recurrent miscarriage is associated with a family history of ischaemic heart disease: a retrospective cohort study

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Objective To determine whether women experiencing recurrent miscarriage were more likely to have a family history of cardiovascular disease.
Design Retrospective cohort study.
Setting Women having a first birth in Scotland between 1992-2006.
Sample 74,730 first births were linked to the hospital admission and death certification data for the women's parents through the women's birth certificates.
Methods The incidence of cardiovascular disease in the women's parents was related to the number of miscarriages experienced prior to their daughters' first births using a Cox proportional hazards model.
Main outcome measures Death or hospital admission of the women's parents for ischaemic heart disease (IHD), cerebrovascular disease (CVD) or venous thromboembolism (VTE).
Main results There was an increased incidence of IHD in the parents of women who experienced two miscarriages prior to their first birth (hazard ratio 1.25, 95% confidence intervals 1.04-1.49) and parents of women who experienced three or more miscarriages prior to their first birth (hazard ratio 1.56, 95% confidence intervals 1.14-2.15). Adjustment for the characteristics of the women at the time of the first birth was without material effect. There was no significant association between miscarriage and family history of CVD or VTE. There was no significant association between the number of therapeutic abortions prior to the first birth and the incidence of any type of cardiovascular disease in the women's parents.
Conclusions The parents of women who experience recurrent miscarriage are more likely to experience IHD. Recurrent miscarriage and IHD may have common patho-physiological pathways and genetic predispositions.

Key words: epidemiology, family history, miscarriage, ischaemic heart disease, cerebrovascular disease, venous thromboembolism.

Introduction.

Studies in the 1950s and 1960s demonstrated that women who experienced miscarriage were more likely to have IHD in later life.[1] However, it was unclear if this was independent of the total number of pregnancies, which has itself been identified as a risk factor for IHD.[2] We addressed this studying 129,290 women having first births in Scotland and related their subsequent experience of IHD to the number of miscarriages and therapeutic abortions experienced prior to their first birth.[3] That study confirmed a specific association between miscarriage and the subsequent risk of IHD. We speculated that the association may indicate common risk factors for miscarriage and IHD, which may be inherited or acquired. In the present study we sought to determine whether there was evidence for common inheritable risk factors for both miscarriage and IHD by studying the relationship between women's experience of miscarriage prior to the first birth and their parents' incidence of cardiovascular disease.

Methods.

Data and record linkage

We used a linked dataset which has previously been described in detail.[4] In brief, we used a national registry of pregnancy outcome data, the Scottish Morbidity Record 02 (SMR02), to obtain information about women having their first birth. We then used identifiers for the mother (first name, unmarried name and date of birth) to link this record to her own birth certificate using a probability-based matching approach. The parents' names and dates of births were recorded on the birth certificate and this was then used to link the SMR02 pregnancy data to the parents' records for death (the General Registrar's Office, GRO) or hospital admission (SMR01). We identified hospital admissions for cardiovascular disease, specifically, ischaemic heart disease (IHD), cerebrovascular disease (CVD) or venous thromboembolism (VTE). We utilized SMR02 records from 1992-2006. The start date was chosen as smoking was only recorded from this year onwards and the end date represented the latest period that data were available at the time of the linkage. The birth certificate database was maintained in a computerized form from 1967 onwards. Hence, we were able to perform the linkage for women who were born in Scotland from 1967 onwards. Death certificate and SMR01 records were available between 1981 and 2006. Hence, we were able to identify events in the parents during this period. Approval of the study was provided by the Privacy Advisory Committee of the Information Services Division of NHS Scotland.

Definitions.

The number of previous miscarriages and therapeutic abortions was self-reported by the women. Hence, this would have included losses occurring in the community (i.e. not requiring hospital admission). However, further details of the losses, such as gestational age, were not available. Hence, miscarriage was defined as previous spontaneous loss prior to viability. Demographic characteristics were available from the SMR02 for the women at the time of their first births. Postcode of residence at the time of the first birth was used to derive Carstairs socioeconomic deprivation scores.[5] Smoking was defined as the smoking status of the woman at the time of first attendance for prenatal care. Maternal height was measured in centimetres and the value used was that documented in each woman's clinical record. Maternal age was defined as the age of the mother at the time of birth. Marital status was defined as married or unmarried. First singleton livebirth was defined as records where all previous pregnancies had all ended in either miscarriage or therapeutic abortion and the current pregnancy ended in an infant born weighing 400g or more between 24 and 43 weeks gestational age, excluding stillbirths and multiple pregnancy. Events in the women's parents were defined on the basis of International Classification of Disease (ICD) codes listed in the principal position of the hospital record (SMR01) or death certificate (GRO). Ischaemic heart disease was defined as either 410-414 (ICD9) or I20-25 (ICD10); CVD was defined as either 430-438 (ICD9) or I60–I69 or G45 (ICD10); and VTE was defined as either 453.8, 453.9 or 415.1 (ICD9) or I82.8, I82.9, or I26 (ICD10).

Statistical analysis

Continuous variables were summarized by the median and inter-quartile range (IQR) and comparisons between groups were performed using the Kruskal-Wallis test. Unadjusted comparisons of categorical data were performed using the Chi square test for trend. The *P* values for all hypothesis tests were two-sided and statistical significance was assumed at $P<0.05$. The aim of the analysis was to estimate the measure of association between miscarriage in the women and the experience of IHD in her parents. The approach we took was to use miscarriage as the exposure and to use IHD in the parents as the event. The rationale for this is addressed in the discussion. The relative hazard of cardiovascular disease in the women's parents was estimated using a Cox proportional hazards model, with parental age as the time scale. The unit of analysis was the parents and the number of previous losses, miscarriage or therapeutic abortions, experienced by their daughters was the exposure. The analyses were clustered on the parental identifier to allow dependence between siblings (some parents had more than one daughter included in the cohort). Covariables with >5% missing values (height and smoking status) were imputed using multiple imputation by chain equations.[6] Five imputed datasets were created by replacing missing values for height and smoking status with simulated values from a set of imputation models constructed from all covariables and all outcome variables (i.e. the Nelson-Aalen estimators for parental age at disease onset and the censoring indicators). Distributions of imputed values were visually checked for comparability with the observed data. Almost identical results were obtained from analyses of the complete-cases. All available maternal characteristics were included in multivariable analyses. Categorical covariables were modelled by dummy variables and maternal age and height were treated continuously. The baseline hazard for the Cox model was stratified by maternal age quintiles. Assessment of linearity was performed using fractional polynomials and assessment of the proportional hazards assumption was performed using the schoenfeld

residuals in the observed data (i.e. not the imputed data).[7] Where the proportional hazards assumption was violated, analyses were stratified on the given variable. All statistical analyses were performed using the Stata software package (Stata Corporation, Texas, USA), version 10.1.

Results.

Our previous linkage and cohort selection resulted in 120,317 pregnancy records from a total of 78,294 women (see previous publication for details of selection process[4]). From this group, we now excluded 45,580 records which were not first births and 7 records with a missing value for the primary exposure (number of prior miscarriages). This resulted in a dataset of 74,730 first births, with data on number of previous miscarriages for the women and data on hospital admission or death of the parents between 1981 and 2006 with cardiovascular disease. The basic characteristics of the women are described in relation to the number of miscarriages experienced prior to the first birth (Table 1). Women experiencing previous miscarriages tended to be older, more likely to be married and were more likely to smoke. Linkage identified 51,729 fathers of these women and 51,105 mothers of these women (some mothers had daughters in the cohort who had different fathers). Among the fathers, there were records for death or hospital admission for 5,345 IHD events, 1,454 CVD events and 288 VTE events. Among the mothers, there were records for death or hospital admission for 1,908 IHD events, 1000 CVD events and 319 VTE events.

Table 1. Summary of maternal characteristics (n=74,730).

	Number of previous miscarriages				
	0	1	2	3 or more	
	n=66,934	n=6,671	n=901	n=224	*P=
Age					
Median (IQR), years	20 (18-23)	21 (19-24)	22 (20-25)	23 (20-25)	<0.001
Marital status					
Un-married	60 865 (90.9)	5 915 (88.7)	765 (84.9)	188 (83.9)	<0.001
Married	6 069 (9.1)	757 (11.4)	136 (15.1)	36 (16.1)	
Socio-economic deprivation category					
1 (least deprived)	1,371 (2.0)	125 (1.9)	25 (2.8)	0 (0.0)	0.03
2	5,342 (8.0)	546 (8.2)	68 (7.6)	13 (5.8)	
3	11,569 (17.3)	1,088 (16.3)	135 (15.0)	36 (16.1)	
4	18,060 (27.0)	1,795 (26.9)	230 (25.5)	69 (30.8)	
5	13,742 (20.5)	1,420 (21.3)	208 (23.1)	47 (21.0)	
6	9,615 (14.4)	972 (14.6)	123 (13.7)	24 (10.7)	
7 (most deprived)	7,235 (10.8)	725 (10.9)	112 (12.4)	35 (15.6)	
Height					
Median	163	163	163	162	0.75
(IQR), cm	(158-167)	(159-167)	(159-167)	(158-167)	
Missing, n (%)	13 375 (20.0)	1 351 (20.3)	196 (21.8)	59 (26.3)	
Smoking status					
Non smoker	29,653 (44.3)	2,611 (39.1)	340 (37.7)	74 (33.0)	<0.001
Smoker	24,182 (36.1)	2,796 (41.9)	368 (40.8)	107 (47.8)	
Ex-Smoker	8,237 (12.3)	787 (11.8)	116 (12.9)	18 (8.0)	
Missing	4,862 (7.3)	477 (7.2)	77 (8.6)	25 (11.2)	

Data are n (%) unless stated otherwise. IQR denotes inter-quartile range
*Kruskal-Wallis test or Chi square test for trend, as appropriate

The risk of each type of event in the parents was then analyzed using a Cox proportional hazard model, with the daughters' experience of miscarriage prior to the first birth as the main exposure. Univariate analysis demonstrated that there was a significant relationship between the number of miscarriages experienced prior to the women's first births and the incidence of IHD in their parents (Table 2). There was a 25% increase in risk among parents of women with 2 previous losses and a 56% increase in risk among parents of women with 3 or more losses. Associations were adjusted for the other characteristics of the women at the time of the first birth. Adjustment for the maternal characteristics at the time of the first birth was without material effect. The specificity of relationships was examined by comparison with associations with the daughters' experience of therapeutic abortions prior to the first birth. There was no independent and statistically significant association between the number of previous therapeutic abortions and the incidence of IHD in the women's parents. There was no significant relationship between the number of miscarriages experienced prior to the first birth and the risk of CVD (Table 3) or VTE (Table 4) in the women's parents.

Table 2. Early pregnancy losses prior to first singleton livebirth and parental risk of ischaemic heart disease

	Death or hospital admission of parents due to IHD			
	Unadjusted		Adjusted*	
	HR (95% CI)	P=	HR (95% CI)	P=
Miscarriages				
0	1.00		1.00	
1	1.02 (0.94, 1.10)	0.004	1.04 (0.96, 1.12)	0.002
2	1.25 (1.04, 1.49)		1.29 (1.08, 1.55)	
3 or more	1.56 (1.14, 2.15)		1.53 (1.11, 2.11)	
Per miscarriage increase	1.08 (1.02, 1.14)	0.004	1.09 (1.03, 1.15)	0.001
Therapeutic abortions				
0	1.00		1.00	
1	0.91 (0.84, 0.99)	0.10	0.96 (0.88, 1.04)	0.59
2	0.84 (0.65, 1.09)		0.91 (0.70, 1.18)	
3 or more	1.15 (0.65, 2.01)		1.21 (0.68, 2.14)	
Per abortion increase	0.93 (0.87, 1.00)	0.047	0.97 (0.90, 1.04)	0.40

*Adjusted for maternal age in years, marital status, smoking status, socio-economic deprivation category and height and stratified by quintile of maternal age.
IHD denotes ischaemic heart disease, HR denotes hazard ratio, CI denotes confidence intervals

Table 3. Early pregnancy losses prior to first singleton livebirth and parental risk of cerebro-vascular disease

	Death or hospital admission of parents due to CVD			
	Unadjusted		Adjusted*	
	HR (95% CI)	P=	HR (95% CI)	P=
Miscarriages				
0	1.00		1.00	
1	1.05 (0.92, 1.19)	0.83	1.07 (0.94, 1.22)	0.57
2	1.10 (0.80, 1.53)		1.17 (0.84, 1.62)	
3 or more	0.93 (0.52, 1.90)		0.94 (0.47, 1.87)	
Per miscarriage increase	1.03 (0.94, 1.12)	0.54	1.05 (0.96, 1.15)	0.31
Therapeutic abortions				
0	1.00		1.00	
1	0.94 (0.82, 1.09)	0.87	1.00 (0.87, 1.16)	0.97
2	0.99 (0.66, 1.50)		1.11 (0.73, 1.68)	
3 or more	0.82 (0.26, 2.56)		0.94 (0.30, 2.94)	
Per abortion increase	0.96 (0.85, 1.07)	0.43	1.01 (0.90, 1.13)	0.87

*Adjusted for maternal age in years, marital status, smoking status, socio-economic deprivation category and height and stratified by quintile of maternal age
CVD denotes cerebro-vascular disease, HR denotes hazard ratio, CI denotes confidence intervals

Table 4. Early pregnancy losses prior to first singleton livebirth and parental risk of venous thrombo-embolism

	Death or hospital admission of parents due to VTE			
	Unadjusted		Adjusted*	
	HR (95% CI)	P=	HR (95% CI)	P=
Miscarriages				
0	1.00		1.00	
1	0.74 (0.55, 1.00)	0.14	0.76 (0.56, 1.03)	0.19
More than 1	1.03 (0.57, 1.87)		1.07 (0.59, 1.95)	
Per miscarriage increase	1.03 (0.94, 1.12)	0.54	1.05 (0.96, 1.14)	0.28
Therapeutic abortions				
0	1.00		1.00	
1	1.00 (0.75, 1.34)	0.99	1.05 (0.79, 1.41)	0.94
More than 1	0.93 (0.42, 2.08)		1.05 (0.47, 2.36)	
Per abortion increase	0.99 (0.79, 1.24)	0.91	1.04 (0.83, 1.30)	0.73

*Adjusted for maternal age in years, marital status, smoking status, socio-economic deprivation category and height and stratified by quintile of maternal age
VTE denotes venous thrombo-embolism, HR denotes hazard ratio, CI denotes confidence intervals

Discussion

The main finding of the present study is that there was an increased incidence of IHD in the parents of women who experienced multiple miscarriages prior to their first birth. There was evidence of a "dose-dependent" relationship with a 25% increased risk in the parents of women experiencing 2 losses and a 56% increase in the parents of women experiencing 3 or more losses. The association did not appear to be explained by a confounding effect of the women's age, marital status, smoking status, socio-economic deprivation or height, as adjustment for these factors had no material effect. Neither was there an association between therapeutic abortion and the risk of any type of cardiovascular disease in the women's parents. We interpret these data as supporting the hypothesis that there may be common inheritable risk factors for both miscarriage and IHD.

Many studies have demonstrated that women who experience complications during pregnancy, such as pre-eclampsia, preterm birth and intra-uterine growth restriction, are at increased risk of developing cardiovascular disease in later life.[8-11] We have interpreted these observations as indicating that there are common predisposing factors for pregnancy complications and cardiovascular disease, stating "that occult cardiovascular, microvascular, or hemostatic dysfunction is manifested in pregnancy complications during reproductive years and in overt cardiovascular disease in later life".[12] We recently reported the relationship between late pregnancy complications and family history of cardiovascular disease. We demonstrated that the parents of women who experienced pre-eclampsia, preterm birth or delivery of a small for gestational age infant during pregnancy had an increased incidence of cardiovascular disease.[4] However, a significant proportion of the associations was lost following statistical adjustment for the characteristics of the women at the time of the pregnancy (age, marital status, smoking status, socio-economic deprivation and height).[4] We concluded that there were common risk factors for late complications of pregnancy and cardiovascular disease which demonstrated familial aggregation. The attenuation of the association in multivariate analysis led us to conclude that these were, in whole or in part, environmental in nature. In contrast, in the present analysis, adjustment for the same series of maternal characteristics had no material effect on the association between miscarriage and family history of IHD. Hence, we hypothesize that the most plausible explanation for the association between recurrent miscarriage and family history of IHD is the existence of common genetic or epigenetic risk factors for both conditions. Further research should address whether women with a history of recurrent miscarriage have higher rates of carriage of known genetic predisposing risk factors for IHD. Studies should also address whether they differ in relation to other risk factors, such as hypertension, insulin resistance, dyslipidaemia, elevated high sensitivity C reactive protein and vascular dysfunction, including endothelial dysfunction. It is possible that a history of recurrent miscarriage may be clinically useful in identifying women who would benefit from screening for cardiovascular risk factors.

The lack of association between women's recurrent miscarriage and her parents' experience of VTE is consistent with other recent evidence. A number of studies have suggested that there are associations between inherited and acquired thrombophilia and recurrent miscarriage.[13] However, two recent large-scale studies failed to demonstrated beneficial effects of anti-coagulant treatment on pregnancy outcome among women with recurrent miscarriage.[14;15] These observations suggest that, in a significant proportion of women, recurrent miscarriage is not related to a pro-thrombotic tendency and the current data are consistent with this view. An important caveat to this interpretation is that there were fewer VTE events than IHD. Consequently, the confidence intervals for the associations are also consistent with an association between recurrent losses and family history of VTE of up to a 14% increase per previous miscarriage (Table 4). Similarly, the association with CVD had confidence intervals which were consistent with a comparable relationship to IHD and the negative result should not be interpreted as excluding a significant association.

In the present analysis, we used a Cox proportional hazards model, with age as the time scale, to quantify variation in the incidence of cardiovascular disease in the women's parents. This approach may be counterintuitive, as events in the parents could have either preceded or followed the experience of miscarriages in the daughters. Moreover, it may seem more intuitive to study miscarriage as the "event" with family history of IHD as the exposure. However, all measures of familial association have weaknesses[16] and the approach we employed had two major strengths. First, the analysis of family history of heart disease was limited to the parents. The experience of heart disease in first degree relatives will depend on the number of siblings. If there are inheritable predispositions to miscarriage, it is possible that the number of siblings a woman has would vary according to her propensity to experience miscarriage. By confining analysis to the parents, we overcame this possible source of bias. Second, women who are older are more likely to have older parents. The older the parents, the more likely they are to have experienced disease. Women who experienced multiple miscarriages were older than those who had not (Table 1). These characteristics could, therefore, lead to an association between miscarriage and IHD through confounding by age. However, by modelling IHD in the parents using a Cox model with age as the time scale, we were able to compare the incidence of IHD independently of variation in the parental age. A more conventional indicator of family history of IHD is self-reported history of IHD in a first-degree relative. However, if we had used such a measure in the present analysis, the results would have been vulnerable to biases related to systematic variation in the number of siblings and the age of the women's parents in relation to the primary exposure. Hence, although the current approach to assessing family history is different from many previous studies, the method employed addressed two important potential sources of bias.

The strengths of the present analysis are that we were able to study a large number of women and were able to compare associations between previous miscarriage and therapeutic abortion. Moreover, all definitions were obtained from registries, hence these were not open to bias through selective recall, as could occur in a case control study. However, our study also has a number of weaknesses. The association was relatively modest with an approximate 50% increase in the incidence of IHD in the women's parents. However, the current study was the result of a previously stated hypothesis[3] and the P value for the multivariate analysis was 0.001. Hence, it is very unlikely to be a chance finding. The SMR02 lacked data on the gestational age of previous miscarriage. Hence, we were unable to determine whether the associations were related to first trimester losses, second trimester losses, or both. Furthermore, due to the constraints of the data, we only addressed losses prior to a first pregnancy. Hence, we do not have direct information on women who had losses but no births. Neither do we present information on the association between total number of losses in a woman's life history. Registry based analysis relies on correct coding of both exposures and definitions. Hence, we do not have access to information that allows confirmation of either, such as cotinine assay for smoking status or the results of diagnostic tests for the parental experience of disease. Similarly, we lack information on specific causes of recurrent miscarriage, such as balanced chromosomal translocation in the parents, or diagnosis of antiphospholipid syndrome. Furthermore, as previously discussed in detail,[4] the linkage process favoured matching records from younger and unmarried women. The current cohort is neither a random nor representative sample of the Scottish population. Nevertheless, we have addressed an important question for the first time using a large scale dataset and the results suggest a significant association. Moreover, a previous analyses relating birth weight, pre-eclampsia and preterm birth to the mother's subsequent risk of cardiovascular disease using the same data sources[8] has been replicated in

multiple subsequent studies in many different countries.[9-11]

In conclusion, we found that there was an increased incidence of IHD in the parents of women who experienced multiple miscarriages prior to their first birth. We hypothesize that there are common pathophysiological pathways linking IHD and recurrent miscarriage. This hypothesis makes the prediction that genetic risk factors for IHD will also be associated with an increased risk of recurrent miscarriage.

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Disclosure of interests
None of the authors has any form of conflict of interest in relation to this work.

Contribution to authorship
GS had the idea. GS and JH designed the data linkage. JH performed the data linkage and extracted the data. GS and AW performed the data analysis. GS drafted the paper. All authors critically reviewed the manuscript and approved the final version.

Approvals
The record linkage was approved by the Privacy Advisory Committee of the Information Services Division of NHS Scotland.

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