Caesarean section and risk of unexplained stillbirth in subsequent pregnancy

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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**

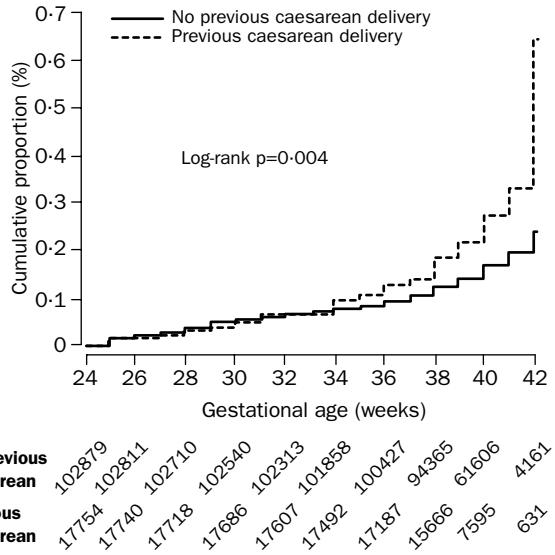

Figure 1: **Cumulative proportion of unexplained stillbirths per week of gestation**

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

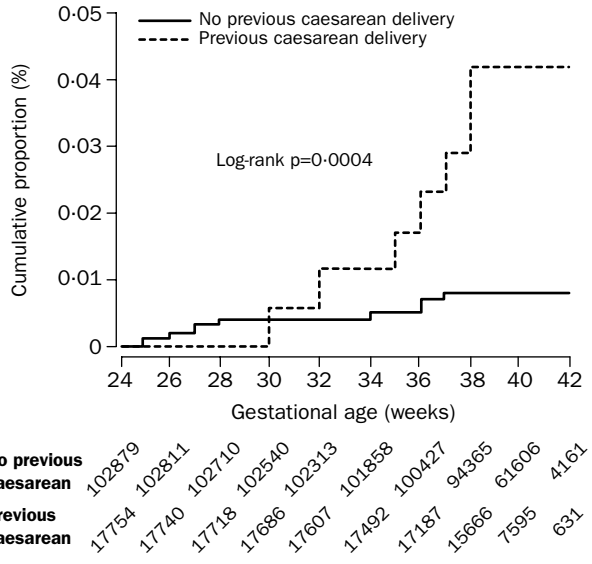

Figure 2: **Cumulative proportion of stillbirths due to maternal disease per week of gestation**

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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