Risk of Recurrent Stillbirth in Subsequent Pregnancies

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Financial Disclosure

Kathleen Lamont was awarded an Elphinstone scholarship from the university of Aberdeen, Scotland. In addition, money from a NHS Grampian endowment fund financed storage of data. Sohinee Bhattacharya reports that money was paid to their institution from the NHS Grampian Endowment fund, Medical Research Scotland, and the Wellcome Trust ISSF fund. Sohinee Bhattacharya's husband has co-authored previous publications based on a similar dataset. He is the Head of School of medicine, medical Sciences and Nutrition at the University of Aberdeen where she is also employed. The other authors did not report any potential conflicts of interest.

The author has confirmed compliance with the journal's requirements for authorship.

Running foot: Recurrent stillbirth

Precis

Compared with women who have a live birth, women who experience a stillbirth in a first pregnancy have a higher risk of stillbirth in any subsequent pregnancy.

Abstract

Objective To compare the prospective risk of stillbirth between women with and without a stillbirth in their first pregnancy.

Methods We conducted a cohort study using perinatal data from Finland, Malta and Scotland. Women who had at least two singleton deliveries were included. The exposed and unexposed cohorts comprised women with a stillbirth and livebirth in their first pregnancy respectively. The risk of stillbirth in any subsequent pregnancy was assessed using a Cox proportional hazards model. Time-to-event analyses were conducted to investigate if first pregnancy outcome had an effect on time to, or the number of pregnancies preceding subsequent stillbirth.

Results The pooled dataset included 1,064,564 women, 6,288 (0.59%) with a stillbirth and 1,058,276 with a live birth in a first pregnancy. Compared to women with a live birth, women with an initial stillbirth were more likely to have a subsequent stillbirth, adjusted hazard ratio (HR) 2.25, 95% CI (1.86 to 2.72). For women with more than two pregnancies the difference in risk of subsequent stillbirth between the two groups increased with the number of subsequent pregnancies. Maternal age <25 or ≥ 40 years, smoking, low socioeconomic status, being single, pre-existing diabetes, preeclampsia, placental abruption or delivery of a growth restricted baby in a first pregnancy were independently associated with subsequent stillbirth. Compared with women with a live birth in the first pregnancy, women with a stillbirth were more likely to have another pregnancy within one year. The absolute risk of stillbirth in a subsequent pregnancy for women with stillbirth and livebirth in a first pregnancy were 2.5% and 0.5% respectively.

Conclusion Compared to women with a live birth in a first pregnancy, women with a stillbirth have a higher risk of subsequent stillbirth irrespective of the number and sequence of the pregnancies. Despite high relative risk, the absolute risk of recurrence was low.

300 Words

Introduction

Results from a systematic review and meta-analysis suggest that previous stillbirth is associated with an increased risk of stillbirth in a subsequent pregnancy.[1] Most studies included in the systematic review looked at first and second pregnancies. Some smaller studies included women with more than two pregnancies and these report conflicting results likely because of low numbers and limited power to demonstrate a statistically significant difference.[2-5]

To investigate the risk of stillbirth recurrence most studies in the literature use retrospective analysis methods, primarily logistic regression models that calculate the odds of having a previous stillbirth accounting for sociodemographic and clinical factors.[1] This approach is unable to predict prospective risk of future pregnancy outcomes at the time of the first stillbirth. Clinically it is important to know prospectively what the risk of a subsequent stillbirth is at the time of the initial stillbirth and identify any modifiable factors that can mitigate that risk. We conducted a large cohort study to investigate how factors including the outcome of a first pregnancy (stillbirth or livebirth), affect the risk of having a stillbirth in any subsequent pregnancy. We hypothesized that compared with women who had a previous live birth; women whose first pregnancy resulted in a stillbirth had an increased risk of stillbirth in any subsequent pregnancy.

Methods

A multi-country registry-based cohort study using individual participant data (IPD) from perinatal databases in Finland, Malta and Scotland was conducted. The study population included all women in each of these countries who had delivered at least two singleton births during the specified timeframe (Finland between 1987 and 2015, Malta 1999 and 2015 and Scotland 1981 and 2015). Because of differences in the definition of stillbirth between countries, the pooled data included singleton live births and stillbirths delivered at 22 or more completed weeks gestation or with a birth weight of 500g (Finland and Malta) and 24 or more completed weeks gestation (Scotland). In each of the participating countries, unique identifiers were used to link pregnancies in the same woman. Women with multiple pregnancies were excluded. Women who had a stillbirth in a first pregnancy formed the exposed cohort; women who had a live birth formed the unexposed cohort. The primary outcome was the occurrence of stillbirth in any subsequent pregnancy.

After obtaining permissions from the data custodians of all three registries a predetermined list of variables was requested and anonymized data were provided. Range and consistency data checks were conducted, inconsistencies discussed with relevant data custodians and clarified and corrected when necessary. Covariates were selected *a priori* based on clinical relevance and directed acyclic graphs. Potential confounders at baseline (at the first pregnancy) included maternal age categorized as (<20, 20-24, 25-29, 30-34, 35-39, ≥40 years), body mass index (BMI), categorized as underweight (<18.5 kg/m^2), normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2) and obese (≥30 kg/m^2), socioeconomic position, smoking status during pregnancy and marital status categorized as married or cohabiting or in a registered partnership (legally affirmed partnership of same or opposite sex partners) and other (never married, separated, divorced, widowed).

The exposed and unexposed groups of women were also compared with regard to occurrence of medical and obstetric conditions in the first pregnancy (defined as the presence of an appropriate International Classification of Diseases (ICD) 9/10 diagnostic code). These included pre-existing diabetes, pre-existing hypertension, anemia, thyroid condition, asthma, urinary tract infection (UTI), epilepsy, threatened miscarriage, gestational diabetes, gestational hypertension, obstetric cholestasis, preeclampsia, placental abruption, placenta previa, antepartum hemorrhage, fetal growth restriction (FGR) and gestational age at birth (defined as completed weeks of gestation) which was categorized as (22-28, 29-32, 33-36, 37-42 and ≥43 weeks' gestation.

The IPD were analysed using a one-step approach, the preferred method for rare outcomes.[7] The proportions of maternal demographic variables, medical and obstetric conditions were compared between the exposed and unexposed cohorts in order to identify potential confounders. Continuous variables were summarised using mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. When the outcome was continuous and normally distributed, the student t-test was used, and the χ^2 test used for categorical variables (Fisher's exact test if the assumptions were not met). All hypothesis tests were two tailed and significance levels were set at $p < 0.05$.

Finland (since 1991) and Scotland provided information on non-smokers, ever or former smokers and smokers, Malta only on non-smokers and smokers. As the Maltese dataset was very small in comparison to the other two it was decided to use all three categories. For socioeconomic position, Finland provided information on the mother's occupational class, Scotland, Carstairs socioeconomic deprivation scores derived from postcode of residence[8] and Malta information on maternal education. Indicators of socioeconomic position all measure aspects of inequality that may have consequences for health. As these tend to be correlated with each, other educational attainment has been used as a proxy measure for socioeconomic status.[9] A composite socioeconomic variable was created and categorized into low and high socioeconomic status. For Finland we categorized upper-white collar workers as high socioeconomic status and white-collar workers, blue-collar workers and others as low socioeconomic status. For Malta, university level education was categorised as high socioeconomic status, post-secondary or secondary education, primary, special or no education, low socioeconomic status. For Scotland, Carstairs categories 1 and 2 were categorised as high socioeconomic status, categories 3,4 and 5, low socioeconomic status.

To conduct time-to-event analysis, an event variable indicating whether the woman had a stillbirth in any subsequent pregnancy, and an indicator for the total number of pregnancies were calculated in each of the datasets. Two "time" variables were also included. The first to examine the interval in years to stillbirth in a subsequent pregnancy, the second to examine the interval in terms of the number of pregnancies to stillbirth in a subsequent pregnancy. Years to stillbirth in a subsequent pregnancy was derived by subtracting year of index pregnancy from the year of the subsequent stillbirth, all other births treated as censored. For each woman, the starting point was taken as the date of the index birth, a stillbirth (exposed group) or a live birth (unexposed group). Not all women in the study will experience the event (subsequent stillbirth). Kaplan-Meier curves were plotted to show the cumulative probability of no subsequent stillbirth for each group. To investigate the effect of independent risk factors multivariable modeling was performed using Cox proportional hazards regression adjusting for first pregnancy outcome (livebirth or stillbirth), maternal age, BMI, marital status, smoking status, socioeconomic status, pre-existing diabetes, pre-existing hypertension, preeclampsia, placental abruption, placenta previa, antepartum hemorrhage, FGR and gestational age at birth. Country was included in the model as a covariate, and for cross-country comparison, Scotland was chosen as the reference category. Adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are presented as are the absolute risk (AR) and the numbers needed to harm (NNH). The AR is the difference in risk of stillbirth in a subsequent pregnancy between women with and without stillbirth in their first. NNH indicates how many women on average need to be exposed to stillbirth in a first pregnancy for one woman to experience a subsequent stillbirth. Violation of the proportional hazards assumption was checked visually by comparing plots of the log of the negative log of the Kaplan-Meier estimates of the survival function versus the log of time.

We used multiple imputation[10] to impute missing values for BMI, smoking status, marital status, socioeconomic status and gestational age at birth. A high proportion of data were missing for BMI and smoking, however we thought adjustment for these was important. Much smaller proportions of data were missing for the other variables. Missing values for these variables were created using multiple imputation by chained equations.[11] Logistic regression was used for imputing binary variables (marital status and deprivation category) and ordinal logistic regression for categorical variables (BMI, maternal age, and gestational age at birth). To improve accuracy of imputed values, year of birth (first pregnancy) was also included as an auxiliary variable. We created 20 imputed datasets[12] that were then combined for pooled estimates.[13] An analysis of complete cases (missing data were coded as "unknown") was also conducted. All statistical analyses were performed using SPSS software, version 24 and Stata version 13.0. Approval was sought and obtained from the relevant authorities in each of the countries (Scotland - Public Benefit and Privacy Panel for Health and Social Care, Ref: 1516-0309; Finland - Finnish Institute for Health and Welfare, No. THL/1719/5.05.00/2015; Malta - Directorate for Health Information and Research Malta, Miriam Gatt August 2016).

Results

A total of 1,064,564 women had both first and subsequent pregnancies in the pooled dataset during the study period. Of these, 6,288 (0.59%) women (2,437/512,267 (0.48%) in Finland, 122/17,624 (0.69%) in Malta and 3,729/534,673 (0.70%) in Scotland), had a stillbirth in a first pregnancy (exposed group), while the remaining 1,058,276 women (509,830 in Finland, 17,502 in Malta and

530,944 in Scotland) had a live birth (unexposed group). Within the study population, 5,697 stillbirths occurred in subsequent pregnancies (2,423 in Finland, 96 in Malta and 3,178 in Scotland). There were 157/6,288 recurrences of stillbirth. For women with stillbirth in a first pregnancy the absolute risk of stillbirth in a subsequent pregnancy was 2.5% as compared to 0.5% for women who had a livebirth; NNH = 50. Over the time span of the data a downward trend was observed in stillbirth rates in Finland, while in Scotland stillbirth rates were fairly static until 2008 when a downward trend was also observed. Stillbirth rates in Malta did not change over time.

Table 1 shows univariable comparisons of maternal demographics and medical and obstetric conditions in the first pregnancy between the two comparison groups. Women in the exposed group were more likely to be younger than 20 or aged 30 and over, be overweight or obese, to smoke during pregnancy, not live with a partner, belong to lower socioeconomic status, have pre-existing diabetes, experience a threatened miscarriage and to develop preeclampsia, placenta previa, placenta abruption or antepartum hemorrhage. Babies born to women in the exposed group were more likely to be male, growth restricted and much more likely to be born preterm. Compared with women in the unexposed group, women in the exposed group were less likely to have anemia or to develop gestational diabetes or gestational hypertension.

A high proportion of data were missing for BMI (81.6%) and smoking (39.2%). For the other imputed variables (marital status, socioeconomic status and gestational age at birth) <10% were missing. We found that women who had a stillbirth were more likely to have missing information. We also found that women who had information missing for BMI, whether they had a live birth, or a stillbirth were also more likely to have information missing on smoking during pregnancy. Compared with women who had a live birth in their first pregnancy, women who had a stillbirth were less likely to attend their first antenatal appointment ≤ 12 weeks' gestation. As information on BMI and smoking is recorded at the first antenatal appointment (between 8 and 12 weeks pregnant), this may provide some explanation why women with a stillbirth were more likely to have missing information. Missing data patterns are presented in Appendix 1, available online at http://links.lww.com/xxx.

Figure 1 shows Kaplan-Meier curves for time to subsequent stillbirth for the exposed and unexposed groups. Figure 2 shows time-to-event analysis for the number of pregnancies to subsequent stillbirth for the exposed and unexposed groups. In Figure 1, the curves show that compared with women who had a live birth in their first pregnancy, women who had a stillbirth were more likely to have a subsequent stillbirth sooner, although in both groups this was still relatively rare. In Figure 2, the curves show that compared with women who had a live birth in their first pregnancy, for women who had a stillbirth, the risk of stillbirth increases with the number of subsequent pregnancies.

Table 2 provides adjusted hazard ratios for stillbirth in a subsequent pregnancy based on first pregnancy outcome and characteristics of the first pregnancy. After controlling for socio-demographic factors and obstetric conditions, stillbirth in a first pregnancy significantly increased the risk of subsequent stillbirth (HR 2.25, 95% CI 1.86 to 2.72). Compared with women in Scotland, women in Finland and Malta were at increased risk of subsequent stillbirth (HR 1.08, 95% CI 1.01 to 1.15 and HR 1.41, 95% CI 1.14 to 1.74, respectively).

Compared with those aged 25-29 years, the risk of subsequent stillbirth was significantly increased if women were <20 years old (HR 1.63, 95% CI 1.49 to 1.77), aged 20-24 (HR 1.25, 95% CI 1.16 to 1.33) or 40 or over (HR 1.68, 95% CI 1.09 to 2.58) at the first pregnancy. Women who smoked (HR 1.12, 95% CI 1.03 to 1.21), did not live with a partner (HR 1.20, 95% CI 1.11 to 1.29) or were of low socioeconomic status (HR 1.14, 95% CI 1.06 to 1.22) in a first pregnancy were also at increased risk of subsequent stillbirth. Pre-existing diabetes (HR 2.42, 95% CI 1.88 to 3.11), preeclampsia (HR 1.27, 95% CI 1.12 to 1.44) and placental abruption (HR 1.41, 95% CI 1.06 to 1.86) in a first pregnancy were all independently associated with subsequent stillbirth when compared to women who did not have these conditions.

Irrespective of a live or a stillbirth, women who had a growth-restricted newborn in their first pregnancy were at significantly increased risk of subsequent stillbirth (HR 1.58, 95% CI 1.39 to 1.81). Compared to women who had first babies born at term (after 37 weeks' gestation), women with babies born preterm (<37 weeks) were at significantly increased risk of subsequent stillbirth, the risk increasing as gestational age of the first birth decreased; HR 1.48, 95% CI 1.33 to 1.65 for women with babies born at 33-36 weeks gestation, HR 2.63, 95% CI 2.22 to 3.12 at 29-32 weeks gestation and HR 2.91, 95% CI 2.37 to 3.58 at 22-28 weeks gestation. Compared with women who did not have these conditions, women who had pre-existing hypertension, placenta previa or antepartum hemorrhage in their first pregnancy were not at increased risk of subsequent stillbirth.

When a complete case analysis was conducted in which missing data were coded as unknown, the interpretation of the results of the Cox model was similar (Appendix 2, available online at http://links.lww.com/xxx).

Discussion

In this large, population-based multi-country cohort we found that women with an initial stillbirth were twice as likely to have a subsequent stillbirth compared with women with a first live birth. For women with more than two pregnancies, the difference in risk of subsequent stillbirth between the two groups increased with the number of subsequent pregnancies. Smoking, being single, low socioeconomic status, diabetes, preeclampsia and placental abruption in a first pregnancy were found to be independent risk factors for subsequent stillbirth. In comparison to women aged 25-29 in their first pregnancy, women under 25 and women 40 and older were at significantly increased risk of subsequent stillbirth. Women whose first pregnancy resulted in the delivery of a growth-restricted or preterm baby, were also at increased risk of having a subsequent stillbirth, the risk increasing with decreasing gestational age at first delivery.

Previous studies have focused on the first and second pregnancies, or first subsequent pregnancy following a stillbirth.[1] This study evaluates the prospective risk of stillbirth in any subsequent pregnancy. As parity increases, a smaller proportion of women contribute to the analysis, particularly in the exposed cohort. Because of this, we did not present stillbirth beyond the fifth pregnancy as the numbers at risk would be too low to be clinically meaningful. Nevertheless the overall pattern remains consistent.

Strengths of this study are the multi-country population-based approach and prospective analysis. Collaborative use of data allowed investigation of a rare outcome such as stillbirth recurrence where large numbers are needed to ensure sufficient statistical power. The cross-national design ensures generalizability to other high-income countries with similar health care structure and low stillbirth rates. Limitations include transition from ICD-9 to ICD-10 codes and possible coding and misclassification errors, for example delay in detecting stillbirth and subsequent intrauterine retention can result in overestimation of FGR, residual confounding and the large amount of data that were missing on key confounding variables such as maternal BMI. We used multiple imputation to maximize efficiency and compared results with a complete case analysis in which missing data were coded as unknown; results were similar. Lack of data on race and ethnicity and our inability to link the dataset to cause of death data are additional limitations.

As in previous research we found that smoking,[14,15] not living with a partner,[4] and low socioeconomic status[16] were independent risk factors for stillbirth in a subsequent pregnancy. While maternal obesity is known to increase the risk of stillbirth,[15] we did not find BMI to be independently associated with an increased risk of stillbirth in a subsequent pregnancy. In high-income countries, smoking and obesity during pregnancy are modifiable risk factors that urgently need addressing.[15,17,18] Evidence shows that smoking cessation interventions can be effective.[19] Effectiveness of interventions for reducing weight in obese pregnant women is less clear.[20] Similarly a meta-narrative review [21] found very little research investigating what might work to reduce socioeconomic inequalities and stillbirth in the UK. Interventions targeted to reduce stillbirth in specific social groups or communities and studies that explore the interactions between risk factors within specific groups are needed.[21]

As found in other studies, placental abruption, FGR and diabetes were independently associated with subsequent stillbirth.[22,23] Previous research[23,24] has found that women with preterm birth, delivery of a small for gestational age at birth infant and preeclampsia in an initial pregnancy are at increased risk of stillbirth in a second pregnancy. These risk factors are confirmed in the current study to hold true for any subsequent stillbirth.

The tendency for preterm birth, preeclampsia, placental abruption and fetal growth restriction to recur, suggests common causal factors for stillbirth related to impaired placental function,[5,23,24,25,26] and the possibility that these conditions predispose to each other.[27] Lean and colleagues[28,29] provide evidence for a link between advanced maternal age and placental dysfunction. Older women are also more susceptible to FGR and placental dysfunction may be a potential mechanism.[29] Further studies are required to determine the factors in the aging environment that are altered, and how they relate to placental function. Development of effective screening methods of the placenta to detect potential problems during pregnancy and targeted interventions may help prevent stillbirth.[30]

In conclusion, women with a stillbirth in their first pregnancy have more than double the risk of stillbirth in any subsequent pregnancy. Despite significantly raised relative risk, the absolute risk remains low. Better screening for placental dysfunction may help identify women at higher risk of stillbirth. Findings from this study also highlight the importance of counseling women regarding modifiable risk factors in order to improve pregnancy outcomes following a stillbirth.

Table 1 Comparison of first pregnancy maternal characteristics between women with a live birth and women who had a stillbirth

Pregnancy and Maternal Characteristics	Stillbirth (n = 6,288) n (%)	Livebirth (n = 1,058,276) n (%)	*p**
Maternal age (years) Mean SD	26.10 (5.66)	25.60 (4.93)	**<.001**
Younger than 20	850 (13.5)	129,878 (12.3)	
20-24	1,745 (27.8)	313,549 (29.6)	
25-29	1,935 (30.8)	383,531 (36.2)	
30-34	1,241 (19.7)	188,528 (17.8)	
35-39	458 (7.3)	39,985 (3.8)	
40 or older	59 (0.9)	2,805 (0.3)	
BMI (kg/m^2) Median (IQR)	24.24 (21.46-28.71)	23.14 (20.96-26.23)	**<.001**
Underweight (<18.5)	33 (3.2)	7,950 (3.7)	
Normal (18.5 to 24.9)	546 (53.0)	135,884 (63.2)	
Overweight (25 to 29.9)	248 (24.1)	46,934 (21.8)	
Obese (≥30)	203 (19.7)	24,171 (11.2)	
Not known	5,258	843,337	
Marital Status			**<.001**
Married or cohabiting or Legal	3,831 (68.8)	751,567 (76.5)	
partnership	1,739 (31.2)	230,648 (23.5)	
Other	718	76,061	
Not known			
Smoking status during pregnancy			**<.001**
Did not smoke	2,413 (69.6)	558,283 (79.3)	
Smoked	873 (25.2)	108,873 (15.5)	
Stopped or former smoker	181 (5.2)	36,894 (5.2)	
Not known	2,821	354,226	
Socioeconomic status			**<.001**
High	1,242 (20.3)	247,639 (23.9)	
Low	4,879 (79.7)	788,315 (76.1)	
Not known	167	22,322	
1st antenatal visit ≤ 12 weeks			**<.001**
Yes	3,602 (65.5)	714,282 (70.9)	
No	1,895 (34.5)	293,340 (29.1)	
Not known	791	50,654	
Pre-existing diabetes			
No	6,203 (98.6)	1,053,614 (99.6)	
Yes	85 (1.4)	4,662 (0.4)	**<.001**
Pre-existing hypertension			
No	6,202 (98.6)	1,046,276 (98.9)	
Yes	86 (1.4)	12,000 (1.1)	0.080
Anemia			
No	6,054 (96.3)	992,533 (93.8)	
Yes	234 (3.7)	65,743 (6.2)	**<.001**
Thyroid condition			

No	6,276 (99.8)	1,056,775 (99.9)	
Yes	12 (0.2)	1,501 (0.1)	0.389
Asthma			
No	6,251 (99.4)	1,051,596 (99.4)	
Yes	37 (0.6)	6,680 (0.6)	0.728
UTI			
No	6,164 (98.0)	1,036,005 (97.9)	
Yes	124 (2.0)	22,271 (2.1)	0.493
Epilepsy			
No	6,266 (99.7)	1,054,633 (99.7)	
Yes	22 (0.3)	3,643 (0.3)	1.00
Threatened miscarriage			
No	6,158 (97.9)	1,047,768 (99.0)	
Yes	130 (2.1)	10,508 (1.0)	**<.001**
Gestational diabetes			
No	6,219 (98.9)	1,042,624 (98.5)	
Yes	69 (1.1)	15,652 (1.5)	**0.014**
Gestational hypertension			
No	6,198 (98.6)	1,037,201 (98.0)	
Yes	90 (1.4)	21,075 (2.0)	**0.002**
Obstetric cholestasis			
No	6,276 (99.8)	1,054,798 (99.7)	
Yes	12 (0.2)	3,478 (0.3)	0.073
Preeclampsia			
No	6,044 (96.1)	1,021,785 (96.6)	
Yes	244 (3.9)	36,491 (3.4)	0.064
Placental abruption			
No	5,755 (91.5)	1,055,271 (99.7)	
Yes	533 (8.5)	3,005 (0.3)	**<.001**
Placenta previa			
No	6,255 (99.5)	1,055,548 (99.7)	
Yes	33 (0.5)	2,728 (0.3)	**<.001**
Antepartum hemorrhage			
No	6,087 (96.8)	1,041,092 (98.4)	
Yes	201 (3.2)	17,184 (1.6)	**<.001**
FGR			
No	5,937 (94.4)	1,035,628 (97.9)	
Yes	351 (5.6)	22,648 (2.1)	**<.001**
Cord or hand prolapse			
No	6,191 (98.5)	1,051,789 (99.4)	
Yes	97 (1.5)	6,487 (0.6)	**<.001**
PROM			
No	6,207 (98.7)	1,034,145 (97.6)	
Yes	81 (1.3)	24,131 (2.3)	**<.001**
Mode of delivery			**<.001**
Unassisted vaginal	4,715 (75.9)	703,887 (66.6)	
Vaginal breech	781 (12.6)	4,928 (0.5)	
Forceps	207 (3.3)	92,447 (8.7)	
Vacuum	60 (1.0)	75,491 (7.1)	
Elective cesarean	33 (0.5)	39,812 (3.8)	
Intrapartum cesarean	413 (6.7)	140,146 (13.3)	
Not known	79	1,565	
Gestation at birth (weeks)			**<.001**
22-28	1,569 (25.1)	3,651 (0.3)	

29-32 33-36 37-42 ≥43 Not known	1,109 (17.7) 1,317 (21.0) 2,238 (35.8) 24 (0.4) 31	7,303 (0.7) 45,137 (4.3) 995,576 (94.4) 3,339 (0.3)3,270	
Neonatal Sex Male Female Undetermined or not specified	 3,382 (54.1) 2,864 (45.9) 42	 543,622 (51.4) 514,626 (48.6) 28	**<.001**

***Statistically significant values are shown in bold**

Figure 1 Kaplan Meier plot of time to stillbirth in any subsequent pregnancy by outcome of index pregnancy

Figure 2 Kaplan Meier plot of the number of subsequent pregnancies to stillbirth in any subsequent pregnancy by outcome of index pregnancy

Table 2 Adjusted HRs for stillbirth in any subsequent pregnancy by first pregnancy outcome and characteristics in women in Finland 1987-2015, Malta 1999-2015 and Scotland 1981-2015

Maternal and obstetric Characteristics	**HR**	**95%CI**	***P**** **(Cox regression)**
1st pregnancy outcome			**<.001**
Stillbirth	2.25	1.86 to 2.72	
Livebirth	1.00		
Country			
Scotland	1.00		
Finland	1.08	1.01 to 1.15	**0.026**
Malta	1.41	1.14 to1.74	**0.001**
Maternal age (years)			
<20	1.63	1.49 to 1.77	**<.001**
20-24	1.25	1.16 to 1.33	**<.001**
25-29	1.00		
30-34	1.06	0.97 to1.15	0.193
35-39	1.08	0.93 to 1.27	0.317
≥40	1.68	1.09 to 2.58	**0.019**
Marital Status			
Married or cohabiting or legal partnership	1.00		
Other	1.20	1.11 to1.29	**<.001**
Smoking status			
Did not smoke	1.00		
Smoked during pregnancy	1.12	1.03 to1.21	**0.006**
Stopped or former smoker	0.98	0.83 to1.14	0.754
Socioeconomic status			
High	1.00		
Low	1.14	1.06 to 1.22	**<.001**
Pre-existing diabetes			
No	1.00		
Yes	2.42	1.88 to 3.11	**<.001**
Pre-existing hypertension			
No	1.00		
Yes	1.04	0.83 to 1.31	0.746
Preeclampsia			
No	1.00		
Yes	1.27	1.12 to 1.44	**<.001**
Placental abruption			
No	1.00		
Yes	1.41	1.06 to1.86	**0.016**
Placenta previa			
No	1.00		
Yes	1.13	0.73 to 1.75	0.595
Antepartum hemorrhage			
No	1.00		
Yes	0.98	0.81 to 1.18	0.811
FGR			
No	1.00		
Yes	1.58	1.39 to1.81	**<.001**
Gestational age at birth (weeks)			
22-28	2.91	2.37 to3.58	**<.001**

29-32	2.63	2.22 to 3.12	**<.001**
33-36	1.48	1.33 to1.65	**<.001**
37-42	1.00		
≥43	0.89	0.56 to 1.42	0.630

***Statistically significant values are shown in bold**

References

1. Lamont K, Scott NW, Jones GT, Bhattacharya S. Risk of recurrent stillbirth: systematic review and meta-analysis. BMJ 2015;350:h3080.

2. Robson S, Chan A, Keane RJ, Luke CG. Subsequent birth outcomes after an unexplained stillbirth: preliminary population-based retrospective cohort study. Aust NZ J Obstet Gynaecol 2001;41(1):29-3

3. Measey MA, Tursan d'Espaignet E, Charles A, Douglass C. Unexplained fetal death: are women with a history of fetal loss at higher risk? Aust N Z J Obstet Gynaecol 2009; 49(2):151-157.

4. Stillbirth Collaborative Research Network Writing Group. Association between stillbirth and risk factors known at pregnancy confirmation. JAMA 2011;14;306(22):2469-2479.

5. Ofir K, Kalter A, Moran O, Sivan E, Schiff E, Simchen MJ. Subsequent pregnancy after stillbirth: obstetrical and medical risks. J Perinat Med 2013;41(5):543-548.

6. Man J, Hutchinson JC, Ashworth M, Heazell AE, Levine S, Sebire NJ. Effects of intrauterine retention and postmortem interval on body weight following intrauterine death: implications for assessment of fetal growth restriction at autopsy. Ultrasound Obstet Gynecol 2016; 48: 574-578.

7. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. J Clin Epidemiol 2008;61(1):41-51.

8. McLoone P, Boddy FA. Deprivation and mortality in Scotland, 1981 and 1991. BMJ 1994;309(6967):1465-1470.

9. Blumenshine P, Egerter S, Barclay C, Cubbin C, Braveman P. Socioeconomic Disparities in Adverse Birth Outcomes. Am J Prev Med 2018;39(3):263-272.

10. Clark TG, Altman DG. Developing a prognostic model in the presence of missing data: an ovarian cancer case study. J Clin Epidemiol 2003;56(1):28-37.

11. Royston P, White IR. Multiple Imputation by Chained Equations (MICE): Implementation in Stata. Journal of Statistical Software 2011;45(4).

12. White IR, Patrick R, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statist Med 2011 02/20; 2018;30(4):377-399.

13. Rubin DB. *Multiple Imputation for Nonresponse in Surveys, Wiley Series in Probability and Statistics*. New York: Wiley; 1987.

14. Hogberg L, Cnattingius S. The influence of maternal smoking habits on the risk of subsequent stillbirth: is there a causal relation? BJOG 2007;114:699-704.

15. Flenady V, Koopmans L, Middleton P, Frøen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet 2011;377(9774):1331-1340.

16. Stephansson O, Dickman PW, Johansson A, Cnattingius S. The influence of socioeconomic status on stillbirth risk in Sweden. Int J Epidemiol 2001;30(6):1296-1301.

17. Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M, et al. Stillbirths: recall to action in high-income countries. Lancet 2016,387 (10019): 691-702.

18. Yao R, Ananth CV, Park BY, Pereira L, Plante LA; Perinatal Research Consortium. Obesity and the risk of stillbirth: a population-based cohort study. Am J Obstet Gynecol 2014;210(5):457.e1-457.e4579.

19. Chamberlain C, O'Mara-Eves A, Oliver S, Caird JR, Perlen SM, Eades SJ, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev 2017;2:CD001055

20. Furber CM, McGowan L, Bower P, Kontopantelis E, Quenby S, Lavender T. Antenatal interventions for reducing weight in obese women for improving pregnancy outcome. Cochrane Database of Systematic Reviews 2013, Issue 1.

21. Kingdon C, Roberts D, Turner MA, et al. Inequalities and stillbirth in the UK: a meta-narrative review BMJ Open 2019;9**:**e029672

22. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ 2013;346:f108

23. Smith GC, Shah I, White IR, Pell JP, Dobbie R. 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. Am J Epidemiol 2007;15;165(2):194-202.

24. Surkan PJ, Stephansson O, Dickman PW, Cnattingius S. Previous pre-term and small-for-gestational age births and the subsequent risk of stillbirth. N Engl J Med. 2004;358(8):777-785.

25. Monari F, Pedrielli G, Vergani P, Pozzi E, Mecacci F, Serena C, et al. Adverse Perinatal Outcome in Subsequent Pregnancy after Stillbirth by Placental Vascular Disorders. PloS one 2016; 11(5):e0155761; e0155761-e0155761.

26. Graham N, Stephens L, Johnstone ED, Heazell AEP. Can information regarding the index stillbirth determine risk of adverse outcome in a subsequent pregnancy? Findings from a single center cohort study. Acta Obstet Gynecol Scand. 2021; 00: 1-10.

27. Wikstrom AK, Stephansson O, Cnattingius S. Previous preeclampsia and risks of adverse outcomes in subsequent nonpreeclamptic pregnancies. Am J Obstet Gynecol 2011; 204: 148–50.

28. Lean SC, Derricott H, Jones RL, Heazell AEP. Advanced maternal age and adverse pregnancy outcomes: A systematic review. PLoS ONE 2017;12(10): e0186287.

29. Lean S, Heazell A, Dilworth M, Mills T, Jones R. Placental Dysfunction Underlies Increased Risk of Fetal Growth Restriction and Stillbirth in Advanced Maternal Age Women. Scientific reports 2017; 7(1):9677; 9677-9677.

30. Heazell AE, Whitworth MK, Whitcombe J, Glover SW, Bevan C, Brewin J. et al. Research priorities for stillbirth: process overview and results from UK Stillbirth Priority Setting Partnership. Ultrasound Obstet Gynecol. 2015.