

Obstetric outcomes subsequent to intrauterine death in the first pregnancy

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Objective To compare obstetric outcomes in the pregnancy subsequent to intrauterine death with that following live birth in first pregnancy.

Design Retrospective cohort study.

Setting Grampian region of Scotland, UK.

Population All women who had their first and second deliveries in Grampian between 1976 and 2006.

Methods All women delivering for the first time between 1976 and 2002 had follow up until 2006 to study their next pregnancy. Those women who had an intrauterine death in their first pregnancy formed the exposed cohort, while those who had a live birth formed the unexposed cohort.

Main outcome measures Maternal and neonatal outcomes in the second pregnancy, including pre-eclampsia, placental abruption, induction of labour, instrumental delivery, caesarean delivery, malpresentation, prematurity, low birthweight and stillbirth.

Results The exposed cohort ($n = 364$) was at increased risk of pre-eclampsia (OR 3.1, 95% CI 1.7–5.7); placental abruption (OR 9.4, 95% CI 4.5–19.7); induction of labour (OR 3.2, 95% CI 2.4–4.2); instrumental delivery (OR 2.0, 95% CI 1.4–3.0); elective (OR 3.1, 95% CI 2–4.8) and emergency caesarean deliveries (OR 2.1, 95% CI 1.5–3.0); and prematurity (OR 2.8, 95% CI 1.9–4.2), low birthweight (OR 2.8, 95% CI 1.7–4.5) and malpresentation (OR 2.8, 95% CI 2.0–3.9) of the infant as compared with the unexposed cohort ($n = 33\ 715$). The adjusted odds ratio for stillbirth was 1.2 and 95% CI 0.4–3.4.

Conclusion While the majority of women with a previous stillbirth have a live birth in the subsequent pregnancy, they are a high-risk group with an increased incidence of adverse maternal and neonatal outcomes.

Keywords Intrauterine death, obstetric outcome, stillbirth, subsequent pregnancy.

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Introduction

Pregnancy carries with it a degree of anxiety in the majority of women, even those who have had a positive pregnancy experience in the past. Stillbirth rates in Scotland in 2005 were 5.3 per 1000 births.¹ Pregnancy following an experience of intrauterine death does not only induce fear of an adverse outcome in the minds of women and their carers, but also might in fact confer greater risk to the pregnancy, although the evidence on this is conflicting.

In order to fully inform our women and healthcare providers regarding expected outcomes of future pregnancies and level of antenatal care following stillbirth, our aim was to conduct a retrospective study of the affected local population. This provided us with relevant information in terms of

problems to anticipate among our own population, but was also a source of reassurance from relatively positive outcomes. We felt that it was necessary to add to the current body of data as there are relatively few studies of a similar design published to date. Information regarding outcomes after unexplained intrauterine death is of particular interest, and these women formed almost half of our exposed cohort.

A search of Ovid Medline database using search terms 'stillbirth' OR 'intrauterine death' and 'obstetric/pregnancy/perinatal outcomes' showed a limited number of studies, especially those that are population based, looking at obstetric and neonatal complications in pregnancies following intrauterine death. While most studies have reported increased rates of prematurity, placental abruption, low birthweight and medical intervention to deliver in pregnancies following

stillbirth,^{2–5} others have found no such increase.⁶ The risk of recurrence of stillbirth has been reported to be increased by two- to ten-fold,^{7–10} while other studies have not demonstrated this increase.^{2,3,5,6} Studies on outcomes after stillbirth have included cohorts with varying inclusion criteria from those where there is any previous history of stillbirth of any cause, irrespective of parity,^{2,3} to case–control matched cohorts for age and parity,⁶ to only low-risk women with unexplained stillbirth.¹⁰

The Aberdeen Maternity and Neonatal Databank (AMND) provides details of all pregnancies within a well-defined local geographical area with a fairly stable population, dating back to the 1950s.¹¹ Details of outcomes and complications for every pregnancy are recorded, including miscarriage, pre-eclampsia in varying severities, antepartum haemorrhage (APH) of various causes, gestation at delivery and causes of intrauterine death in accordance with ICD-9 (ninth revision by the World Health Organization) definitions. This large database therefore provides the unique opportunity to study the effect of stillbirth on subsequent reproductive performance.

In this study, we aimed to compare pregnancy outcomes in two cohorts in their second pregnancy (who were therefore matched for parity): those who had a stillbirth in their first pregnancy, with those who had a live birth in their first pregnancy, to test the hypothesis that stillbirth in an initial pregnancy predisposes women to adverse obstetric outcomes in the next pregnancy.

Methods

This was a retrospective cohort study. The subjects were women who delivered their first singleton babies between 1976 and 2002 inclusive, and subsequently became pregnant again by 2006 inclusive. The exposed cohort had an intrauterine death in the first pregnancy, while the comparison group delivered a live infant in the initial pregnancy.

AMND was used to provide details of the subjects' pregnancies and socio-demographic details. To be included in the 'exposed' group, a 'pregnancy outcome' would have to be coded as 'stillbirth', rather than live birth or neonatal death. To be coded as 'stillbirth', the intrauterine death must have been diagnosed after 20 weeks of gestation and before delivery. All causes of intrauterine death were included in the main analysis. Causes of stillbirth are recorded in the databank, in accordance with ICD-9 definitions of disease.

Social and demographic factors are recorded in the databank, with age, social class, body mass index (BMI) (kg/m²) and smoking status being considered in this study. Age is coded as a continuous variable in the AMND in complete years at the time of delivery. This variable is 100% complete. Social class is based on the women's partners' occupations at the time of the pregnancy and is categorised according to the registrar general's classification for 1951. Women's own social class is also

coded according to the same classification system, but shows less of a distribution, most women tending to belong to non-manual class III. For single women, where husband/partner's social class is unavailable, the women's own social class is used for analysis. The BMI at the time of the first antenatal booking visit is calculated by dividing the weight recorded at the time of the visit by the square of the height recorded at the same time. Smoking habits are coded according to self-reported number of cigarettes smoked per day and was recoded into a binary variable 'smokers' or 'nonsmokers' for ease of analysis.

Outcome variables studied included occurrence of pre-eclampsia, which is recorded in the data set as 'albuminuric hypertension' of varying degrees, this was recoded to include all women of moderate and severe pre-eclampsia plus eclampsia as an individual variable. Antepartum haemorrhage is coded as either abruption, placenta praevia or 'other APH'. These were recoded into individual variables. Method of delivery is coded as spontaneous vaginal delivery, varying types of instrumental deliveries, assisted breech, destructive or caesarean deliveries. The total number of caesarean deliveries was recoded into a separate variable, while all types of instrumental delivery were grouped together and recoded as one variable. A variable exists as 'type of labour' including, 'spontaneous', 'induced' and 'elective section' which were recoded as separate variables.

Perinatal outcomes included gestational age at delivery, which was simply recoded from number of weeks to those less than 37 weeks and those less than 34 weeks, as two separate variables under the headings 'preterm' and 'very preterm'. Both ultrasound (USG) as well as self-reported last menstrual period dates have been used in the database to record gestational age. Since 1986, when USG was routinely used for dating, this is used to record the gestational age, while prior to this it was carried out by dates alone. Birth-weight was recoded from absolute values, to those more or less than 2500 g as a binary variable.

Statistical analyses were conducted using Statistical Package for Social Scientists (SPSS v 14.0; SPSS Inc., Chicago, IL, USA). Pregnancy outcomes were compared using univariate and multivariate statistical analysis. Continuous variables were compared using Student's *t* test for normally distributed variables and Mann–Whitney test for nonparametric variables. Categorical variables were tested by means of the chi-square test. Multivariate analysis was conducted on each outcome using binary logistic regression (backward likelihood ratio method). Crude and adjusted odds ratios with 95% CI were calculated. Statistical significance was set at a *P* value of 0.05. All odds ratios calculated were adjusted for BMI, marital status, husband/partner's social class, smoking status, interpregnancy interval and year of delivery. Induced labour was also adjusted for pre-eclampsia and abruption. Instrumental delivery and caesarean delivery were also adjusted for pre-eclampsia, malpresentation and induced labour. Preterm

delivery was additionally adjusted for pre-eclampsia, antepartum haemorrhage, induced labour and previous preterm delivery; while malpresentation was adjusted for preterm delivery. Stillbirth was also adjusted for pre-eclampsia, abruption, preterm delivery and low birthweight, and low birthweight was adjusted for pre-eclampsia, abruption, preterm delivery and sex of baby.

Missing data: Data on smoking status were available for only 75% of subjects. Moreover, the antenatal booking weight was missing in 20.9% of women for whom the BMI could not be calculated. However, there was no bias detected in the missing data towards one or other of the comparison groups, therefore, data were analysed excluding the women with missing variables.

Results

There were 364 women who had had a stillbirth in their first pregnancy and returned with a second pregnancy. These formed the exposed cohort, while 33 715 women who had experienced an initial live birth formed the comparison group.

The cause distribution of stillbirth in the first pregnancy is presented in Figure 1, and a comparison of the socio-demographic characteristics in the exposed and unexposed cohorts in Table 1. There was no statistically significant difference

Cause distribution of stillbirths in primigravidae 1976–2002

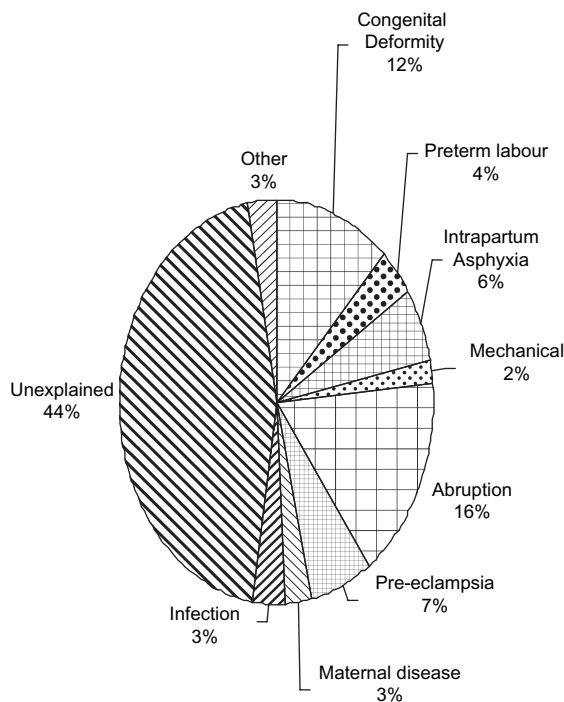


Figure 1. Cause distribution of stillbirths in primigravidae 1976–2002.

between the mean ages of the two groups. BMI was significantly different with the stillbirth group having a higher median BMI (24.4 [IQR {interquartile range} 5.8] versus 23.6 [IQR 4.7]). The exposed cohort was less likely to be married or cohabiting (295 [81%] versus 28 731 [85.2%]), and less likely to belong to a higher social class (I/II) (44 [12.1%] versus 6267 [18.6%]). The stillbirth group were much more likely to be smokers {149 (53.8%) versus 9698 (38.1%)} than the comparison group. The mean interpregnancy interval differed in the two groups of women (2.0 [SD 0.2] years versus 3.2 [SD 0.1]).

Obstetric complications in the two groups are compared and presented in Table 2. The exposed cohort was at increased risk of pre-eclampsia (adjusted OR 3.1, 95% CI 1.7–5.7) and placental abruption (adjusted OR 9.4, 95% CI 4.5–19.7). The type of labour was more likely to be induced (adjusted OR 3.2, 95% CI 2.4–4.2) and result in elective caesarean delivery (adjusted OR 3.1 95% CI 2–4.8). The mode of delivery was more likely to be instrumental (adjusted OR 2.0 95% CI 1.4–3.0) or by caesarean (adjusted OR 2.1 95% CI 1.5–3.0). Risk of prematurity at less than 37 weeks of gestation was increased (adjusted OR 2.8 95% CI 1.9–4.2) in the exposed cohort, low birthweight (adjusted OR 2.8, 95% CI 1.7–4.5) and malpresentation were also more common (adjusted OR 2.8 95% CI 2.0–3.9) in the exposed group. There were more stillbirths in the exposed group (1.4% as compared with 0.5%); however, this was statistically insignificant when adjusted for confounders (OR 1.2, 95% CI 0.4–3.4).

Discussion

Our results from this study demonstrate that intrauterine fetal death in an initial pregnancy increases obstetric and perinatal complication rates in a subsequent pregnancy. In keeping with other studies,^{2–5} the results show that the risk of low birthweight, prematurity, placental abruption and intervention at delivery are more common and suggest that pre-eclampsia and malpresentation may be significantly more common following a history of stillbirth.

Risk factors for stillbirth include extremes of age, smoking and being overweight.^{12–15} The risk associated with increased maternal age and BMI is particularly important as these factors are becoming increasingly prevalent. In our study, we did not demonstrate a difference in mean maternal age between the two groups, perhaps because of a balance being struck by increased incidence at each end of the reproductive age spectrum. Our findings regarding risk associated with raised BMI and smoking status agree with most published research.

Known causes of stillbirth include, among many others, fetal anomalies, fetal hydrops, pre-eclampsia and other maternal disease. These are factors that may recur or persist during a second pregnancy. Reports, however, suggest that 12–50% of all stillbirths may remain unexplained after investigation.^{16–19}

Table 1. Comparison of characteristics between women with and without a live birth in their first pregnancy

Characteristics*	Previous stillbirth <i>n</i> = 364	Previous live birth <i>n</i> = 33 715	<i>P</i> value***
Age at pregnancy event (years)	24.4 (5.0)	24.9 (4.6)	0.08
BMI (kg/m ²)	24.4 (5.8)	23.6 (4.7)	< 0.001
Married or cohabiting	295 (81%)	28 731 (85.2%)	0.03
Husband/partner's social class (1/2)	44 (12.1%)	6267 (18.6%)	0.001
Smokers**	149 (53.8%)	9698 (38.1%)	0.001
Interpregnancy interval (years)	2.0 (0.2)	3.2 (0.1)	< 0.001

*Expressed as mean (SD), median (IQR) or number (%).

**Refers to available data (24% data were missing).

***Statistically significant values are shown in bold.

There is conflicting evidence in the literature on the risk of recurrence of stillbirth. Some studies have not demonstrated an increased recurrence risk of subsequent stillbirth, but this has mostly been with cohorts where the previous stillbirth has been unexplained.^{2,5,6} Sharma *et al.* (2007)¹⁰ did report the risk of recurrence of stillbirth in the second pregnancy to be almost six times higher in women with a stillbirth in their first pregnancy as compared with those with a first pregnancy live birth. Their cohorts, however, only included low-risk women (age <35 years, absence of smoking) and included stillbirths from all causes (apart from those due to congenital anomalies),

including those where maternal conditions like diabetes and pre-eclampsia might have contributed to the outcome. In our cohort, unexplained stillbirths accounted for 44% of all stillbirths. While the unadjusted odds ratio for recurrence of stillbirth was significantly increased in the exposed cohort, when adjusted for pre-eclampsia, abruption, preterm delivery and low birthweight this did not show a significant difference. This result might be in keeping with those from previous studies that do suggest that there is an overall increased risk of recurrence of stillbirth,^{2,5,9,10} but not perhaps when the previous stillbirth is unexplained. It could also be due to our exposed

Table 2. Risk of subsequent obstetric complications in women with a stillbirth in their first pregnancy

Complications	Previous stillbirth <i>n</i> = 364, <i>n</i> (%)	Previous live birth <i>n</i> = 33 715, <i>n</i> (%)	<i>P</i> value*	Unadjusted OR (95% CI)	Adjusted OR** (95% CI)	<i>P</i> value (adjusted)*
Pre-eclampsia	20 (5.7)	769 (2.3)	0.001	2.6 (1.6–4.1)	3.1 (1.7–5.7)	0.001
Placental abruption	12 (3.3)	136 (0.4)	< 0.001	8.4 (4.6–15.3)	9.4 (4.5–19.7)	< 0.001
Placenta praevia	2 (0.5)	117 (0.3)	0.52	1.59 (0.4–6.4)		
Other APH	31 (8.5)	2359 (7.0)	0.26	1.23 (0.9–1.79)		
Induced labour***	180 (49.5)	7139 (21.2)	< 0.001	3.64 (2.9–4.5)	3.2 (2.4–4.2)	< 0.001
Instrumental delivery****	48 (13.2)	2151 (6.4)	< 0.001	2.3 (1.6–3.0)	2.0 (1.4–3.0)	< 0.001
Caesarean section****	121 (33.2)	5041 (15.0)	< 0.001	2.8 (2.3–3.5)	2.1 (1.5–3.0)	< 0.001
Elective C-section****	71 (19.5)	2919 (8.7)	< 0.001	2.6 (2.0–3.3)	3.1 (2.0–4.8)	< 0.001
Preterm delivery*****						
< 34 weeks	4 (1.1)	226 (0.7)	0.32	1.6 (0.6–4.5)		
< 37 weeks	66 (18.1)	1895 (5.6)	< 0.001	3.7 (2.8–4.9)	2.4 (1.7–3.4)	< 0.001
Malpresentation*****	81 (22.3)	2931 (8.7)	< 0.001	3.0 (2.3–3.9)	2.8 (2.0–3.9)	< 0.001
Stillbirth*****	5 (1.4)	179 (0.5)	0.03	2.6 (1.1–6.4)	1.2 (0.4–3.4)	0.8
Neonatal death	1 (0.3)	143 (0.4)	0.6	0.7 (0.1–4.6)		
Birthweight <2500 g*****	66 (18.1)	1701 (5.0)	< 0.001	4.2 (3.2–5.5)	2.8 (1.7–4.5)	< 0.001

*Statistically significant values are shown in bold.

**All odds ratio adjusted for BMI, marital status, husband/partner's social class and smoking, interpregnancy interval and year of delivery.

***Induced labour also adjusted for pre-eclampsia and abruption.

****Instrumental delivery and caesarean section also adjusted for pre-eclampsia, malpresentation and induced labour.

*****Preterm delivery also adjusted for pre-eclampsia, antepartum haemorrhage, induced labour and previous preterm delivery.

*****Malpresentation also adjusted for preterm delivery.

*****Stillbirth also adjusted for pre-eclampsia, abruption, preterm delivery and low birthweight.

*****Lowbirthweight also adjusted for pre-eclampsia, abruption, preterm delivery and sex of baby.

cohort not being large enough to demonstrate a statistically significant difference.

The findings of an increased incidence of pre-eclampsia, low birthweight and placental abruption in the exposed cohort in a subsequent pregnancy might reflect an underlying impaired placental function and development that might have existed even in the first pregnancy, albeit subclinically and undetectable by investigations, contributing to the stillbirth. It is also in keeping with findings from recent studies that show that the risk of subsequent stillbirth is increased even with previous live birth where the pregnancy has been complicated by pre-eclampsia and small-for-gestational-age birth.^{20,21}

The definition of stillbirth used in the AMND includes those occurring after 20 weeks of gestation. This is likely to produce overlap with studies looking at outcomes following mid-trimester fetal loss. One such study showed a poor prognosis for the second pregnancy following loss at 13–24 weeks,²² including a 5% stillbirth rate. This may suggest an increased risk with a history of mid-trimester loss when compared with previous third-trimester loss. Conversely, Sharma *et al.* (2007)¹⁰ have shown that previous stillbirth conferred greater risk for subsequent early (fetal death between 20 and 28 weeks) than late stillbirths (>29 weeks).

The strengths of our study include the fact that information is recorded in the AMND as and when the obstetric events occur, thereby minimising recall bias. Stringent coding criteria and consistency checks are in place adding to the reliability of the data. The data are collected from a geographically defined area making it population based and therefore more generalisable. So far there are only a few population-based studies on outcomes after previous stillbirth,^{9,10} and this study could add to that body of evidence. Our data span 30 years and during this time changes in clinical practice are bound to have occurred, especially in relation to monitoring of fetal and maternal wellbeing and management of obstetric complications. To take this into account, we have included the year of delivery as a continuous variable in our logistic regression models. Unlike some previous studies^{2,7,8,23} we have adjusted all our odds ratios for confounders including BMI and smoking which are important causes of adverse outcomes.^{7,8} As in the studies by Sharma *et al.* (2006 and 2007),^{9,10} in order to reduce potential bias from parity and any other previous adverse obstetric history like a first-trimester miscarriage, we only included women who were in their second pregnancy following an outcome in the previous pregnancy that was beyond 20 weeks of gestation. This is in contrast to some other reported studies.^{2,5,23}

A potential weakness of this study is that women in whom severe pre-eclampsia, fetal chromosomal abnormalities and pre-existing or pregnancy related maternal disease with a high risk of recurrence, resulted in a first pregnancy stillbirth, may not have become pregnant again or who had subsequent early pregnancy losses and were therefore not included in the exposed cohort

group. Another weakness of this study is the missing data—data were missing on some key variables including smoking and BMI in one-fifth to one-quarter of women. But as the missing data were evenly distributed over both the exposed and unexposed groups, this is unlikely to be a major source of bias. Also, while these data and the results are true for our local population, it is still a relatively small number of subjects on which to draw conclusions to apply to the wider population.

Further research using national data would include a larger cohort group, giving more reliable results. In particular, this would be of use in confirming or refuting the suggestion that risk of stillbirth in second pregnancy is not significantly raised following unexplained stillbirth in first pregnancy. Risk of recurrent stillbirth is likely to be the data of greatest interest to affected parents, while incidence of identifiable and treatable complications of pregnancy may be of greatest interest to health providers.

In conclusion, we have shown that a stillbirth in the first pregnancy does indicate increased risk in the subsequent pregnancy of low birthweight, prematurity, placental abruption, pre-eclampsia and intervention at delivery, but the risk of a second stillbirth is not increased in the absence of known risk factors.

Contribution to authorship

M.B. was responsible for analysis of data and for writing the first draft of the paper. A.S. conceived the research idea and was responsible for supervising M.B. S.B. was responsible for facilitating data extraction and supervising data analysis. All three authors contributed to writing of the final draft of the paper.

Details of ethics approval

Permission was obtained from the Caldicott guardians of the AMND prior to data extraction and an anonymised dataset was handed to the named researchers. All such observational studies on anonymised data sets are covered by approval from the North of Scotland Research Ethics Committee as per letter dated 5 December 2006.

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