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Previous caesarean delivery and the risk of unexplained stillbirth: retrospective cohort study and meta-analysis.

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Short running title: Previous caesarean and unexplained stillbirth.

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Abstract

Objective To determine whether caesarean delivery in the first pregnancy is a risk factor for unexplained antepartum stillbirth in the second.

Design A population based retrospective cohort study and meta-analysis.

Setting All maternity units in Scotland.


Methods Time-to-event analysis and random effect meta-analysis.

Main outcome measure Risk of unexplained antepartum stillbirth in the second pregnancy.

Results There were 88 stillbirths among 23,688 women with a previous caesarean (2.34 per 10,000 women per week) and 288 stillbirths in 104,897 women who previously delivered vaginally (1.67 per 10,000 women per week, p=0.002). When analysed by cause, women with a previous caesarean had an increased risk (hazard ratio [95%CI], p) of unexplained stillbirth (1.47 [1.12–1.94], p=0.006) and, as previously observed, the excess risk was apparent from 34 weeks onwards. The risk did not differ in relation to the indication of the caesarean and was independent of maternal characteristics and previous obstetric complications. We identified three other comparable studies (two in North America and one in Europe), and meta-analysis of these studies showed a statistically significant association between previous caesarean delivery and the risk of antepartum stillbirth in the second pregnancy (pooled hazard ratio [HR], 1.40; 95% CI 1.10–1.77, p=0.006).

Conclusion Women who have had a previous caesarean delivery are at increased risk of unexplained stillbirth in the second pregnancy.

Tweetable abstract: Caesarean first delivery is associated with an increased risk of unexplained stillbirth in the next pregnancy

Keywords Caesarean, unexplained, stillbirth, second pregnancy.

Introduction
In 2012 the rate of caesarean delivery in England reached a record high of 25% which was more than double the rate in 1990. A significant proportion of the increased caesarean rate can be attributed to the rise of primary caesarean sections. While many primary caesarean deliveries are clinically indicated, the most recent National Institute for Health and Clinical Excellence (NICE) guideline gives women the option to choose planned caesarean delivery without medical indication after discussing the overall risks and benefits compared to vaginal delivery. It is essential, therefore, that women considering caesarean delivery are provided with reliable estimates of these risks.

We reported in 2003 that previous caesarean delivery was associated with an increased risk of unexplained stillbirth among women having second births in Scotland between 1992 and 1998. Multiple studies have been conducted over the last decade addressing this question. However, they have employed analytic approaches and data sources of highly variable quality, which may explain their heterogeneous findings. A recent meta-analysis reported that caesarean delivery was an independent risk factor for all subsequent stillbirth (i.e. antepartum and intrapartum) but was not a risk factor for antepartum stillbirth. However, the meta-analysis included inappropriately designed studies and reported significant heterogeneity. As such, the results should be interpreted with caution. However, as meta-analyses tend to be highly influential in guideline development, these findings could affect the counselling of women considering primary caesarean section. The aims of the present study were threefold. First, we sought to replicate exactly the methodology of our previous analysis and to apply this to data from women having second births in Scotland over the subsequent 10 years of data collection. Second, we sought to apply some methodological refinements to our previous analytic approach to both the previous and current datasets, principally the use of alternative methods for handling missing data. Third, we conducted a systematic review and meta-analysis of all the literature published after 2003, excluding our own, that used an appropriate analytic approach to study the association between
caesarean delivery in the first birth and antepartum stillbirth in the second.
Methods

We used the same data sources and methods as our previous study. These are described briefly below, along with some additional methodological details.

Data sources

We used linked databases of births and perinatal deaths in Scotland. The Scottish Morbidity Record 02 (SMR02) collects information on clinical, demographic characteristics and outcomes of all patients discharged from Scottish maternity hospitals, and is more than 99% complete. The Scottish Stillbirth and Infant Death Survey (SSBIDS) is a national registry that routinely classifies all perinatal deaths in Scotland based on clinical information obtained from local coordinators and pathologists, and it is almost 100% complete. Both databases have been described in detail elsewhere.

Study population

We included all singleton pregnancies between 1999 and 2008 from women who reported one previous birth. The exclusion criteria were multiple pregnancy, perinatal death ascribed to congenital abnormality or rhesus isoimmunisation, delivery outside 24–43 weeks’ gestation, birth weight less than 500 grams and records with missing values in any of the covariates. We also performed an analysis of a sub-group where we could link the records of the first and second birth, but excluding those with major discrepancies between the data from the two births. We also performed an analysis which included births from 1992 to 2008, i.e. combining the population of the previous study, the population of the complete case analysis from the present study, and records from both periods that had previously been excluded because of missing values for height and smoking status.

Definition of stillbirths
The main outcome of this study was antepartum stillbirth, both all cause and sub-divided by cause. The cause of stillbirth death was classified using a modification of the Wigglesworth classification, as described elsewhere. Deaths were classified by a single medically qualified individual, who had access to postnatal investigations and autopsy results where performed, and this was performed according to direct obstetric causes (in order): toxaemia (pre-eclampsia/eclampsia), haemorrhage (antenaturn), mechanical (including uterine rupture), maternal (including diabetes), miscellaneous, and unexplained. Small for gestational age birth weight is not regarded as an antecedent cause of death in the obstetric classification, and the relatively high proportion of "unexplained" stillbirths reflects a strict application of the term "cause", rather than inadequate clinical information.

**Definition of maternal and obstetric characteristics**

We adjusted for maternal age, height, smoking status, and socioeconomic deprivation as previously described. Maternal age was defined as the age of the mother at the time of her second delivery. Maternal height was recorded in cm. Smoking status (current, past, never) was assessed at the first antenatal visit of the second pregnancy. Socio-economic status was estimated based on the postcode of residence, using Carstairs socio-economic deprivation categories, which, in brief, are based on the proportion of households with unemployment, overcrowding, lack of car ownership, and the social class of the head of the household which in turn is based on education and occupation. The gestational age at birth was defined as the completed weeks of gestation based on the estimated date of delivery and confirmation by ultrasound in the first half of the pregnancy, as previously described.

**Statistical analysis**

Continuous variables were summarized by the median and interquartile range (IQR) and comparisons between groups were performed using the Mann-Whitney U test. Univariate comparisons of categorical data were made by χ² test or Fisher’s exact test as appropriate. All reported p values are two sided and p<0.05 was considered statistically significant. The
risk of events was modelled using time-to-event analysis. Gestational age was the timescale, antepartum stillbirth due to the specified cause was the event and all other births were treated as censored, as previously described.\textsuperscript{4} We used the proportional hazard model for calculating the crude and adjusted hazard ratio.\textsuperscript{11} The proportional hazard assumption was tested using the global test of Grambsch and Therneau.\textsuperscript{12} We used multiple imputation by chained equations for the missing values for all the covariates as they were likely to be missing at random.\textsuperscript{7} Thirty imputations were created\textsuperscript{13} using a set of appropriate imputation models constructed from all the covariates and outcome variables including the event indicator and the Nelson-Aalen estimator of the cumulative hazard $H(T)$ in the imputation model.\textsuperscript{14}

\textbf{Meta-analysis}

Two authors (AAM and COW) conducted the literature search and data extraction from Pubmed, Scopus, and Web of Science, according to the recommendations made by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group\textsuperscript{15} between December 2013 and February 2014. The pre-specified outcome was antepartum stillbirth in the second pregnancy. For exposure we used the search terms “caesarean” OR “cesarean” OR “mode of delivery” and for the outcome the search terms “stillbirth” OR “fetal death”. We limited our search to studies from 2003 onwards as this was the year of the first study published on the topic.\textsuperscript{4} We evaluated the quality of the individual studies using the validated Newcastle-Ottawa Scale.\textsuperscript{16} A random effects meta-analysis was used to combine the study results and allow for between study heterogeneity. The heterogeneity was assessed using the Cochrane $\chi^2$ statistic and the $I^2$ statistic.\textsuperscript{17} Publication bias was evaluated through a funnel plot and Egger’s test. All statistical analysis was done using Stata version 12.1 (StataCorp LP, College Station, Texas).
Results

The linked databases included 524,145 records of singleton births between 1 January 1999 and 31 December 2008. A study cohort of 128,585 was selected following application of inclusion and exclusion criteria (Figure S1). A total of 23,688 (18.4%) women had a history of previous caesarean delivery and these women were older, shorter, less likely to smoke and more likely to live in an area of low socioeconomic deprivation than women who had previously delivered vaginally (Table 1). In their first pregnancy, women who had delivered by caesarean delivered earlier, were more likely to deliver prematurely, more likely to deliver babies of extreme birth weight percentile and had fewer unexplained stillbirths but had similar proportions of other perinatal deaths compared to women that had delivered vaginally (Table 1). In the second pregnancy, women whose first delivery was by caesarean delivered earlier, were more likely to deliver prematurely, were more likely to deliver large for gestational age infants and were more likely to have a pregnancy end in stillbirth (Table 1).

The association between previous caesarean delivery and the risk of all cause stillbirth was significant when analysed by time to event analysis (Table S1). When analysed by cause, previous caesarean delivery was associated with increased risks of stillbirth ascribed to maternal disease (principally diabetes mellitus) and unexplained stillbirth (Table S1). For all gestational ages, the hazard ratio for unexplained stillbirth in women with previous caesarean delivery was 1.47 (95% CI 1.12–1.94, p=0.006). The absolute risk difference was 0.1% and the number of caesareans required for one additional antepartum stillbirth was approximately 1000. When the cumulative risk of unexplained stillbirth was plotted against gestational age, the association with previous caesarean delivery and unexplained stillbirth was apparent from 34 weeks’ gestation onwards (Figure 1). The crude and adjusted hazard ratios for stillbirth prior to 34 weeks gestational age were 1.11 (95% CI 0.65–1.91) and 1.19 (95% CI 0.67–2.11). The crude and adjusted hazard ratios for stillbirth at or after 34 weeks
gestational age were 2.40 (95% CI 1.64–3.50) and 2.22 (95% CI 1.50–3.30). Hence, as
previously, all further analyses were confined to the risk of stillbirth at or after 34 weeks of

gestation.

We next focused the analysis on women where we could link the records of the first and
second pregnancy. The association between previous caesarean delivery and unexplained
stillbirth remained strong when confined to women whose first birth was at term (Table 2).
The association was also similar when the previous section had been performed before the
onset of labour, after less than 10 hours of labour, or after 10 or more hours of labour. The
association was also similar when adjusted for maternal characteristics, inter-pregnancy
interval, and the outcome of the first pregnancy. Finally, the risk of unexplained stillbirth was
not elevated among women whose first birth was an operative vaginal delivery (i.e. forceps
or vacuum extraction, Table 2).

Our original report and the analysis above both utilised records with complete data only. We
replicated the analysis of both datasets using multiple imputation to handle records with
missing data for all covariates. The overall study cohort from 1992 to 2008 included 318,829
second births that resulted in 642 unexplained stillbirths, of which 391 occurred after 34
weeks gestation. The crude hazard ratio for unexplained stillbirth at or after 34 weeks
gestational age associated with previous caesarean delivery was 1.57 (95% CI 1.23–2.00,
p<0.001). After confining the analysis to linked records of first and second pregnancies (n=
251,422) and adjusting for maternal characteristics and previous pregnancy complications
(preterm birth, birth weight percentile and perinatal death), the hazard ratio for unexplained
antepartum stillbirth at or after 34 weeks was 1.92 (95% CI 1.46–2.52, p<0.001). The
association between previous caesarean delivery and unexplained stillbirth was virtually
identical when we compared 1992–1998 and 1999–2008 (Figure S2).
The flow diagram of the literature search results is shown in Figure S3. For the meta-analysis we identified 3 retrospective cohort studies, other than our own, that performed time to event analysis of the risk of antepartum stillbirth in the second pregnancy comparing women whose first birth was by caesarean with women whose first birth was vaginal (Table S2). These were all based in high-income countries (Canada, Germany, and USA) and were of adequate quality (Table S3). All three reported a hazard ratio of greater than one, although only one study was statistically significant at p<0.05. Pooling the three studies, the summary HR is 1.40 (95% CI 1.10–1.77) and the association is statistically significant (p=0.006, Figure 2). The number of studies included in the meta-analysis is small which makes the assessment for publication bias difficult, but there was no clear evidence for publication bias (Figure S4).
Discussion

Main findings

This study confirms our previous finding that caesarean delivery in the first pregnancy is an independent risk factor for unexplained antepartum stillbirth in the second.4 As in our previous report, the increased risk became apparent from the 34th week of gestation onwards. Adjusting for maternal characteristics, inter-pregnancy interval, and first pregnancy outcomes (birth weight percentile, preterm birth, and perinatal death) had no material effect on the association. The risk was similar whether the previous caesarean had been performed before labour, after less than 10 hours of labour, or after 10 or more hours of labour. The association remained significant when we included records that had been excluded due to missing values in our previous analysis. We conclude that it is extremely unlikely that our first report was a chance finding.

Strengths and limitations of this study

A major strength of the present study was that we had detailed information on both maternal characteristics and the outcome of the previous pregnancy. Hence, we were able to confirm that the association between previous caesarean delivery and the risk of stillbirth was very similar whether the previous caesarean was performed prior to the onset of labour, and was also independent of the duration of labour. The indications for caesarean at these points in relation to labour are very different. This makes it unlikely that the observed association is due to confounding by the indication for the previous caesarean. We had detailed information on other maternal characteristics and aspects of the outcome of the first pregnancy. The fact that the association was unaffected by adjustment for any of these further strengthens the plausibility of a causal association. However, we lacked information on maternal body mass index, which is associated with both the risk of caesarean delivery21 and the risk of stillbirth.22 However it is unlikely that this might explain the current findings as
both obesity and morbid obesity are associated with an approximately 70% increase in the
risk of stillbirth,\textsuperscript{22,23} which is similar in strength to the association with previous caesarean.\textsuperscript{21}

Generally, in order for a characteristic to act as a confounder, the confounder would have to be much more strongly associated with the outcome than the exposure of interest. According to the Wigglesworth classification system deaths ascribed to pre-existing hypertension or pre-gestational diabetes would be classified as “maternal”, hence it is unlikely that these would be significant confounders in our analysis for unexplained stillbirth. However, it remains possible that the association could be affected by other unmeasured confounders.

\textbf{Interpretation of results and comparison with other studies}

During the decade following our first report of this association, numerous studies were published analysing the risk of stillbirth in relation to previous caesarean delivery. Most of these studies included intrapartum stillbirths in their analysis.\textsuperscript{24-31} This can be a significant confounder because of the different aetiology of intrapartum stillbirth which is strongly associated with the mode of second delivery.\textsuperscript{32,33} A meta-analysis\textsuperscript{5} reported a significant increase in the risk for all stillbirths (pooled odds ratio [OR], 1.23, 95% CI, 1.08–1.40), but no statistically significant association with antepartum stillbirth (pooled OR, 1.27; 95% CI 0.95–1.70). However, many of the included studies had inconsistencies and weaknesses in the methods of data collection and statistical analysis. For example, one study\textsuperscript{34} in the meta-analysis included nulliparous women, despite the fact that nulliparity is an independent risk factor for stillbirth\textsuperscript{22,23} and nulliparous women, by their nature, cannot have had a prior caesarean delivery. That study reported a lower risk of stillbirth among women with a previous caesarean delivery, most likely reflecting negative confounding by parity. The variable quality of studies included in the meta-analysis is the likely explanation for the statistically significant evidence of heterogeneity and the summary results should be interpreted with caution.
When considering whether an association is potentially causal, one issue is its biological plausibility. This is intrinsically problematic when the outcome is unexplained stillbirth: it is difficult to address biological pathways when the pathophysiology of the outcome is incompletely understood. However, the majority of stillbirths are thought to be related to placental dysfunction. Placental development involves complex interactions between the invading trophoblast and both the decidua and myometrium. Moreover, normal placental function requires vasodilation of the uterine circulation and failure of the development of low resistance patterns of flow velocity waveform in the uterine arteries is associated with an increased risk of stillbirth. Given that caesarean delivery involves the generation of a scar, that previous caesarean is associated with other abnormalities of the placenta (such as abruption and morbid adherence of the placenta), and that the procedure of caesarean delivery frequently involves ligation of major branches of the uterine arteries, we believe that it is plausible that previous caesarean could lead to impaired placental function in subsequent births. Interestingly, both of our analyses of data from Scotland and all three of the other studies which plotted cumulative risk of stillbirth in second pregnancies found that the risk of antepartum stillbirth after previous caesarean was apparent after 34 weeks’ gestation. Further studies will be required to determine the biological significance of this finding.

Conclusion

Caesarean delivery clearly has multiple benefits. However, effective counselling requires clear information on the balance of risks and benefits associated with a given woman’s individual characteristics and circumstances. We confirm that caesarean delivery in a first pregnancy is associated with an increased risk of stillbirth in the second. These findings underline the importance of identifying the factors which lead to primary caesarean delivery, and developing approaches to reduce the number of these procedures. We recommend that future research should be directed at trying to understand better the mechanisms that might link previous caesarean delivery and the risk of stillbirth. In particular, it would be interesting
to determine the effect of previous caesarean on the physiological changes which take place in uterine blood flow with advancing gestational age.
Acknowledgements

Disclosure of interest

No conflicts of interest to declare (ICMJE disclosure forms are available online)

Contributors

GCSS had the original idea and designed the study. MF and JP acquired the data. AAM, AMW and GCSS undertook the statistical analysis. AAM and COW performed the meta-analysis. AAM and GCSS drafted the manuscript. All authors revised and approved the final report. GCSS is the guarantor.

Ethics

The work was approved by the Privacy Advisory Committee of the Information Services Division of NHS Scotland.

Funding

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Acknowledgement

No acknowledgement.
References


Figure legends

Figure 1: Cumulative proportion of unexplained antepartum stillbirth per week of gestation. Scotland, 1999–2008. Log-rank p=0.006.

Figure 2: Meta-analysis, using a random effect model, of previous studies, excluding our own, on the association between caesarean section and the risk of antepartum stillbirth in the second pregnancy. (Heterogeneity: Chi²= 2.18, (d.f=2), p=0.336; Tau²=0.0042; I²= 8.3%; Overall effect: Z= 2.74, P=0.006). OR= Odds ratio, CI= Confidence intervals
Table 1: Maternal characteristics and obstetric outcome in relation to previous caesarean section (n= 128 585), Scotland 1999-2008.

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>No previous caesarean (n= 104 897)</th>
<th>Previous caesarean (n=23 688)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median [IQR])</td>
<td>30 (25–33)</td>
<td>31 (28–35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm (median [IQR])</td>
<td>164 (160–168)</td>
<td>162 (157–167)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years (median [IQR])</td>
<td>30 (25–33)</td>
<td>31 (28–35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm (median [IQR])</td>
<td>164 (160–168)</td>
<td>162 (157–167)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deprivation category, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2 (Least deprived)</td>
<td>22 066 (21.0%)</td>
<td>6005 (25.3%)</td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>63 305 (60.4%)</td>
<td>13 924 (58.8%)</td>
<td></td>
</tr>
<tr>
<td>6–7 (Most deprived)</td>
<td>19 526 (18.6%)</td>
<td>37 59 (15.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non–smoker</td>
<td>68 020 (64.9%)</td>
<td>16 980 (71.7%)</td>
<td></td>
</tr>
<tr>
<td>Ex–smoker</td>
<td>26 781 (25.5%)</td>
<td>4539 (19.2%)</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>10 096 (9.6%)</td>
<td>2169 (9.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outcome second pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpregnancy interval, days</td>
<td>893 (517–1549)</td>
<td>842 (502–1387)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age at delivery, weeks (median [IQR])</td>
<td>40 (39–40)</td>
<td>39 (38–40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age at delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24–32 weeks, n (%)</td>
<td>868 (0.8%)</td>
<td>267 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>33–36 weeks, n (%)</td>
<td>3783 (3.6%)</td>
<td>1181 (5.0%)</td>
<td></td>
</tr>
<tr>
<td>37–43 weeks, n (%)</td>
<td>100 246 (95.6%)</td>
<td>22 240 (93.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight, g (median [IQR])</td>
<td>3490 (3145–3820)</td>
<td>3460 (3120–3820)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5th percentile, n(%)</td>
<td>3526 (3.4%)</td>
<td>831 (3.5%)</td>
<td>0.3</td>
</tr>
<tr>
<td>&gt;95th percentile, n (%)</td>
<td>8436 (8.0%)</td>
<td>2646 (11.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antepartum stillbirth, n (%)</td>
<td>287 (0.3%)</td>
<td>88 (0.4%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Outcome first pregnancy**</td>
<td>(n= 79 138)</td>
<td>(n=17 850)</td>
<td></td>
</tr>
<tr>
<td>Gestational age at delivery, weeks (median [IQR])</td>
<td>40 (39–41)</td>
<td>40 (38–41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age at delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24–32 weeks, n (%)</td>
<td>778 (1.0%)</td>
<td>512 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>33–36 weeks, n (%)</td>
<td>3334 (4.2%)</td>
<td>1316 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>37–43 weeks, n (%)</td>
<td>75 026 (94.8%)</td>
<td>16 022 (89.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight, g (median [IQR])</td>
<td>3350 (3030–3660)</td>
<td>3450 (3020–3830)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birthweight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5th percentile, n (%)</td>
<td>4311 (5.5%)</td>
<td>1102 (6.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;95th percentile, n (%)</td>
<td>2632 (3.3%)</td>
<td>1556 (8.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perinatal death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained stillbirth, n (%)</td>
<td>353 (0.5%)</td>
<td>6 (0.03%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>247 (0.3%)</td>
<td>66 (0.4%)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*By Mann–Whitney U, χ², or Fischer’s exact test as appropriate.

**Including only linked records of first and second pregnancy.
Table 2: The association between the mode of delivery in the first pregnancy and the risk of unexplained stillbirth in the second, Scotland 1999–2008.

<table>
<thead>
<tr>
<th>Mode of delivery first term birth (n=90 300)</th>
<th>Crude HR (95% CI)</th>
<th>p</th>
<th>Adjusted HR* (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CS, n= 15 856</td>
<td>2.45 (1.66–3.63)</td>
<td>&lt;0.001</td>
<td>2.44 (1.62–3.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-labour CS, n=6827</td>
<td>2.29 (1.32–3.98)</td>
<td>0.003</td>
<td>2.27 (1.29–3.98)</td>
<td>0.004</td>
</tr>
<tr>
<td>CS after &lt;10h labour, n=3531</td>
<td>2.09 (0.96–4.53)</td>
<td>0.06</td>
<td>1.99 (0.91–4.34)</td>
<td>0.09</td>
</tr>
<tr>
<td>CS after ≥10h labour , n=5498</td>
<td>2.90 (1.67–5.04)</td>
<td>&lt;0.001</td>
<td>3.03 (1.70–5.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Operative vaginal delivery, n=20 020</td>
<td>0.69 (0.41–1.18)</td>
<td>0.18</td>
<td>0.76 (0.44–1.31)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

HR=hazard ratio, CI=confidence intervals, CS= Caesarean section

*Adjusted for maternal age, height, social deprivation, smoking, interpregnancy interval, and features of the first pregnancy: birth weight percentile and perinatal death.

All analyses include only births at or after 34 weeks’ gestation in the second pregnancy.
<table>
<thead>
<tr>
<th>Study</th>
<th>Cases/Participants (n)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osborne et al. 2012</td>
<td>21 / 10996</td>
<td>2.60 (1.09, 6.20)</td>
</tr>
<tr>
<td>Wood et al. 2008</td>
<td>265 / 158502</td>
<td>1.36 (0.98, 1.89)</td>
</tr>
<tr>
<td>Franz et al. 2008</td>
<td>1386 / 629815</td>
<td>1.30 (0.94, 1.80)</td>
</tr>
<tr>
<td>Overall (I-squared = 8.3%, p = 0.336)</td>
<td></td>
<td>1.40 (1.10, 1.77)</td>
</tr>
</tbody>
</table>
Table S1. Risk of antepartum stillbirth at or after 24 weeks’ gestation in relation to previous caesarean delivery (n= 128 585), Scotland 1999-2008.

<table>
<thead>
<tr>
<th>Cause of stillbirth</th>
<th>No previous caesarean</th>
<th>Previous caesarean</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=104 897)</td>
<td>(n=23 688)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>Incidence**</td>
<td>Number</td>
</tr>
<tr>
<td>All causes</td>
<td>287</td>
<td>1.67</td>
<td>88</td>
</tr>
<tr>
<td>Toxaemia</td>
<td>9</td>
<td>0.05</td>
<td>5</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>42</td>
<td>0.24</td>
<td>6</td>
</tr>
<tr>
<td>Mechanical</td>
<td>6</td>
<td>0.03</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>Maternal</td>
<td>14</td>
<td>0.08</td>
<td>9</td>
</tr>
<tr>
<td>Maternal (excluding diabetes)</td>
<td>8</td>
<td>0.05</td>
<td>3</td>
</tr>
<tr>
<td>Unexplained</td>
<td>214</td>
<td>1.24</td>
<td>66</td>
</tr>
</tbody>
</table>

*p* Log rank test

**Per 10 000 women per week.
<table>
<thead>
<tr>
<th>Studies</th>
<th>Country/Study period</th>
<th>Study design and source</th>
<th>Cohort size</th>
<th>Number of stillbirths in cohort</th>
<th>Stillbirth definition</th>
<th>Exclusions</th>
<th>Adjustment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood 2008</td>
<td>Canada, 1991-2004</td>
<td>Retrospective cohort, regional perinatal data from 81 hospitals in Alberta, Canada</td>
<td>158 502</td>
<td>265</td>
<td>Antepartum unexplained, &gt;24 weeks</td>
<td>Intrapartum stillbirths, multiple gestations, congenital abnormalities, gestation &lt;24 or &gt;42 weeks, non second pregnancies</td>
<td>Maternal age, weight, smoking, pre-pregnancy hypertension and diabetes</td>
<td></td>
</tr>
<tr>
<td>Franz 2008</td>
<td>Germany, 1987-2005</td>
<td>Retrospective cohort, regional registry offices in Bavaria</td>
<td>629 815</td>
<td>1386</td>
<td>Antepartum unexplained, &gt;23 weeks</td>
<td>Intrapartum stillbirths, multiple gestations, congenital abnormalities, gestation &lt;23 or &gt;42 weeks, non second pregnancies</td>
<td>Diabetes mellitus, smoking, maternal age, BMI, previous premature birth, previous SGA infant, previous perinatal death</td>
<td>No data linkage for successive pregnancies, dataset may be under-reported before 1997</td>
</tr>
<tr>
<td>Osborne 2012</td>
<td>USA, 4 study periods between 1994-2002</td>
<td>Retrospective cohort, single centre</td>
<td>10 996</td>
<td>21</td>
<td>Antepartum &gt;24 weeks</td>
<td>Intrapartum stillbirths, multiple gestations, congenital abnormalities, gestation &lt;24 or &gt;43 weeks, non second pregnancies</td>
<td>No reported adjusted OR or HR</td>
<td>No cause of death, no adjusted analysis</td>
</tr>
</tbody>
</table>

BMI = body mass index, SGA = small for gestational age, OR = odds ratio, HR = hazard ratio
**Table S3.** Quality assessment of included studies through the Newcastle-Ottawa scale.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome/ Exposure</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood, 2008</td>
<td>****</td>
<td>**</td>
<td>***</td>
<td>9</td>
</tr>
<tr>
<td>Franz, 2008</td>
<td>***</td>
<td>**</td>
<td>**</td>
<td>7</td>
</tr>
<tr>
<td>Osborne, 2012</td>
<td>***</td>
<td>*</td>
<td>***</td>
<td>7</td>
</tr>
</tbody>
</table>

†According to the Newcastle–Ottawa Scale for non-randomised studies in meta-analyses the maximum score for all fields is 9 stars (selection 4 stars, comparability 2 stars, and outcome or exposure 3 stars).
524 145 singleton births (1999-2008)

176 263 (33.63%) second births

**Exclusions: n = 376 (0.21%)** (due to 1 or more of the following)
- Perinatal death due to congenital malformation or rhesus isoimmunisation (n= 200, 0.11%)
- Gestational age: <24 & >43 weeks (n= 122, 0.07%)
- Birth weight: <500gr (n= 85, 0.05%)

**Missing data: n = 47 302 (26.89%)** (due to 1 or more of the following)
- History of previous caesarean delivery (n= 452, 0.26%)
- Maternal height (n= 41 644, 23.68%)
- Maternal age (n= 1, <0.01%)
- Deprivation category (n= 585, 0.33%)
- Smoking (n= 16 299, 9.27%)
- Mode of delivery (n= 29, 0.02%)
- Birth weight (n= 110, 0.06%)
- Infant sex (n= 15, 0.01%)

128 585 second births with full records (Cohort 1)

**Record linkage exclusions: n = 31 597 (24.57%)**
- Records could not be linked to data of the 1st birth (n= 24 419, 18.99%)
- Inter-pregnancy errors (n= 6883, 5.35%)
- Missing values of 1st pregnancy characteristics (n= 295, 0.23%)

96 988 second births with complete data on both pregnancies (Cohort 2)

**Figure S1.** Selection of the study cohorts
Figure S2. Risk of unexplained stillbirth from 34 weeks’ gestation onwards after caesarean section compared to vaginal delivery for the two study periods (1992–1998, 1999–2008), including women with missing data for all covariates. A. Crude hazard ratio (HR, 95% CI) for all records (n= 141 705 pregnancies in the 1992–1998 period, n=172 869 in the 1999–2008 period; 4255 records excluded where the woman delivered before the 34th week of gestation). B. Adjusted hazard ratio (aHR, 95% CI) for linked records (n= 116 007 pregnancies in the 1992–1998 period, n=132 391 in the 1999–2008 period; 3024 records excluded where the woman delivered before the 34th week of gestation). Adjusted for maternal age, height, smoking status, deprivation category and features of first pregnancy: preterm birth, birth weight percentile, and perinatal death. Covariates were imputed where missing.
Records identified through database searching (n = 3818)

Additional records identified through other sources (n = 1)

Records after duplicates removed (n = 3605)

Records screened (n = 3605)

Records excluded (n = 3576)

Full-text articles assessed for eligibility (n = 29)

Full-text articles excluded (n = 26)
  - Letters or conference abstracts (n = 9)
  - Systematic reviews (n = 2)
  - No report of association (n = 4)
  - Included intrapartum stillbirths (n = 8)
  - Included parity ≠ 1 (n = 2)

Studies included in qualitative synthesis (n = 3)

Studies included in quantitative synthesis (meta-analysis) (n = 3)

Figure S3. Flow diagram of study exclusion and inclusion for the meta-analysis
Egger’s test ($P=0.1$).

**Figure S4.** Funnel plot of the association between caesarean section in the first pregnancy and antepartum stillbirth in the second.