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

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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.

Participants 128 585 second births, 1999-2008.

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 deliveryin England reached a record high of 25% which was more than double the rate in 1990.[1] A significant proportion of the increased caesarean rate can be attributed to the rise of primary caesarean sections.[2] While many primary caesarean deliveries are clinically indicated, the most recent National Institute for Health and Clinical Excellence (NICE) guideline[3] gives women the option to choose planned caesarean deliverywithout 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.[4] 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[5] 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,[6] 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.[7] 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

78 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.[4] 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.[8]

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,[4] 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,[9] as described elsewhere.[8] 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 (antepartum), 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.[4] 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[10] 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.[4]

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 χ^2 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.[4] We used the proportional hazard model for calculating the crude and adjusted hazard ratio.[11] The proportional hazard assumption was tested using the global test of Grambsch and Therneau.[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.[7] Thirty imputations were created[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.[14]

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[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.[4] We evaluated the quality of the individual studies using the validated Newcastle-Ottawa Scale.[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 χ^2 statistic and the I^2 statistic.[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

186 gestational age were 2.40 (95% CI 1.64–3.50) and 2.22 (95% CI 1.50–3.30). Hence, as
187 previously, all further analyses were confined to the risk of stillbirth at or after 34 weeks of
188 gestation.
189
190 We next focused the analysis on women where we could link the records of the first and
191 second pregnancy. The association between previous caesarean delivery and unexplained
192 stillbirth remained strong when confined to women whose first birth was at term (Table 2).
193 The association was also similar when the previous section had been performed before the
194 onset of labour, after less than 10 hours of labour, or after 10 or more hours of labour. The
195 association was also similar when adjusted for maternal characteristics,inter-pregnancy
196 interval, and the outcome of the first pregnancy. Finally, the risk of unexplained stillbirth was
197 not elevated among women whose first birth was an operative vaginal delivery (i.e. forceps
198 or vacuum extraction, Table 2).
199
200 Our original report and the analysis above both utilised records with complete data only. We
201 replicated the analysis of both datasets using multiple imputation to handle records with
202 missing data for all covariates. The overall study cohort from 1992 to 2008 included 318 829
203 second births that resulted in 642 unexplained stillbirths, of which 391 occurred after 34
204 weeks gestation. The crude hazard ratio for unexplained stillbirth at or after 34 weeks
205 gestational age associated with previous caesarean delivery was 1.57 (95% CI 1.23–2.00,
206 p<0.001). After confining the analysis to linked records of first and second pregnancies (n=
207 251 422) and adjusting for maternal characteristics and previous pregnancy complications
208 (preterm birth, birth weight percentile and perinatal death), the hazard ratio for unexplained
209 antepartum stillbirth at or after 34 weeks was 1.92 (95% CI 1.46–2.52, p<0.001). The
210 association between previous caesarean delivery and unexplained stillbirth was virtually
211 identical when we compared 1992–1998 and 1999–2008 (Figure S2).
212

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,[18] Germany,[19] and USA[20]) 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 delivery[21] 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,[22,23] which is similar in strength to the association with previous caesarean.[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.

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.[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.[32,33] A meta-analysis[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[34] in the meta-analysis included nulliparous women, despite the fact that nulliparity is an independent risk factor for stillbirth[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.[35] 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.[36] 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)[37], and that the procedure of caesarean delivery frequently involves ligation of major braches 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

309 to determine the effect of previous caesarean on the physiological changes which take place

310 in uterine blood flow with advancing gestational age.

311

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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.

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332 References

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334 (1) Department of Health. NHS maternity statistics, England 2011/12. 2013.

335 (2) Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications
336 contributing to the increasing cesarean delivery rate. Obstet Gynecol 2011;
337 118(1):29-38.

338 (3) NICE. Clinical guideline 132: Caesarean section. National Institute for Health and
339 Care Excellence; 2011.

340 (4) Smith GCS, Pell JP, Dobbie R. Caesarean section and risk of unexplained stillbirth in
341 subsequent pregnancy. Lancet 2003; 362(9398):1779-1784.

342 (5) O'Neill SM, Kearney PM, Kenny LC, Khashan AS, Henriksen TB, Lutomski JE et al.
343 Caesarean delivery and subsequent stillbirth or miscarriage: systematic review and
344 meta-analysis. PLoS One 2013; 8(1):e54588.

345 (6) Harbour R, Miller J. A new system for grading recommendations in evidence based
346 guidelines. BMJ 2001; 323(7308):334-336.

347 (7) Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG et al. Multiple
348 imputation for missing data in epidemiological and clinical research: potential and
349 pitfalls. BMJ 2009; 338:b2393.

350 (8) Pasupathy D, Wood AM, Pell JP, Fleming M, Smith GCS. Rates of and factors
351 associated with delivery-related perinatal death among term infants in Scotland.
352 JAMA 2009; 302(6):660-668.

353 (9) Hey EN, Lloyd DJ, Wigglesworth JS. Classifying perinatal death: fetal and neonatal
354 factors. BJOG 1986; 93(12):1213-1223.

355 (10) McLoone P, Boddy FA. Deprivation and mortality in Scotland, 1981 and 1991. BMJ
356 1994; 309(6967):1465-1470.

357 (11) Hosmer D, Lemeshow S. Applied Survival Analysis. New York, NY: John Wiley &
358 Sons; 1999.

359 (12) Grambsch P, Therneau T. Proportional hazards test and diagnostics based on
360 weighted residuals. Biometrika 1994; 81:515-526.

361 (13) White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues
362 and guidance for practice. Stat Med 2011; 30(4):377-399.

363 (14) White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med
364 2009; 28(15):1982-1998.

365 (15) Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al. Meta-
366 analysis of observational studies in epidemiology: a proposal for reporting. Meta-
367 analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;
368 283(15):2008-2012.

369 (16) Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the
370 quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25(9):603-
371 605.

372 (17) Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med
373 2002; 21(11):1539-1558.

374 (18) Wood SL, Chen S, Ross S, Sauve R. The risk of unexplained antepartum stillbirth in
375 second pregnancies following caesarean section in the first pregnancy. BJOG 2008;
376 115(6):726-731.

377 (19) Franz MB, Lack N, Schiessl B, Mylonas I, Friese K, Kainer F. Stillbirth following
378 previous cesarean section in Bavaria/Germany 1987-2005. Arch Gynecol Obstet
379 2009; 279(1):29-36.

380 (20) Osborne C, Ecker JL, Gauvreau K, Lieberman E. First birth cesarean and risk of
381 antepartum fetal death in a subsequent pregnancy. J Midwifery Womens Health
382 2012; 57(1):12-17.

383 (21) Crane SS, Wojtowycz MA, Dye TD, Aubry RH, Artal R. Association between pre-
384 pregnancy obesity and the risk of cesarean delivery. Obstet Gynecol 1997;
385 89(2):213-216.

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

389 (23) The Stillbirth Collaborative Research Network Writing Group. Association between
390 stillbirth and risk factors known at pregnancy confirmation. JAMA 2011;
391 306(22):2469-2479.

392 (24) Bahtiyar MO, Julien S, Robinson JN, Lumey L, Zybert P, Copel JA et al. Prior
393 cesarean delivery is not associated with an increased risk of stillbirth in a subsequent
394 pregnancy: analysis of U.S. perinatal mortality data, 1995-1997. Am J Obstet
395 Gynecol 2006; 195(5):1373-1378.

396 (25) Kennare R, Tucker G, Heard A, Chan A. Risks of adverse outcomes in the next birth
397 after a first cesarean delivery. Obstet Gynecol 2007; 109(2 Pt 1):270-276.

398 (26) Salihu HM, Sharma PP, Kristensen S, Blot C, Alio AP, Ananth CV et al. Risk of
399 stillbirth following a cesarean delivery: black-white disparity. Obstet Gynecol 2006;
400 107(2 Pt 1):383-390.

401 (27) Gray R, Quigley MA, Hockley C, Kurinczuk JJ, Goldacre M, Brocklehurst P.
402 Caesarean delivery and risk of stillbirth in subsequent pregnancy: a retrospective
403 cohort study in an English population. BJOG 2007; 114(3):264-270.

404 (28) Olusanya BO, Solanke OA. Predictors of term stillbirths in an inner-city maternity
405 hospital in Lagos, Nigeria Preventable viable stillbirths in developing countries B.O.
406 Olusanya & O.A. Solanke. Acta Obstetricia et Gynecologica Scandinavica 2009;
407 88(11):1243-1251.

408 (29) Taylor LK, Simpson JM, Roberts CL, Olive EC, Henderson-Smart DJ. Risk of
409 complications in a second pregnancy following caesarean section in the first
410 pregnancy: a population-based study. Med J Aust 2005; 183(10):515-519.

411 (30) Hemminki E, Shelley J, Gisster M. Mode of delivery and problems in subsequent
412 births: A register-based study from Finland. American Journal of Obstetrics and
413 Gynecology 2005; 193(1):169-177.

414 (31) Richter R, Bergmann RL, Dudenhausen JW. Previous caesarean or vaginal delivery:
415 which mode is a greater risk of perinatal death at the second delivery? Eur J Obstet
416 Gynecol Reprod Biol 2007; 132(1):51-57.

417 (32) Smith GCS, Pell JP, Cameron AD, Dobbie R. Risk of perinatal death associated with
418 labor after previous cesarean delivery in uncomplicated term pregnancies. JAMA
419 2002; 287(20):2684-2690.

420 (33) Crowther CA, Dodd JM, Hiller JE, Haslam RR, Robinson JS. Planned vaginal birth or
421 elective repeat caesarean: patient preference restricted cohort with nested
422 randomised trial. PLoS Med 2012; 9(3):e1001192.

423 (34) Ohana O, Holcberg G, Sergienko R, Sheiner E. Risk factors for intrauterine fetal
424 death (1988-2009). J Matern Fetal Neonatal Med 2011; 24(9):1079-1083.

425 (35) Smith GCS, Fretts RC. Stillbirth. Lancet 2007; 370(9600):1715-1725.

426 (36) Smith GCS, Yu CK, Papageorghiou AT, Cacho AM, Nicolaides KH. Maternal uterine
427 artery Doppler flow velocimetry and the risk of stillbirth. Obstet Gynecol 2007;
428 109(1):144-151.

429 (37) Getahun D, Oyelese Y, Salihu HM, Ananth CV. Previous cesarean delivery and risks
430 of placenta previa and placental abruption. Obstet Gynecol 2006; 107(4):771-778.

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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,[4] on the association between caesarean section and the risk of antepartum stillbirth in the second pregnancy. (Heterogeneity: Chi^2= 2.18, (d.f=2), p=0.336; Tau^2=0.0042; I^2= 8.3%; Overall effect: Z= 2.74, P=0.006). OR= Odds ratio, CI= Confidence internvals

Table 1: **Maternal characteristics and obstetric outcome in relation to previous caesarean section (n= 128 585), Scotland 1999-2008.**

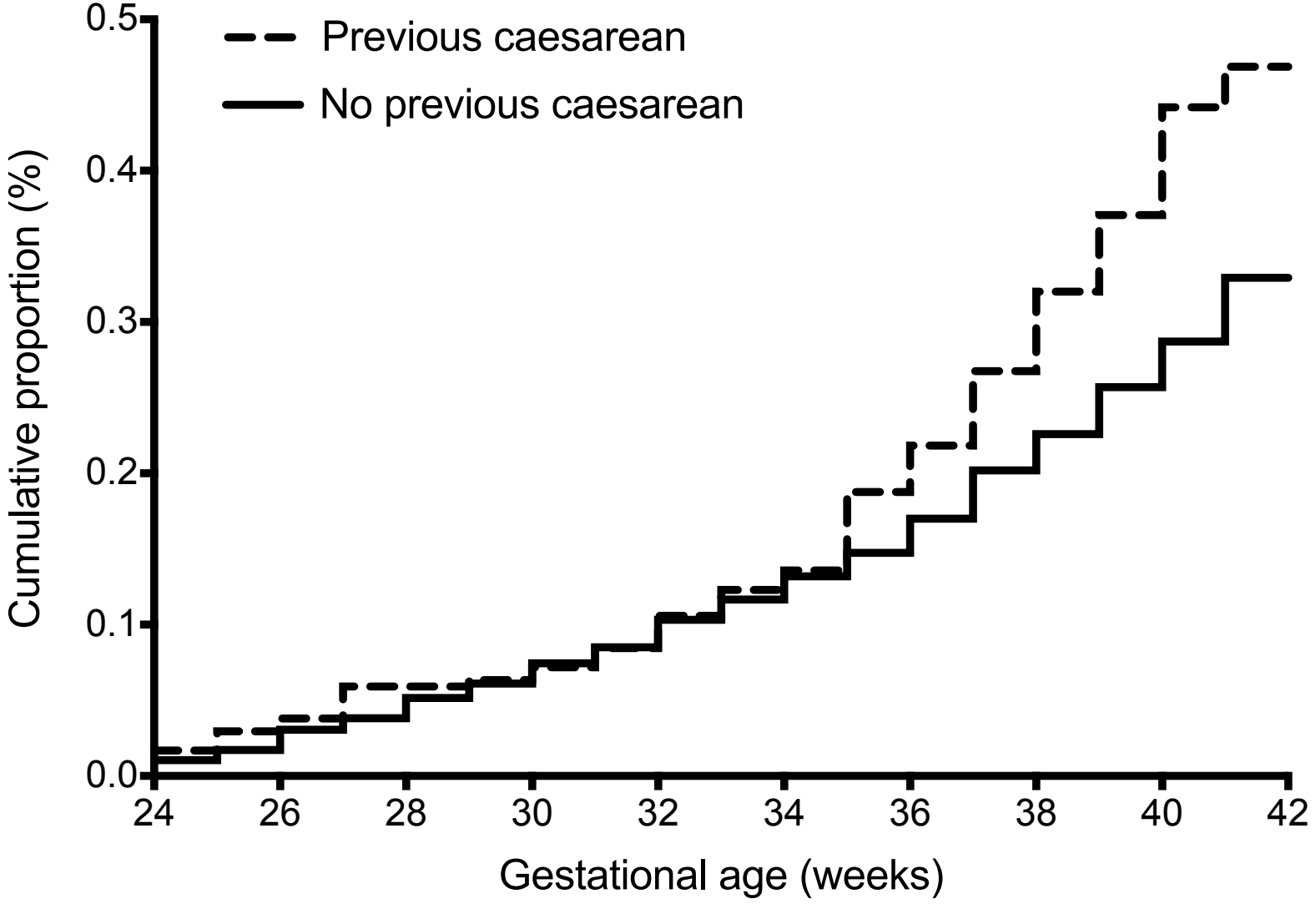
	No previous caesarean (n= 104 897)	**Previous caesarean (n=23 688)**	**p***
Maternal characteristics			
Age, years (median [IQR])	30 (25–33)	31 (28–35)	<0.001
Height, cm (median [IQR])	164 (160–168)	162 (157–167)	<0.001
Deprivation category, n (%)			
1–2 (Least deprived)	22 066 (21.0%)	6005 (25.3%)	
3–5	63 305 (60.4%)	13 924 (58.8%)	
6–7(Most deprived)	19 526 (18.6%)	3759 (15.9%)	<0.001
Smoking status, n (%)			
Non–smoker	68 020 (64.9%)	16 980 (71.7%)	
Ex–smoker	26 781 (25.5%)	4539 (19.2%)	
Smoker	10 096 (9.6%)	2169 (9.1%)	<0.001
Outcome second pregnancy			
Interpregnancy interval, days (median [IQR])	893 (517–1549)	842 (502–1387)	<0.001
Gestational age at delivery, weeks (median [IQR])	40 (39–40)	39 (38–40)	<0.001
Gestational age at delivery			
24–32 weeks, n (%)	868 (0.8%)	267 (1.1%)	
33–36 weeks, n (%)	3783 (3.6%)	1181 (5.0%)	
37–43 weeks, n (%)	100 246 (95.6%)	22 240 (93.9%)	<0.001
Birth weight, g (median [IQR])	3490 (3145–3820)	3460 (3120–3820)	<0.001
Birth weight			
<5th percentile, n(%)	3526 (3.4%)	831 (3.5%)	0.3
>95th percentile, n (%)	8436 (8.0%)	2646 (11.2%)	<0.001
Antepartum stillbirth, n (%)	287 (0.3%)	88 (0.4%)	0.01
Outcome first pregnancy**	**(n= 79 138)**	**(n=17 850)**	
Gestational age at delivery weeks, (median [IQR])	40 (39–41)	40 (38–41)	<0.001
Gestational age at delivery			
24–32 weeks, n (%)	778 (1.0%)	512 (2.9%)	
33–36 weeks, n (%)	3334 (4.2%)	1316 (7.4%)	
37–43 weeks, n (%)	75 026 (94.8%)	16 022 (89.7%)	<0.001
Birth weight, g (median [IQR])	3350 (3030–3660)	3450 (3020–3830)	<0.001
Birthweight			
<5th percentile, n (%)	4311 (5.5%)	1102 (6.2%)	<0.001
>95th percentile, n (%)	2632 (3.3%)	1556 (8.7%)	<0.001
Perinatal death			
Unexplained stillbirth, n (%)	353 (0.5%)	6 (0.03%)	<0.001
Other, n (%)	247 (0.3%)	66 (0.4%)	0.22

*By Mann–Whitney U, χ^2, 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.**

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

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.



No previous caesarean	104897	104815	104700	104531	104274	103695	102198	95558	59783	2627
Previous caesarean	23688	23666	23629	23569	23484	23314	22799	20928	8395	403

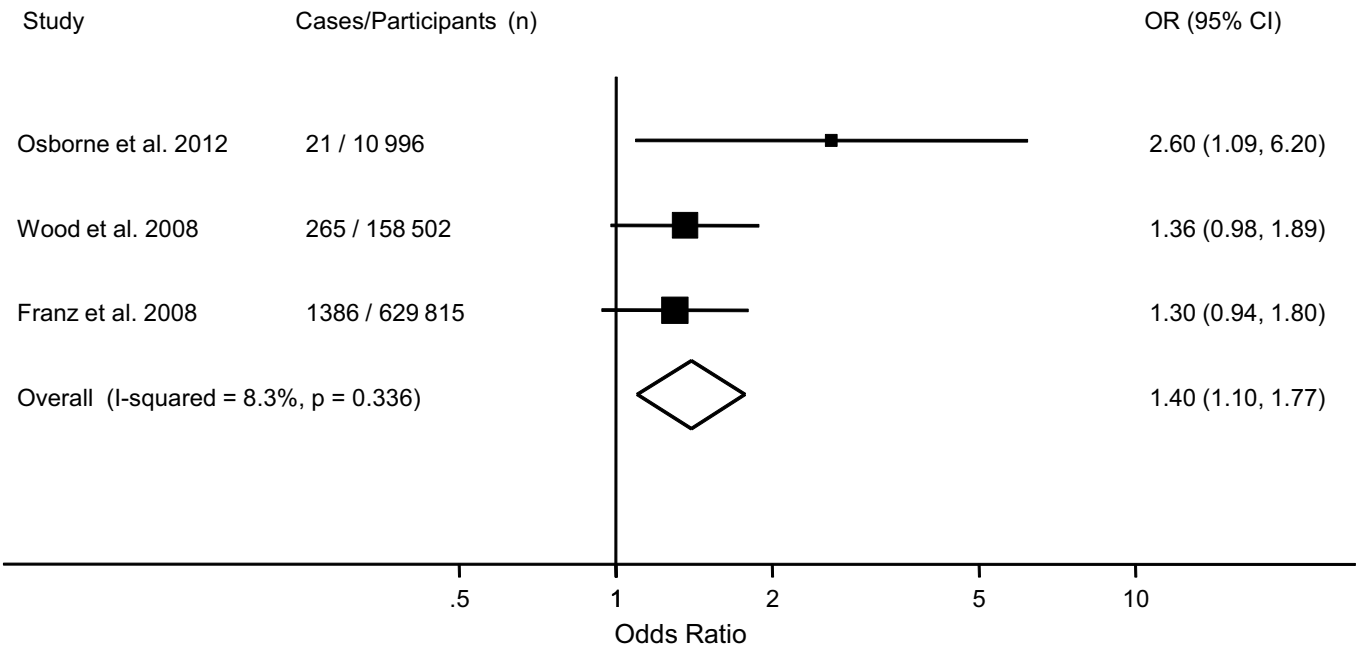

Study
Cases/Participants (n)
OR (95% CI)
Osborne et al. 2012
21 / 10 996
2.60 (1.09, 6.20)
Wood et al. 2008
265 / 158 502
1.36 (0.98, 1.89)
Franz et al. 2008
1386 / 629 815
1.30 (0.94, 1.80)
Overall (I-squared = 8.3%, p = 0.336)
1.40 (1.10, 1.77)
.5
1
2
5
10
Odds Ratio

Table S1. Risk of antepartum stillbirth at or after 24 weeks' gestation in relation to previous caesarean delivery (n= 128 585), Scotland 1999-2008.

	No previous caesarean (n=104 897)		Previous caesarean (n=23 688)		p*
	Number	Incidence**	Number	Incidence**	
Cause of stillbirth					
All causes	287	1.67	88	2.34	0.002
Toxaemia	9	0.05	5	0.13	0.09
Haemorrhage	42	0.24	6	0.16	0.32
Mechanical	6	0.03	2	0.05	0.55
Miscellaneous	2	0.01	0	0	0.50
Maternal	14	0.08	9	0.24	0.008
Maternal (excluding diabetes)	8	0.05	3	0.08	0.43
Unexplained	214	1.24	66	1.75	0.006

*Log rank test
**Per 10 000 women per week.

Table S2. Characteristics of included studies.

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

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.

Studies	Selection	Comparability	Outcome/ Exposure	Total Score†
Wood, 2008	****	**	***	9
Franz, 2008	***	**	**	7
Osborne, 2012	***	*	***	7

†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).

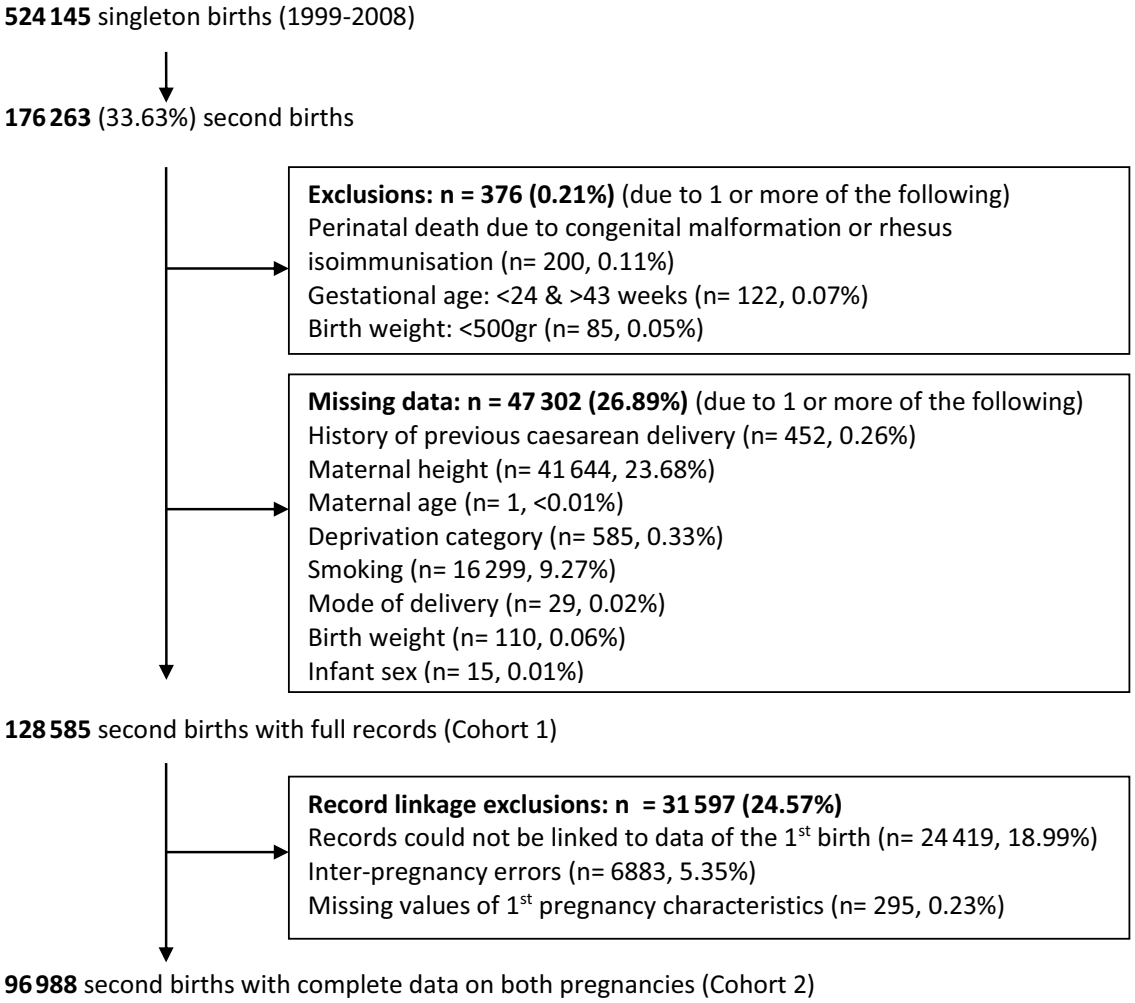


Figure S1. Selection of the study cohorts

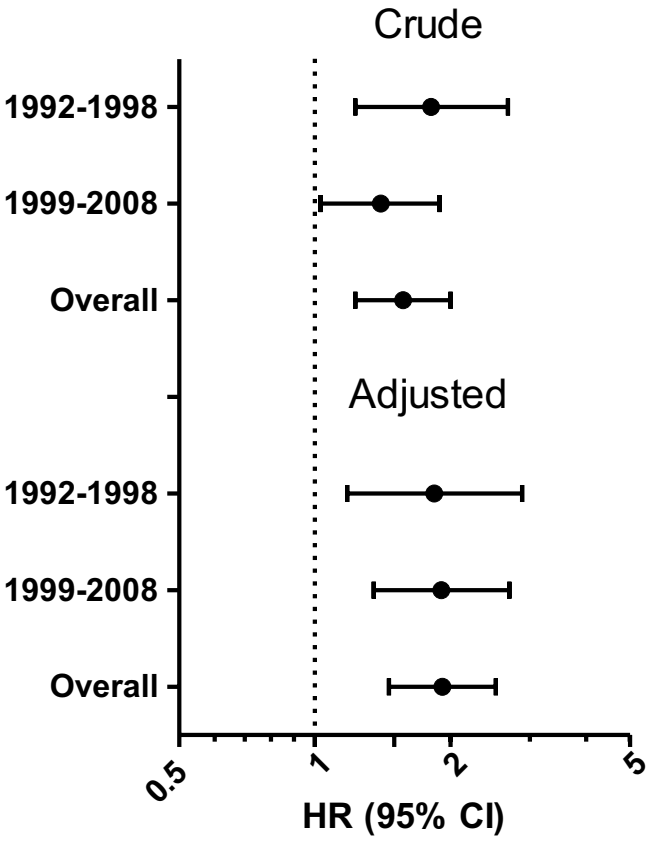


Figure S2. Risk of unexplained stillbirth from 34 weeks' gestation onwards after caesarean section compared to vaginal delivery for the two study periods (1992–1998, 1999–2008), including women with missing data for all covariates. **A**. Crude hazard ratio (HR, 95% CI) for all records (n= 141 705 pregnancies 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.

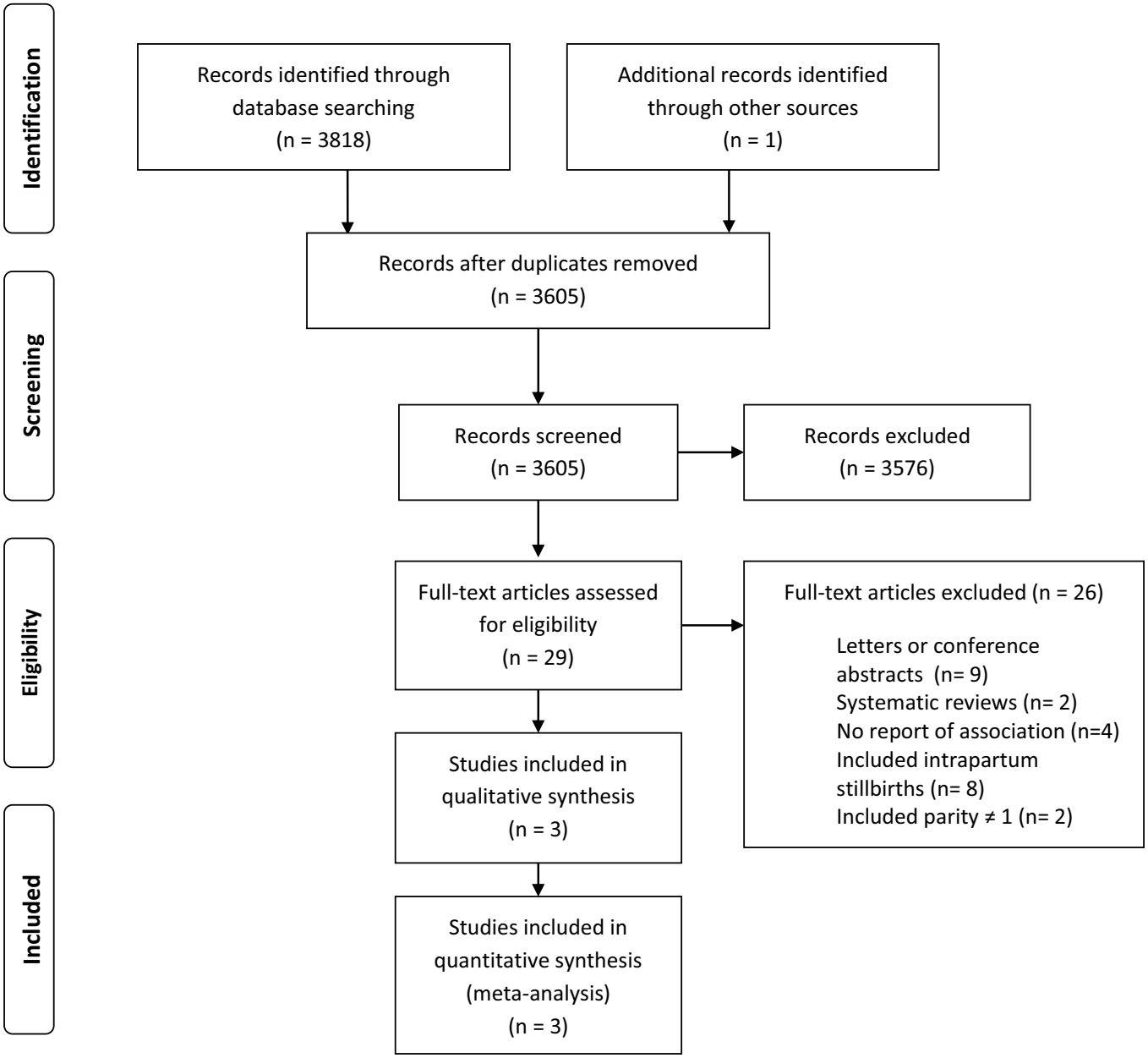
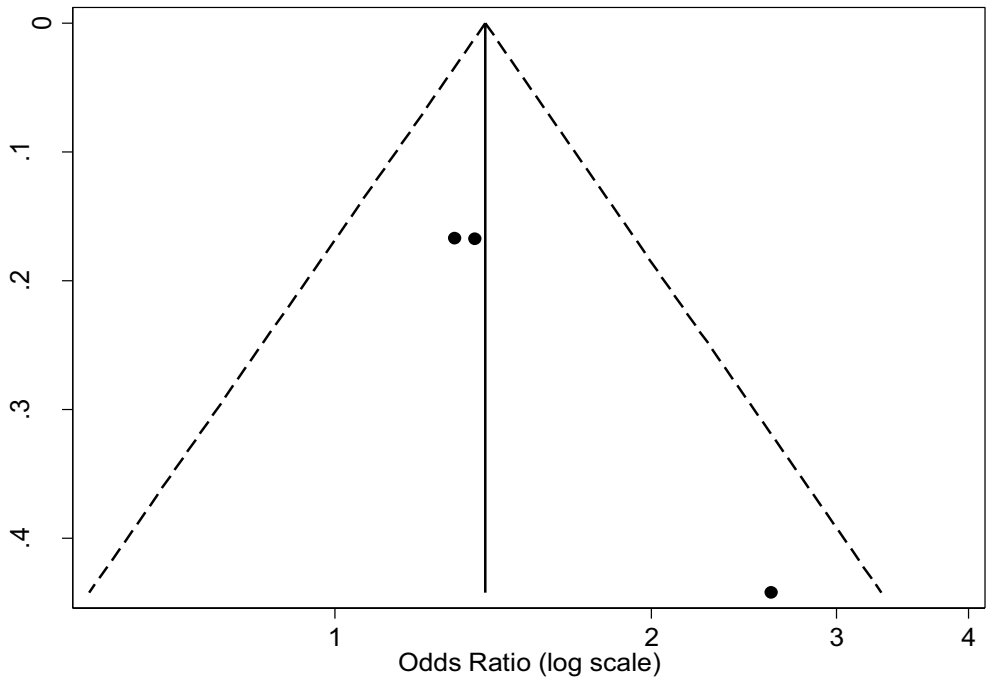


Figure S3. Flow diagram of study exclusion and inclusion for the meta-analysis



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.