Risk of stillbirth after a previous caesarean delivery: A Swedish nationwide cohort study

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Abstract

Objectives To investigate the risk of stillbirth in relation to; 1) a previous CD compared to those following a vaginal birth (VB); and 2) vaginal birth after caesarean (VBAC) compared to a repeat CD. **Design** Population-based cohort study. **Setting** The Swedish Medical Birth registry **Population** Women with their first and second singletons between 1982 and 2012. **Methods** Multivariable logistic regression models were performed to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI) of the association between CD in the first pregnancy and stillbirth in the second pregnancy and the association between VBAC and stillbirth. Sub-group analyses were performed by types of CD and timing of stillbirth (antepartum and intrapartum). **Main outcome measures** Stillbirth (antepartum and intrapartum fetal death). **Results** Of the 1,771,700 singleton births from 885,850 women,117,114 (13.2%) women had a CD in the first pregnancy, and 51,755 had VBAC in the second pregnancy. We found a 37% increased odds of stillbirth (aOR:1.37 [95% CI, 1.23–1.52]) in women with a previous CD compared to VB. The odds of intrapartum stillbirth was higher in previous pre-labour CD group (aOR:2.72 [95% CI, 1.51–4.91]) than the previous in-labour CD group (aOR:1.35 [95% CI, 0.76–2.40,]), although not statistically significant in the latter case. No increased odds was found for intrapartum stillbirth in women who had VBAC (aOR:0.99 [95% CI, 0.48–2.06]) compared to women who had a repeat CD, whereas women with antepartum stillbirth were more likely to have a VBAC (aOR:4.49 [95% CI, 3.55–5.67]). **Conclusions** This study confirms that a CD is associated with an increased risk of subsequent stillbirth, with a greater risk among pre-labour CD. This association is not solely mediated by increases in intrapartum asphyxia, uterine rupture or attempted VBAC. Further research is needed to understand this association, but these findings might help health care providers to reach optimal decisions regarding mode of birth, particularly when CD is unnecessary.

Introduction

Globally, Caesarean delivery (CD) rates doubled from 12% in 2000 to 21% (i.e. 29.7 million births) in 2015. However, evidence exists that 6.2 million CDs are performed annually without medical indications[2]. While CD can be a life-saving intervention for both the mother and the baby to reduce complications associated with childbirth, it is also performed in situations when neither the mother nor the fetus is at risk of complications. Increasing maternal age at first pregnancy, increasing body mass index (BMI), fetal malpresentation, and repeated CD (women with a previous CD) have been noted as the main factors contributing to the increased CD rate[3-5]. Although Sweden has one of the lowest CS rates in Europe, the CD rate has also increased over the last two decades from 15.5% in 2000 to almost 18% in 2020, with approximately 83–88% of the total

increase accounting for repeat CD[6, 7]. Due to the increased frequency of CD, studies have been conducted to assess the impact of CD on subsequent pregnancy outcomes[8], particularly the risk of stillbirth[9, 10] and preterm birth[11, 12].

Stillbirth, a baby born with no signs of life, is one of the most common serious adverse pregnancy outcomes. Approximately 2 million babies were stillborn at or after 28 weeks' gestation in 2019, with a global rate of 13.9 per 1000 births[15]. In high-income countries (HIC), stillbirth rates vary widely from 1.3 to 8.8 per 1,000 births[16]. A systematic review and meta-analysis conducted in 2011 to identify important risk factors for stillbirth in HIC reported a 21% increased odds of stillbirth (odds ratio (OR):1.21 [95% confidence interval (CI), 1.07–1.37]) in mothers with a previous CD[17]. Similarly, a more recent meta-analysis reported a 23% increased odds of stillbirth following CD (pooled OR:1.23 [95% CI, 1.08–1.40])[9]. Although both reviews reported similar findings, they were limited by high heterogeneity due in part to variation in the cause and timing of stillbirth. A 2020 Norwegian cohort study also reported a slightly higher odds of stillbirth following CD (adjusted OR (aOR):1.45 [95% CI, 1.22–1.73])[18], but the authors did not evaluate the impact of the type of CD on the reported associations[18]. Given the increasing rates of CD, a potential association between CD, specifically unnecessary CD, and subsequent stillbirth is of significant concern.

In pregnancies following a CD, birth can be achieved either by a repeat planned CD, known as elective repeat caesarean section (ERCS) or attempting a vaginal birth, known as vaginal birth after caesarean (VBAC). Limited studies have evaluated perinatal outcomes relating to VBAC[18, 19], and evidence on the association between VBAC and stillbirth is lacking and require further investigations. Therefore, we conducted this population-based cohort study to investigate if offspring in deliveries following a previous CD have a higher risk for stillbirth than offspring where the mother had a previous VB. We also examined the risk of stillbirth in women who had a VBAC delivery compared to those who had an ERCS.

Methods:

Study design and data sources

In this nationwide population-based cohort study, we used data from the Swedish Medical Birth Register (MBR), covering about 99% of all births in Sweden, and we included women with singleton births between January 1, 1982, and December 31, 2012.

The obstetric history of each woman, including data on comorbidity (such as diabetes, hypertension, and cardiovascular diseases), was obtained from the MBR and the Swedish National Patient Register (NPR). Data from these registers were linked using a unique Swedish personal identification number[20]. All diagnoses and complications during pregnancy or delivery are classified according to the Swedish version of the International Classification of Diseases (ICD), using the ICD-8 until 1986, the ICD-9 (1987 to 1996), and the ICD-10 since 1997. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (S1 Table).

Study population

The study cohort consisted of women who had their first two births between 1982 and 2012. Women who had singleton birth with available data on the mode of delivery on the 1st delivery were included. We excluded records where the first pregnancy was a multiple gestation or resulted in stillbirth. Ethical approval was obtained from Regional Ethical Review Board in Stockholm.

Mode of delivery

Mode of birth was categorised into VB and CD. We further subclassified this as follows: (1) spontaneous VB [reference group], (2) assisted delivery (vacuum/forceps), (3) pre-labour CD (before the onset of labour), (4)

in-labour CD (after the onset of labour), and (5) unspecified CD, where data on the type of CD were not available. The variable was defined this way to assess the effect of specific types of mode of birth in the 1st birth on the risk of stillbirth in the second pregnancy.

Then we considered mode of birth in both first and second births in order to assess the impact of VBAC on the risk of stillbirth, in which mode of delivery was grouped as follows: (1) repeat CD (CD in both pregnancies, [reference group]), (2) VBAC, (3) first VB and subsequent CD, and (4) VB in both pregnancies. It should be noted that mode of delivery recorded in the MBR is the 'final' mode of delivery, which may differ from the woman's intended mode of delivery. For example, a woman may attempt a trial of labour after a CD and fail, ending up with an in-labour CD. Thus, our study groups represent a good reflection of what happens in 'real-world' situations.

Outcome

The outcome of interest was stillbirth (antepartum and intrapartum fetal death). We used data from the Swedish MBR to identify stillbirths in the second pregnancy. This was defined as fetal death after 28 completed weeks (until June 2008) and fetal death after 22 completed weeks since July 2008.

We classified stillbirth into explained and unexplained stillbirth using an adapted version of the ReCoDe (RElevant COndition at DEath) classification system. The ReCoDe classification system is designed in a hierarchical manner to organise relevant clinical conditions associated with death in utero. It contains nine main categories, starting from**A** (conditions affecting the fetus) to **I**(unclassified), and each category is divided into several subgroups[22]. These categories include a wide range of clinical conditions related to the fetus, the placenta, the mother, and intrapartum conditions. On the other hand, unexplained cases are divided into two subcategories; cases with irrelevant conditions despite information or cases lacking available information[22].

We used the diagnosis variables from the MBR and NPR to classify stillbirth according to the underlying conditions of the ReCoDe classification system. All diseases and complications during pregnancy or delivery were classified according to the Swedish version of ICD codes. In addition, small for gestational age (SGA) was defined as a birthweight below 2 standard deviations (SDs) of the population mean birthweight adjusted for sex-specific and gestational age distributions or according to ICD codes (codes are shown in Table S2).

Statistical analysis

Maternal and birth characteristics are presented according to stillbirth and mode of delivery (Tables S3-S5) using frequency and percentages. Logistic regression models were performed to evaluate all associations using crude ORs and aORs, along with 95% CIs. First, we estimated the odds of stillbirth in the second birth following a CD in the first delivery, compared with the outcome of second deliveries following a prior VB. Second, we expanded the exposure variable to evaluate the impact of specific types of mode of delivery, specifically pre-labour CD and in-labour CD, on the associations. Finally, in a third model, we considered the mode of delivery in the first and second births to estimate the odds of stillbirth in women with a VBAC compared to women with a repeat CD. For completeness, we report the results for all the mode of delivery combinations in the first and second births.

Adjusted models included maternal age, BMI, smoking, education, country of origin, year of delivery, comorbidities (diabetes, chronic hypertension, cardiovascular disease), and pregnancy-related disorders (gestational diabetes, gestational hypertension, and preeclampsia) in the first pregnancy. We added a missing data category to control for missing data on BMI and smoking.

We undertook subgroup analysis based on ReCoDe classification categories, including a specific cause of stillbirth for explained stillbirths (cases with a known condition for death). We conducted separate analyses for causes of death restricted to stillbirths caused by: (a) lethal congenital anomaly, (b) SGA\fetal growth restriction, (c) any cord issue, (d) placental abruption, (e) any placental abnormalities, (f) any maternal

conditions, (g) uterine rupture, (h) intrapartum asphyxia/birth trauma. We additionally evaluated the association between a previous CD and explained stillbirth (including any relevant condition), unexplained stillbirth (including cases without relevant condition), and finally relevant versus no relevant condition (Table S7).

We did sensitivity analyses according to birth defects, preeclampsia, gestational diabetes, preterm birth, SGA, and time period. We also calculated the population attributable fraction (AF) (details are shown in Appendix page 2).

Statistical analyses were performed using Stata version 16.1 (StataCorp, Texas, USA), and all tests were two-sided with a 5% significance level.

Results

During the study period (1982-2012), 1,771,700 singleton births from 885,850 women were identified as eligible participants. Of the 885,850 women in the cohort, 2,428 had stillbirth in the second pregnancy (2,292 were antepartum stillbirths and 136 were intrapartum stillbirths), resulting a rate of 2.7 per 1,000 births. Women who had stillbirth in second pregnancy were older, more likely to be smokers, had higher BMI and had higher rates of chronic hypertension and diabetes, but lower gestational age compared with women who had live birth in their second pregnancy (Table 1).

The ReCoDe classification system indicated that fetal causes accounted for approximately 27% of the total stillbirths and the SGA\fetal growth restriction was the most frequent factor (21.2%, Table 2). The second most frequent cause was placental abruption (5.5%), followed by intrapartum asphyxia (4.4%).

The demographic characteristics of women and their babies according to mode of delivery are shown in Tables S3-S5. In first pregnancy, 117,114 (13.2%) mothers had a CD, while 768,736 (86.7%) had a VB. In the second pregnancy, almost half (53.6%) of the women with a previous CD also had CD in their subsequent pregnancy compared with 46.3% women who had VBAC. While 5.4% of mothers who had VB in first pregnancy had CD in their subsequent pregnancy.

Table 3 presents the crude and adjusted ORs of the association between CD in the first pregnancy and the risk of subsequent stillbirth. After adjusting for potential confounders, mothers with a previous CD had higher odds for antepartum stillbirth (aOR:1.35 [95% CI, 1.21–1.51]), intrapartum stillbirth (aOR:1.67 [95% CI, 1.09–2.53]), and any stillbirth (aOR:1.37 [95% CI, 1.23–1.52]) compared with mothers with a previous VB.

Analyses by type of CD in the first pregnancy showed increased odds of any subsequent stillbirth in women with a pre-labour CD (aOR:1.31 [95% CI, 1.09–1.58]) and in-labour CD (aOR:1.36 [95% CI, 1.19–1.55]), compared to women with a previous VB (Table 4). The odds of antepartum stillbirth was similarly higher in mothers with a previous pre-labour CD (aOR:1.24 [95% CI, 1.02–1.50]) and in-labour CD (aOR:1.36 [95% CI, 1.19–1.55]), compared to mothers with a previous VB. However, the risk of intrapartum stillbirth was higher in pre-labour CD group (aOR:2.72 [95% CI, 1.51–4.91]) than the in-labour CD group (aOR:1.35 [95% CI, 0.76–2.40,]), although not statistically significant for the latter group. Additionally, there was no statistically significant association between subsequent stillbirth and prior instrumental VB (Table 4).

Compared to women with a repeat CD, women with VBAC had an increased odds of antepartum stillbirth (aOR:4.49 [95% CI, 3.55–5.67]), but no association was found for intrapartum stillbirth (aOR:0.99 [95% CI, 0.48–2.06]) (Table S6). Similar results were found when VBAC was grouped according to type of CD in the second pregnancy into: (1) VB after pre-labour CD and (2) VB after in-labour CD. Both types of CD were associated with a greater odds of antepartum stillbirth but not intrapartum stillbirth (Table S10).

On the other hand, women who had CD after VB had an increased odds for both antepartum stillbirth (aOR:2.50 [95% CI, 1.92–3.25]) and intrapartum stillbirth (aOR:3.01 [95% CI, 1.67–5.43]) compared to

women who had a repeat CD (Table S6). However, in the subgroup analyses by types of CD, the increased odds of antepartum and intrapartum stillbirth was only observed in women who had in-labour CD after VB (aOR:3.67 [95% CI, 2.76–4.89] and 5.86 [95% CI, 3.20–10.7], respectively, Table S10) suggesting that increased risk of stillbirth could be due to complications during birth.

The results from the subgroup analysis by cause of stillbirth according to ReCoDe classification (Table S7) suggested that maternal conditions (aOR:1.78 [95% CI, 1.31–2.42]) and intrapartum asphyxia (aOR:2.04 [95% CI, 1.41–2.97]) have a significant impact on the association between CD and subsequent stillbirth. However, the results of other causes did not reach a statistically significant level (Table S7). Additionally, we found a 69% increased odds of explained stillbirth, with any known relevant condition (OR:1.69 [95% CI, 1.46–1.94]), but almost no effect for the unexplained cases (OR:1.08 [95% CI, 0.92–1.27]). We also found that the risk of unexplained stillbirth differed with gestational age. In an additional analysis of restricted gestational age [?]34 weeks (N= 872,351), the odds of unexplained stillbirth was 1.18 [95% CI, 1.00–1.38]), but this has attenuated after adjusting for confounding factors to 1.11 [95% CI, 0.94–1.30].

Results from sensitivity analyses were similar to the main findings (Appendix pages 1-2, Tables S8-S9). The population AF associated with prior CD was 0.049, meaning that CD in the first pregnancy accounted for approximately 5% of all subsequent stillbirths in the studied population.

Discussion

Main Findings

In the present study, we assessed the association between CD and subsequent stillbirth, and the impact of VBAC on stillbirth using data from Swedish MBR. The results show that women with a prior CD had an increased risk of subsequent stillbirth by 37%, and the risk was similar for both pre-labour CD (31% increase) and in-labour CD (36% increase). Pre-labour CD was associated with subsequent intrapartum stillbirth, but not in-labour CD. We also found an increased odds of antepartum stillbirth in women who had VBAC (compared to women who had a repeat CD), but no increased odds for intrapartum stillbirth in this group.

Strengths and limitations

The strengths of the present study include the use of national register-based data and the ability to make a linkage between registers which minimises risk of selection bias. As this is one of the largest studies investigating the risk of stillbirth following a previous CD, we were also able to conduct several subgroup and sensitivity analyses. We further classify stillbirth based on timing into antepartum and intrapartum stillbirth, as well as into explained and unexplained stillbirths. We restricted the analyses to singletons because CD and pregnancy complications related to stillbirth are more common in multiple gestations[35]. We also restricted the analyses to mothers who had live births in their first pregnancy since women with a history of stillbirth have nearly 5 times higher risk of subsequent stillbirth[21]. Limitations to the study include the possibility of misclassification for data on the clinical conditions (explaining cause of stillbirth) since data on some conditions, such as vasa praevia, were only available in ICD-9 and ICD-10. Other limitations related to unmeasured confounders as this is an observational study.

Implications (in light of other evidence)

Our finding regarding the increased risk for subsequent stillbirth in pregnancies with a previous CD is consistent with several other studies[18, 24-28]. However, most of the previous studies had inconsistencies and weaknesses in the methods and statistical analysis. For example, most studies did not exclude stillbirth from the first birth which is strongly associated with subsequent stillbirth[21].

Our findings agree with those from a recent Norwegian cohort study of 294 598 singleton second births, which reported a 33% increased odds of antepartum stillbirth (aOR:1.33 [95% CI, 1.08–1.63)] and a 84% increased odds of intrapartum stillbirth (aOR:1.84 [95% CI, 1.00–3.38])[18], although the timing of CD was not considered in this study.

When analysed by cause of fetal death, excess risk was apparent of unexplained stillbirth from 34 weeks' gestation as previously observed[10, 26]. It should be noted however that both studies failed to adjust for maternal comorbidities and our results attenuated to almost no effect in the adjusted model.

We found no increased odds of intrapartum stillbirth in women who had VBAC compared to those with repeat CD. It must be acknowledged however that there were few cases of intrapartum stillbirth (n=13) in women who had a VBAC. To our knowledge, none of the previous studies assessed the risk of stillbirth while adjusting for potential confounders in women who had a VBAC, possibly due to the rarity of this event. Findings from a systematic review and meta-analysis suggested a higher rate of perinatal mortality in women who had VBAC compared with a planned repeat CD (0.13% versus 0.05%), but no data were reported on stillbirth[19].

Two studies reported inconsistent results for the association between perinatal death and neonatal death in women with a first CD undergoing VBAC[29, 30]. Smith *et al.* assessed the risk of perinatal mortality, including intrapartum stillbirth and neonatal death using a large Scottish registry data of 313,238 singleton births and reported 11 times greater odds (aOR:11.7 [95% CI, 1.4–101.6]) compared to women with a repeat CD[29]. However, the reported CI was very wide, and the authors did not adjust for maternal comorbidities. The second study by O'Neill *et al* .[30] evaluated the risk of neonatal and infant death in women with a VBAC compared to women with a repeat CD using data from the Danish registry, including 61,626 births. The authors reported no increased odds of late neonatal death (aOR:0.97 [95% CI, 0.22–4.32) or infant death (aOR:1.12 [95% CI, 0.79 –1.59])[30].

Our analysis demonstrates that maternal conditions (including hypertensive disorders of pregnancy) and intrapartum asphyxia have a significant impact on the association between CD and subsequent stillbirth. This provides information that could formulate a causal hypothesis for the observed association. A case control study found that the uterine artery Doppler waveform between 18-22 weeks' gestation is more likely to be notched (14.5% vs. 6%, $p<0.001$) and have a higher average pulsatility index (1.25 vs 1.16, $p<0.02$) in women who had an elective CD compared to a VB[31]. Notably, women who had a prior CD also have a higher incidence of preeclampsia[32, 33]. Further research is required to further understanding of a causal relationship between CD and stillbirth; these studies suggest that investigation of impaired placental blood flow merits further exploration.

In case of antepartum stillbirth, it is common practice and a safe option for women with a previous CD to have VBAC as most of the risk of VBAC relates to the fetus[34]. Both the Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynecologists encourage that VB should be offered over CD in case of antepartum stillbirth.[34] This could explain the observed association between VBAC and antepartum stillbirth.

Conclusions

The findings of this study reinforce that a prior CD is associated with an increased risk of subsequent stillbirth, with the greatest risk for subsequent intrapartum stillbirth in women who had a previous pre-labour CD. The association could be explained, to some extent, by underlying maternal and intrapartum conditions. These findings might help women and health care providers to reach optimal decisions regarding mode of delivery. Considering the important public health consequences of stillbirth, further large-scale studies are needed to confirm findings of the present study, particularly to evaluate the association between VBAC and intrapartum stillbirth, as this will strengthen the current recommendations for the management of pregnancy following CD.

Author Contribution

ASK and AEPH conceived the study, SA and ASK prepared the data and conducted the statistical analysis. SA drafted the manuscript with support from all co-authors. All co-authors critically revised the manuscript, and have given approval of the submitted version.

Conflict of interest

None

Data availability statement

Research data are not shared

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Table 1. Maternal characteristics and infant characteristics in the second pregnancy

	Live birth (n= 883,422)	**Stillb**
Age (years), mean (SD)	29.6 (4.6)	30.2 (5
Age (years), (n, %)		
<20	4,066 (0.4)	20 (0.8
20-29	440,475 (49.8)	1,108 (
30-39	421,130 (47.6)	1,218 (
40	17,751 (2.0)	82 (3.3
Smoking, (n, %)		
Non-smokers	726,149 (82.2)	1,829 (
1-9 cigarettes/day	73,248 (8.2)	211 (8
10 cigarettes/day	36,623 (4.1)	146 (6
Missing	47,402 (5.3)	242 (9
Body mass index kg/m^2, (n, %)		
Underweight: <18.5	22,722 (2.5)	36 (1.4
Normal: [?]18.5 to <25	445,420 (50.4)	959 (3
Overweight: [?]25 to <30	158,019 (17.8)	490 (2
Obese: [?]30	63,832 (7.2)	283 (1
Missing	193,429 (21.9)	660 (2
Country of origin, (n, %)		
Sweden	752,195 (85.1)	1,976 (
Other Scandinavian	22,039 (2.4)	45 (1.8
Non-Scandinavian	108,079 (12.2)	402 (1
Missing	1,109 (0.1)	14 (0.5
Diabetes, (n, %)	5,968 (0.6)	45 (1.8
Cardiovascular disease, (n, %)	1,057 (0.1)	4 (0.1)
Chronic hypertension, (n,%)	4,538 (0.5)	35 (1.4
Hypertensive disorders of pregnancy, (n, %)*	19,112 (2.1)	65 (2.6
Gestational diabetes, (n, %)	5,508 (0.6)	27 (1.1
Types of delivery, (n,%)		
Spontaneous VB	727,531 (85.7)	1,974 (
Vacuum/forceps	21,803 (2.5)	34 (1.4
Pre -labour CD	55,577 (6.5)	66 (2.8
In-labour CD	38,223 (4.5)	192 (8

Unspecified CD	5,393 (0.6)	27 (1.1
Year of first birth, (n, %)		
1982-1989	132,873 (15.0)	333 (1
1990-1999	329,875 (37.3)	904 (3
2000-2012	420,674 (47.6)	1,191 (
Gestational age at birth in weeks, mean (SD)	39.4 (1.6)	35.3 (4
Birthweight in grams, mean (SD)	3616.7 (539.1)	2545.3
Sex, (n, %)		
Female	429,129 (48.5)	1,205 (
This include preeclampsia and gestational hypertension	*This include preeclampsia and gestational hypertension	*This

Table 2. Classification of stillbirth according to the ReCoDe (relevant condition at death) system

Group A: Fetus	
Group B: Umbilical cord	
Group C: Placenta	
Group D: Amniotic fluid	
Group E: Uterus	
Group F: Mother	
Group G: Intrapartum	
Group H: Other Trauma	
Group I: Unclassified	
Total	

Includes fetal abnormality/damage +Other placental complications include placenta infarction, placental insufficiency, and c

Table 3. OR with 95% CIs for stillbirth in the second pregnancy of 117,114 mothers who had a caesarean delivery in the first pregnancy compared with 768,736 mothers who had a vaginal birth in the first pregnancy

1st birth	

Vaginal birth
Any caesarean delivery

Vaginal birth
Any caesarean delivery

Vaginal birth
Any caesarean delivery
Adjusted for maternal age, body mass index, smoking, education, country of origin, year of delivery, and comorbidities (car

Table 4. ORs with 95% CIs of the associations between mode of delivery in the first pregnancy and stillbirth in the subsequent pregnancy

1st birth

Spontaneous VB
Vacuum/forceps
Pre-labour CD
In-labour CD
Unspecified CD

Spontaneous VB
Vacuum/forceps
Pre-labour CD
In-labour CD
Unspecified CD

Spontaneous VB
Vacuum/forceps
Pre-labour CD
In-labour CD
Unspecified CD
Abbreviations: CD, caesarean delivery; VB, vaginal birth *Adjusted for maternal age, body mass index, smoking, educatio

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`SUPPLEMENTARY MATERIAL.docx` available at https://authorea.com/users/604532/articles/634346-risk-of-stillbirth-after-a-previous-caesarean-delivery-a-swedish-nationwide-cohort-study