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The risk of unexplained antepartum stillbirth in second pregnancies following caesarean section in the first pregnancy

SL Wood,[a] S Chen,[b] S Ross,[a] R Sauve[c]

[a] Department of Obstetrics and Gynecology, University of Calgary, Foothills Hospital, Calgary, Alberta, Canada [b] Partnership for Research and Education in Mother's and Infants, Calgary Health Region, Foothills Hospital, Calgary, Alberta, Canada [c] Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada

Correspondence: Dr SL Wood, Department of Obstetrics and Gynecology, University of Calgary, Foothills Hospital, 1403 29th Street, NW Calgary, Alberta, Canada T2N 2T9. Email stephen.wood@calgaryhealthregion.ca

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Objective To determine if a previous caesarean section increases the risk of unexplained antepartum stillbirth in second pregnancies.

Study design Retrospective cohort study.

Setting Large Canadian perinatal database.

Population 158 502 second births.

Methods Data were obtained from a large perinatal database, which supplied data on demographics, pregnancy complications, maternal medical conditions, previous caesarean section and pregnancy outcomes.

Main outcome measures Total and unexplained stillbirth.

Results The antepartum stillbirth rate was 3.0/1000 in the previous caesarean section group compared with 2.7/1000 in the previous vaginal delivery group ($P = 0.46$). Multivariate logistic regression modelling, including terms for maternal age (polynomial), weight >91 kg, smoking during pregnancy, pre-pregnancy hypertension and diabetes, did not document an association between previous caesarean section and unexplained antepartum stillbirth (OR 1.27, 95% CI 0.92–1.77).

Conclusion Caesarean section in the first birth does not increase the risk of unexplained antepartum stillbirth in second pregnancies.

Keywords Caesarean section, risk factors, stillbirth.

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Introduction

Stillbirth continues to be an important problem in modern obstetrics with the latest US data demonstrating a rate of 6.4/1000.[1] Stillbirth rates have declined in the developing world since the 1950s but not to the same extent as neonatal deaths.[2] Attempts to lower the stillbirth rate further may be hampered by the incomplete understanding of the cause of the majority of stillbirths.[3] Several classification schemes have been suggested to characterise stillbirths and provide some indication of the causes. Among the most commonly used is the standard Wigglesworth classification or a number of subsequently described modifications.[4] There is, however, no universally accepted method for determining the precise cause of stillbirth, and therefore, the definition of 'unexplained' stillbirth may vary significantly between studies.

A number of factors have been consistently associated with stillbirth such as advanced maternal age, smoking during pregnancy, infections, diabetes, hypertension and more recently obesity. A recent paper gained widespread attention when it reported a significantly increased risk of unexplained antepartum stillbirth in women who had had a previous caesarean section.[5] However, that study was unable to control for the potential confounding of maternal obesity, which is associated with both stillbirth and caesarean section.[6] Nevertheless, a possible association between caesarean section and subsequent stillbirth is of significant concern as the rates of caesarean section continue to rise in North America.[7,8] Given the potential impact of this association, we sought to investigate this in our provincial perinatal database. We chose to study the risk of antepartum stillbirths in 'non-anomalous fetus' as this would be most informative to practitioners,

and our findings would not depend significantly on the exact classification system used.

Methods

Data for the study were obtained from the databases of the Alberta Perinatal Health Program (http://www.aphp.ca). The perinatal database contains pregnancy, delivery and pregnancy outcome data for over 350 000 births from 81 hospitals in Alberta Canada. Perinatal data for all births are submitted to the programme either as paper copies of the provincial delivery record or through an electronic extract. Perinatal mortality data collection includes additional information available from other perinatal forms such as the prenatal record and pathology reports. Every effort is made to ensure accuracy of the data at both the data source and by the Alberta Perinatal Health Program. Validation is performed on the data to check for errors and inconsistencies in documentation and coding. Perinatal and delivery records of all perinatal deaths are reviewed by the Hospital Perinatal Mortality Committee and then forwarded for further review to the provincial Reproductive Care Committee. After review, the committee classifies all stillbirths using the Wigglesworth coding system and enters the data in an electronic database.[4,9]

The study population was defined as women having a second birth recorded in the perinatal database for the years 1991–2004. Information was obtained on demographic characteristics, pregnancy complications, mode of delivery and outcome live birth or stillbirth. Information on potential confounding factors such as maternal diabetes, maternal weight, hypertension and smoking during pregnancy was also extracted. The actual maternal weight was not available but was dichotomised as less than or greater than 91 kg. The Reproductive Care Committee database was then searched for all identified stillbirths. Further information such as presumed cause of stillbirth, Wigglesworth classification and the results of the autopsies, if performed, were obtained. The primary outcome was defined, *a priori*, as antepartum stillbirth occurring before the onset of labour at greater than 24 weeks of gestation in nonanomalous fetuses without any obvious cause. The stillbirth data were reviewed by one author (S.L.W.), who was blinded to the mode of delivery in the first pregnancy, to ensure that only cases that met our outcome criteria were included. We specifically choose not to remove cases with abruption, growth restriction or pregnancy-induced hypertension. Our rationale was that a possible biological mechanism of caesarean section influencing subsequent pregnancy could be uterine scarring. This could presumably lead to poor placentation and consequences such as pregnancy-induced hypertension, abruption and growth restriction.

Analysis was planned in advance with multivariate logistic regression controlling for maternal age, diabetes, hypertension, smoking in pregnancy and weight >91 kg. A posteriori decision was made to also perform a survival analysis with a Cox proportional hazards model to allow easier comparison with some of the previous studies. All analysis was performed using Stata version 9. The study was approved by our local ethics review board.

Results

Data were obtained from the Alberta Perinatal Health Program for 158 502 second births. A flow chart of the study population is provided in Figure 1. Of these, 573 (0.4%) were missing the variable for previous caesarean section so they were excluded. The characteristics of the subjects are displayed in Table 1. The stillbirth rate in the group with a previous caesarean section was 4.6/1000 compared with 3.9/1000 in the previous vaginal delivery group ($P = 0.10$). Of the stillbirths, 21% in the previous caesarean section group and 19% in the previous vaginal delivery group were intrapartum (Figure 1). The antepartum stillbirth rate was 3.0/1000 in the previous caesarean section group compared with 2.7/1000 in the previous vaginal delivery group ($P = 0.46$). Of the 331 antepartum stillbirths ≥24 weeks identified in the perinatal database, 321 (97%) were confirmed by matching to the Reproductive Care Committee database. Of this group, 38 stillbirths had documented significant fetal anomalies and were removed from analysis. A further five cases were coded as intrapartum stillbirths and were also removed. After blinded review of the cases, a further 13 stillbirths were excluded from analysis. Of these, one was a fetal death at 15 weeks (with prolonged retention *in utero* until 24 weeks), four had nonimmune hydrops, four had cytomegalovirus or parvovirus infections, two followed maternal hypovolemic shock secondary to trauma in motor vehicle accidents, one with fetal bleeding after cordocentesis and one after intrapartum fetal bleeding from a vasa praevia. Of the remaining 265 stillbirths, there were 63 (2.1/1000) in the previous caesarean section group compared with 202 (1.6/1000) in the previous vaginal delivery group ($P = 0.06$).

The risk of antepartum stillbirth by gestational age is displayed in Figure 2. The other outcomes of the pregnancies are provided in Table 1. The rates of premature delivery less than 32 or 37 weeks and the frequency of low birthweight (<2500 g) were similar between those who had had a previous caesarean section and those who had not. The results of the univariate analysis are displayed in Table 2. Previous caesarean section was not significantly associated with unexplained antepartum stillbirth in the unadjusted analysis (OR 1.32, 95% CI 1.0–1.76) ($P = 0.06$). Maternal age >35 years and pre-pregnancy hypertension were associated with antepartum stillbirth. Maternal weight >91 kg, pre-pregnancy diabetes and smoking during pregnancy did not have statistically significant associations with stillbirth.

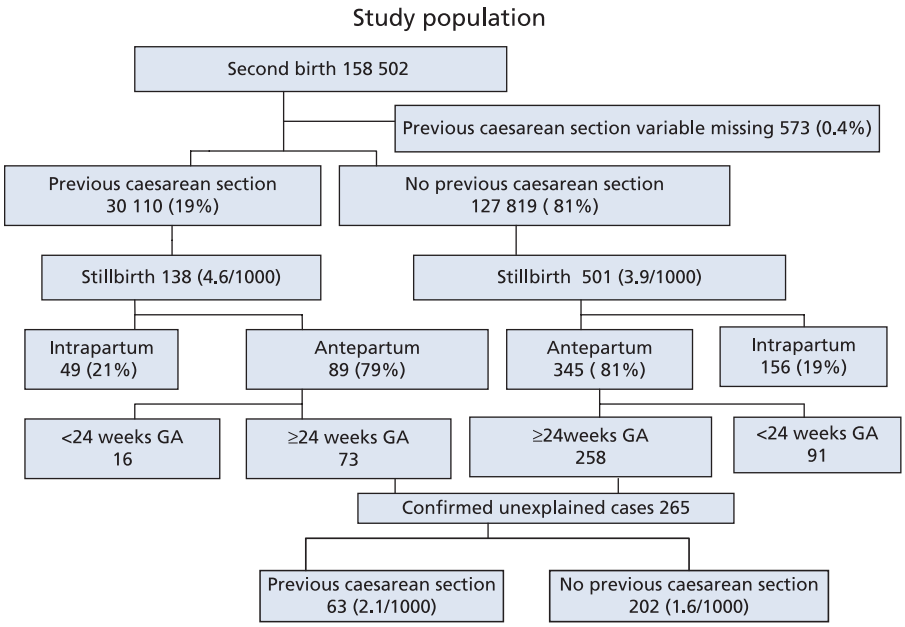

Figure 1. Study population. GA, gestational age.

In a significant number of subjects (23 549), data were not complete on all potential confounding factors such as maternal weight, smoking during pregnancy, pre-pregnancy diabetes and hypertension. Further review of the database revealed that this variable was not coded at all contributing hospitals until 1996. We felt that these were very important potential confounding factors, which had not been considered in some of the previous studies. Therefore, in the final logistic regression analysis, these cases could not contribute to the analysis. This resulted in a reduction in the number of cases of stillbirths from 265 to 210 and in the effective sample size from 158 502 to 132 590. The final multivariate logistic regression model included terms for maternal age (polynomial), weight >91 kg, smoking during pregnancy, pre-pregnancy hypertension and diabetes. (Table 3) In this model, previous caesarean section was not a significant risk factor for unexplained antepartum stillbirth (OR 1.27, 95% CI 0.92–1.77). The results did not change with removal of subjects who had

Table 1. Baseline characteristics

	No previous caesarean section (n = 127 819)	Previous caesarean section (n = 30 110)
Maternal characteristics		
Maternal age, mean (SD)	28.6 (5.9)	30.1 (5.5)
Gestational age, mean (range)	39.1 (24–44)	38.8 (24–44)
Weight ≥91 kg, *n* (%)	6621 (5.2)	2707 (9.0)
Smoking, *n* (%)	22 225 (17.4)	4477 (14.9)
Hypertension, *n* (%)	625 (0.6)	250 (1.0)
Diabetes, *n* (%)	604 (0.5)	318 (1.1)
Outcome of second pregnancy		
Induction of labour, *n* (%)	31 937 (25)	4117 (13.7)
Spontaneous vaginal delivery, *n* (%)	107 932 (84.4)	6172 (20.5)
Caesarean section, *n* (%)	7939 (6.2)	198 977 (66.1)
Delivery, *n* (%)		
≤32 weeks	1838 (1.4)	470 (1.5)
<37 weeks	7512 (5.8)	1919 (6.4)
>41 weeks	18887 (14.8)	3145 (10.4)
Birthweight in g, mean (SD)	3432 (624)	3433 (653)
Birthweight ≤2500 g, *n* (%)	5631 (4.4)	1407 (4.7)

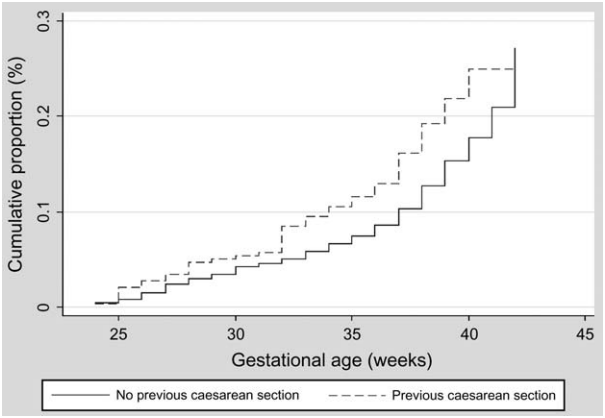

Figure 2. Cumulative proportion of unexplained antepartum stillbirths per week of gestation.

Table 2. Univariate analysis for unexplained antepartum stillbirth >24 weeks

	OR (95% CI)	*P* value
Previous caesarean section	1.32 (1.0–1.76)	0.06
Maternal age >35 years	1.56 (1.16–2.11)	0.004
Weight >91 kg	1.48 (0.94–2.32)	0.08
Smoking	1.12 (0.81–1.60)	0.49
Pre-pregnancy diabetes	2.61 (0.97–7.02)	0.06
Pre-pregnancy hypertension	3.70 (1.52–9.02)	0.004

a stillbirth in their first pregnancy nor with varying the covariates included in the model (data not shown).

Survival analysis documented similar but not identical results to the primary analysis. Unadjusted analysis suggested a borderline statistically significant increased risk of unexplained antepartum stillbirth with previous caesarean section (hazard ratio 1.44 [95% CI 1.04, 1.98]). However, adjusted analysis using the same variables as in the multivariate logistic regression model did not demonstrate a statistically significant increase in risk (hazard ratio 1.36 [0.98, 1.89]).

Discussion

Our study did not demonstrate an increased risk of unexplained antepartum stillbirth in second pregnancies in women who had had a previous caesarean section. This result is in contrast to a previous similar study of Scottish women.[5] Since, we initiated our study, five other studies have evaluated stillbirth risk in pregnancies following caesarean section with mixed results. Salihu *et al.*[10] examined the rates of stillbirth in second pregnancies in Missouri. Overall, they did not find an increased risk of stillbirth in women who had had a previous caesarean section, although on subgroup analysis, they did document an increased risk in African-American women. It should be noted that this study included intrapartum stillbirths as well as antepartum stillbirths and that no detailed data on any of the stillbirths were available to the investigators. Taylor *et al.*[11] reported a similar rate of stillbirth in second births of women in New Zealand who had had a previous caesarean section compared with those who had not. However, this study also included intrapartum stillbirths and those associated with congenital anomalies. The largest study to date was recently reported by Bahtiyar *et al.*[12] who conducted a cross-sectional survey of US perinatal mortality data for the years 1995–97. They documented a statistically significant reduced risk of stillbirth in women with a previous caesarean section. However, this study only assessed term stillbirth and also included women with intrapartum stillbirth. Kennare *et al.*[13] reported an increase in a number of adverse perinatal events in second births in a relatively small sample of women of 8725 Australian women who had had a previous caesarean section. The risk of total stillbirth was increased but was only statistically significant after adjusted analyses. The risk of unexplained stillbirth was apparent in both crude and adjusted analysis, but again, this included both intrapartum and antepartum stillbirths. In the most recent paper, Gray *et al.*[14] used a UK perinatal database with birth data for the years 1968–89. They reported an increased risk of explained stillbirth but no statistically significant increase in the risk of total or unexplained stillbirth. Like several of the previous reports, the available data did not allow for differentiation between intrapartum and antepartum stillbirths. Also, unlike the previous studies, more than one birth per subject was included in the analysis.

Table 3. Multivariate analysis for unexplained antepartum stillbirth >24 weeks

	Adjusted OR (95% CI)	*P* value
Previous caesarean section	1.27 (0.92–1.77)	0.15
Maternal age	0.68 (0.56–0.82)	<0.001
Maternal age squared	1.01 (1.00–1.10)	<0.001
Weight >91 kg	1.38 (0.87–2.19)	0.17
Smoking	1.04 (0.74–1.47)	0.82
Pre-pregnancy diabetes	2.28 (0.84–6.23)	0.11
Pre-pregnancy hypertension	3.09 (1.25–7.63)	0.02

It is apparent that an increased risk of stillbirth in pregnancies after caesarean section has not been consistently observed. As caesarean section itself is not likely to vary significantly between studies, differences in stillbirth definitions or uncontrolled confounding factors are the most likely explanations. The initial Scottish study that generated interest in this question restricted analysis to antepartum stillbirths, and their primary finding was an increased risk of unexplained stillbirth. All of the subsequent studies have included intrapartum stillbirths as well as antepartum stillbirths. Additionally, most have not been able to restrict analysis to fetuses without congenital anomalies or to those without an obvious cause for the stillbirth.

It is difficult to anticipate the effect of including intrapartum stillbirths on the results of these studies. However, one could anticipate that the risk of intrapartum stillbirths would be reduced in women who had had a previous caesarean section as they tend to have a repeat caesarean section and therefore avoid the small but appreciable risk of fetal death in labour. However, this is only the case if the proportion of women who are attempting a trial of labour after caesarean section is low. If this proportion is high then this would nullify this effect and may even reverse it due to the documented higher fetal risk with a trial of labour in part due to the increased risk of uterine rupture.[15]

Ultimately, our study is one of only two where the association between previous caesarean section and antepartum stillbirth has been examined. Our study was unable to replicate the findings of the previous Scottish study,[5] which reported a significant increased risk of unexplained stillbirth in women who had had a previous caesarean section. One possible explanation for this variability in results is the slightly differing definitions of unexplained stillbirths between the two studies. Although this is possible, we do not believe that differences in the definition of unexplained stillbirth would have affected our results. Unlike Smith *et al.*,[5] we did not document differences in the crude rates of total stillbirth, antepartum stillbirth or 'unexplained' antepartum stillbirth >24 weeks between the previous caesarean section group and the vaginal delivery group. Therefore, we feel that it would be highly unlikely that a change in the definition of 'unexplained' stillbirth would differentially increase the proportion of stillbirths in the previous caesarean section group to the point that a statistically significant association emerged.

Low power is always a potential explanation for any negative study, including ours. Still, our study was almost identical to the Scottish study in terms of both the number of subjects included and the number of stillbirths available for analysis. A *post hoc* power calculation indicates that our study had a 99% power to confirm a statistically significant two-fold increase in the risk of stillbirth but only 35% power to do so with an odds ration of 1.3. Admittedly, a larger study may have been able to reach statistical significance with the same degree of association with stillbirth as we observed. However, it is equally likely that the modest association we observed, OR = 1.27, is due to incomplete control of confounding factors. This could either be due to unknown confounders or due to incomplete control of known confounders. In particular, maternal weight was incompletely recorded as we did not have the actual weight recorded in our database, only weight >91 kg. It is possible that the association we observed would have been further attenuated in a logistic regression model with a more precisely measured variable, such as body mass index. It is also worth noting that this factor was not controlled for in most of the previous studies.[5,11–13] Ultimately, as many clinicians would view a potential increase in the risk of stillbirth of 30% to be clinically important, the results of our study cannot be considered as definitively confirming the 'safety' of caesarean section in this regard.

Conclusions

Our study did not confirm previous findings of an increased risk of unexplained stillbirth in women who had had a previous caesarean section. As the association between previous caesarean section and total stillbirth or unexplained stillbirth has not been consistently observed, we think it would be very premature to conclude a causal association exists. However, given the important potential public health implications, further research on this question should be undertaken with other large perinatal databases.

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Details of ethics approval

The study was approved by the University of Calgary Office of Medical Bioethics on 2005/03/17. Protocol #18311.

Contribution to authorship

The study was conceived by S.L.W. S.L.W., R.S., S.R. and S.C. developed the protocol and the analysis strategy. S.C. obtained the data from the perinatal database and prepared the data for analysis. S.W. and S.C. performed the analysis. All authors contributed to the interpretation of the analysis. S.L.W. was the primary author of the manuscript and S.C. prepared the figures. All authors contributed to and reviewed the manuscript.

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