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Cesarean Delivery and Risk for Subsequent Ectopic Pregnancy

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Abstract

Objective—This study aims to examine the risk for subsequent ectopic pregnancy in women with prior cesarean delivery.

Study Design—Women with a history of at least one cesarean delivery in the state of Utah during 1996 to 2011 were identified and compared with women with vaginal delivery only. The primary outcome was subsequent ectopic pregnancy. Data were analyzed by multivariate logistic regression and stratified by first, second, or third live births. Model covariates included maternal age, ethnicity, marital status, education level, gravidity, and prior ectopic pregnancy.

Results—Overall, 260,249 women with at least one live birth were identified. After exclusions, 255,082, 154,930, and 70,228 women had at least one, two, and three prior live births that lead to 531, 199, and 62 subsequent ectopic pregnancies, respectively. Women who had one prior cesarean delivery were not at increased risk for subsequent ectopic pregnancy in relation to women with no prior cesarean delivery. However, women with two of two, two of three, or three of three prior cesareans had increased risk for subsequent ectopic pregnancy with odds ratios (95% confidence interval) of 1.54 (1.06–2.22), 3.50 (1.49–8.24), and 1.99 (1.00–3.98), respectively.

Conclusion—History of two or three cesarean deliveries is associated with increased risk for subsequent ectopic pregnancy.

Keywords

cesarean delivery; ectopic pregnancy; long-term morbidity; risk factors

Cesarean delivery rates have increased dramatically over the past 20 years. By 2009, approximately one-third of all deliveries were by cesarean, an increase of approximately 60% over the preceding 13 years.¹ Along with this increase in cesarean delivery rates,

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however, has come the recognition that cesarean delivery is associated with both short- and long-term maternal morbidities.

Cesarean delivery is associated with longer hospital stays, increased rates of infection (e.g., endometritis, pneumonia, or wound infection), hemorrhage, the need for blood transfusions and venous thromboembolism.^{2–5} Cesarean delivery has also been associated with increased risks for future obstetric complications such as increased surgical morbidity, abnormal placentation, and placenta accreta, a potentially life-threatening condition.^{3,5} Although data are limited, it has been speculated that patients who have had a cesarean delivery may be at increased risk for impaired fertility, spontaneous abortion or ectopic pregnancy, especially cesarean scar ectopic, in subsequent gestations.⁵

Studies to examine subsequent ectopic pregnancy are limited by the ability to conduct thorough follow-up of patients after their initial postpartum discharge. Patients will often not develop a subsequent ectopic pregnancy for years following a cesarean delivery, and for a variety of reasons, such as patient relocation or convenience, care may be given by different providers at varying locations. Accordingly, studies that have examined risk of subsequent ectopic pregnancy have been limited by small numbers, bias due to incomplete follow-up and have reported conflicting results.^{6–12}

The Utah Population Database (UPDB) is a large comprehensive and representative database that links patient-specific information from public and hospital records over a large time span throughout the state of Utah. This provides the ability to capture most, if not all, hospitalizations or procedures that occurred to specific patients within the state of Utah, regardless of the treatment facility and even if the subsequent encounter occurred years after the exposure of interest (i.e., cesarean delivery). Thus, our objective was to utilize the UPDB to examine risk for subsequent ectopic pregnancy in women with history of prior cesarean delivery.

Methods

This was a retrospective cohort study. Data were derived from the UPDB, a large, population-based individual-level resource that links genealogical, medical, and vital records to support medical research. We included women who gave birth in Utah during 1996 to 2011. Records for second and third live births were also included. In cases of multiple live births, the first was selected. This period represents an era where the UPDB holds data on all statewide electronic records based on birth certificates, inpatient discharge records, and ambulatory surgery records.

Identifying whether a birth was delivered via cesarean delivery or vaginally was determined by a combination of two methods: (1) cesarean delivery listed on a Utah birth certificate and (2) cesarean delivery mentioned on a Utah Inpatient Discharge record based on procedure codes (International Classification of Diseases [ICD]-9-CM 74.0, 74.1, 74.2, 74.4, 74.9), even if cesarean delivery was not indicated on the birth certificate. In pregnancies flagged as a cesarean delivery on the birth certificate, data on birth order was assessed, and mothers with inconsistent, incomplete, or illogical sequences of births were excluded. Examples

include fetal deaths later reported as live births, uncertainty about a birth being an adoption or biological, and two singleton births with the same birth order. Ectopic pregnancies were identified using ICD-9-CM diagnosis codes 633.0, 633.1, 633.2, 633.8, or 633.9 or CPT codes 59150, 59151, or 59899. These codes were obtained from the statewide Ambulatory Surgery or Inpatient Discharge records.

The outcome analyzed was ever or never having an ectopic pregnancy following a given live birth, and the data were analyzed using multivariate logistic regression. Analyses were stratified by the first, second, or third live birth. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). Both the Institutional Review Board and the Utah Resource for Genetic and Epidemiologic Research of the University of Utah approved this study. The Institutional Review Boards did not require a written informed consent.

Results

A total of 260,249 women who had a live first birth in the state of Utah during 1996 to 2011 and offspring born in 1996 or later were identified from the UPDB. After exclusions, there were 255,082 women with at least one live birth, 154,930 with at least two live births, and 70,228 with at least three live births. Patient characteristics for the overall cohort are shown in ►Table 1. A total of 531 ectopic pregnancies following at least one live birth were identified (0.2%), 199 of which occurred after two live births (0.1%) and 62 of which occurred after three live births (0.1%). No ectopic pregnancies were identified after four live births, so subsequent analyses were restricted to at least one, two, or three live births.

Descriptive comparisons were made of characteristics and outcomes for those women with at least one prior cesarean delivery with those women who had only vaginal deliveries, stratified by number of total live births (►Table 2). For the cohort of women with at least one live birth, women with at least one cesarean delivery were more likely to be older (24.7 vs. 23.3 years, $p < 0.001$), Hispanic (22.3 vs. 20.8%, $p < 0.001$), and more likely to have had a prior ectopic pregnancy (0.19 vs. 0.15%, $p = 0.04$). The proportion of women having a subsequent ectopic pregnancy was not significantly different among groups ($p = 0.11$). For women with at least two live births, compared with women with vaginal delivery only, women with cesarean delivery were again more likely to be older (26.9 vs. 25.8 years, $p < 0.001$) and Hispanic (23.3 vs. 21.6%, $p < 0.001$). There was no significant difference in either the proportion of women who had a history ectopic pregnancy ($p = 0.17$) or developed a subsequent ectopic pregnancy ($p = 0.17$). Results were similar for women with three live births.

Similarly, we compared characteristics and outcomes for women with at least one prior cesarean delivery with those women who had only vaginal deliveries, stratified by both number of total live births, and number of prior cesarean deliveries (►Table 3). Though there was a trend toward increased risk of subsequent ectopic pregnancy with increasing number of prior cesarean deliveries, the difference was not statistically significant.

We next utilized logistic regression models to assess risk for subsequent ectopic pregnancy after the first, second, or third live birth, respectively (►Table 4). Covariates in these models were maternal age at the time of the relevant live birth, Hispanic ethnicity, marital status, education level, and whether there were any prior ectopic pregnancies. For the first birth analysis, the model examined the effect of mode of delivery on the risk for ectopic pregnancy subsequent to the first birth. For the second birth analysis, the models considered whether one or both prior live births were delivered by cesarean section. Similarly, the third birth analysis considered whether one, two, or all three of the prior live births were delivered by cesarean. For each model, just one prior cesarean delivery was not significantly associated with subsequent ectopic pregnancy. However, when two of two live births were delivered by cesarean, the odds ratio for subsequent ectopic pregnancy was 1.54 (95% confidence interval [CI]: 1.06–2.22). Similarly, if two of three or three of three live births were delivered by cesarean, the odds ratio for subsequent ectopic pregnancy was 3.50 (95% CI: 1.49–8.24) and 1.99 (95% CI: 1.00–3.97), respectively.

Comment

In women with at least two live births, having two or more prior cesarean deliveries is associated with increased risk for subsequent ectopic pregnancy. Ectopic pregnancy complicates approximately 2% of all pregnancies and can lead to significant maternal morbidity and even mortality, accounting for 6% of all pregnancy-related deaths in the United States despite improved methods of diagnosis and treatment.¹³ In addition to risk factors such as prior ectopic pregnancy, history of tubal pathology or surgery, pelvic infection and smoking, cesarean deliveries have been implicated as a risk factor for subsequent ectopic pregnancy.^{8,10,12} Potential pathophysiologic mechanisms that have been suggested include infection and adhesion formation,¹⁴ or in the case of cesarean scar ectopic pregnancy, abnormal embryologic invasion of the scar akin to placenta accreta.⁵

Reports on the association of cesarean delivery with subsequent ectopic pregnancy have yielded conflicting data, and a recently published meta-analysis by O'Neill et al concluded that there is no evidence of an association.¹⁴ After exclusions of any study that did not report on confounders, the primary analysis included 4,716 women and 490 ectopic pregnancies with a pooled crude odds ratio of having an ectopic pregnancy after cesarean delivery of 1.04 (95% CI: 0.52–2.05). Surprisingly, the number of patients with prior cesarean deliveries, the key exposure, was not reported, and all five studies included in the primary analysis were case-control studies. While this is an appropriate study design when the outcome of interest has an incidence as low as ectopic pregnancy,^{9–12,15} the number of patients in each study with a history of at least one cesarean delivery was very low.

Barnhart et al compared 367 cases (i.e., patients with ectopic pregnancy) to 1,659 controls, all of which were selected because they sought treatment for pain or bleeding in the first trimester.⁹ They reported an odds ratio for ectopic pregnancy of 0.81 (95% CI: 0.47–1.04) with history of a single prior cesarean delivery based on 16 cases (4.4%) versus 89 controls (5.5%) with that exposure. Similarly, an odds ratio for ectopic pregnancy of 1.69 (95% CI: 0.78–3.68) was reported for 9 cases (2.4%) versus 24 controls (1.4%) with a history of two or more cesarean deliveries. Kendrick et al included 138 cases and 842 pregnant controls.¹¹

This included just 11 (8.0%) cases compared with 133 (15.8%) controls with one prior cesarean delivery for an odds ratio of 0.4 (95% CI: 0.2–0.9), and 7 (5.1%) cases compared with 30 (3.6%) controls with two or more cesarean deliveries for an odds ratio of 1.5 (95% CI: 0.6–3.6) for ectopic pregnancy. In each of these studies, there was a nonsignificant trend toward increased risk with greater number of cesarean delivery, although the low exposure incidence precludes any definitive conclusions.

The remaining three studies included in the meta-analysis reported the exposure as ever or never having had a cesarean delivery, but the number of cesareans was not specified. A significant protective effect was reported by Machalas et al based on 18 of 361 cases and 52 of 420 pregnant controls with prior cesarean delivery for an odds ratio 0.40 (95% CI: 0.31–0.50).¹⁵ However, in contrast to the protective effect reported for cesarean delivery, the authors still conclude that previous pelvic surgery (including any prior pelvic surgery) increased the risk of ectopic pregnancy. Parazzini et al reported a significant association between prior cesarean and ectopic pregnancy with an odds ratio 8.0 (95% CI: 2.0–32.7).¹² This analysis was based on 38 parous cases compared with 92 parous controls including just 8 cases and 3 controls with history of cesarean delivery. Karaer et al also found a significant association from 225 cases, 20.4% of which (45) had prior cesarean delivery, compared with 375 controls, 11.5% of which (44) had a prior cesarean delivery with an adjusted odds ratio of 2.1 (95% CI: 1.2–3.6) for ectopic pregnancy. Thus, the five studies accounting for the primary analysis in the meta-analysis by O'Neill et al included just 114 cases and 375 controls with at least one prior cesarean delivery.

Hemminki and Meriläinen utilized large, nationwide birth registries in Finland to compare 7,474 women with a cesarean delivery in an index pregnancy to 8,999 age-matched controls and did not find a significant association of cesarean delivery with ectopic pregnancy, though they did report controlling for possible confounders.⁸ For our study, we utilized a larger, statewide, population-based database to address the question of whether cesarean delivery is associated with subsequent ectopic pregnancy. Our initial cohort included 52,078 women with at least one cesarean delivery. Even after restricting our analysis to women with at least two live births, there remained 23,473 women with at least two cesarean deliveries. Additionally, we were able to control for several possible confounders.

We acknowledge that our study has several limitations. In particular, ascertainment of patients with ectopic pregnancy was limited to operative reports and discharge summaries, which are likely to significantly underreport the true prevalence of ectopic pregnancy in the state of Utah during the study period. Improved diagnostic techniques have led to an earlier recognition allowing for nonsurgical, outpatient interventions of unruptured ectopic pregnancies that rarely require admission to the hospital.¹⁶ However, this limitation should not introduce bias as the limitation likely applies equally to both exposed and unexposed patients. Similarly, we found that two or more cesarean deliveries were significantly associated with subsequent ectopic pregnancy in women with either more than two or more than three total live births, but the association of three or more cesarean deliveries with ectopic pregnancy was not significant. Because of limited ability to identify cases of ectopic pregnancy that did not require hospital admission or surgery, there were just 29 women with at least three prior live births and at least one prior cesarean delivery, so we were likely

statistically underpowered to detect a significant result in this group. Regardless, an apparent trend with an odds ratio of 1.99 (95% CI: 1.00–3.97) was noted. Although, we were able to control for several possible confounders in our models (e.g., history of ectopic pregnancy or maternal age), we were unable to account for all variables of interest, including those that might lead to confounding by indication for the cesarean delivery (e.g., history of pelvic infection, prior infertility treatment, or prior pelvic surgery). In addition, we were unable to account for the location of any ectopic pregnancies (e.g., tubal vs. cesarean scar). Cesarean scar ectopic pregnancies are often treated medically and may not have been captured in our dataset. However, this limitation would likely bias toward the null as this may underestimate the number of ectopic pregnancies in patients with prior cesarean delivery. Finally, an additional limitation of the UPDB is that the data are limited to patients who received their care within the state during the time period and movement of patients into and out of the state during that period could result in missed cases, but again, this limitation should apply equally to exposed and unexposed patients.

Our study also had numerous strengths. When studying a relatively uncommon outcome, it is often advantageous to use a case-control study design to identify an adequate number of cases and then examine their exposures compared with controls. As an alternative, the UPDB allowed us to examine a large number of patients using a population-based cohort study design. With the large number of patients in the cohort, we identified more patients with the outcome (i.e., ectopic pregnancy) than had previously been reported, and importantly, we examined a large number of patients who had the exposure of interest (i.e., history of cesarean delivery). In addition, we were able to analyze individuals for the development of ectopic pregnancy for many years after their delivery (up to 15 years for patients delivering in 1996) regardless of where they received care as long as it was in the state of Utah.

In conclusion, a history of two or three prior cesarean deliveries is associated with subsequent ectopic pregnancy. History of multiple prior cesarean deliveries should be considered when determining a patient's individual risk for ectopic pregnancy. Importantly, ectopic is another potential long-term complication of multiple cesarean deliveries and should be taken into account when considering the merits of primary cesarean delivery or elective repeat cesarean delivery versus a trial of labor after cesarean.

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Table 1

Patient characteristics by number of live births

Variable	1 Live birth (<i>n</i> = 255,082)	2 Live births (<i>n</i> = 154,930)	3 Live births (<i>n</i> = 70,228)
Subsequent ectopic pregnancy	531 (0.2%)	199 (0.1%)	62 (0.1%)
Maternal age (y)	23.6 ± 4.7	26.1 ± 4.4	28.1 ± 4.0
Cesarean delivery			
1	52,078 (20.4%)	11,978 (7.7%)	5,502 (7.8%)
2	-	23,473 (15.2%)	2,440 (3.5%)
3		-	7,989 (11.4%)
Prior ectopic pregnancy	410 (0.2%)	261 (0.2%)	117 (0.2%)
Hispanic ethnicity	54,090 (21.2%)	34,128 (22.0%)	15,076 (21.5%)
Not married	56,273 (22.1%)	15,856 (10.2%)	4,899 (7.0%)
Education level (y)	13.3 ± 2.2	13.4 ± 2.0	13.4 ± 1.9

Note: Data are *n* (%) or mean ± SD.

Table 2

Comparison of women with at least one prior cesarean delivery to women with only vaginal deliveries, by number of total live births

1 Live birth			
Variable	Vaginal only (n = 191,708)	1 Cesarean (n = 63,374)	p-Value
Subsequent ectopic pregnancy	383 (0.20%)	148 (0.23%)	0.11
Maternal age (y)	23.3 ± 4.4	24.7 ± 5.2	< 0.001
Prior ectopic pregnancy	290 (0.15%)	120 (0.19%)	0.04
Hispanic ethnicity	39,937 (20.8%)	14,153 (22.3%)	< 0.001
Unmarried	42,433 (22.1%)	13,840 (21.8%)	0.12
Education level (y)	13.3 ± 2.2	13.3 ± 2.2	0.43
2 Live births			
Variable	Vaginal only (n = 115,560)	1 Cesarean (n = 39,370)	p-Value
Subsequent ectopic pregnancy	140 (0.12%)	59 (0.15%)	0.17
Maternal age (y)	25.8 ± 4.2	26.9 ± 4.8	< 0.001
Prior ectopic pregnancy	185 (0.16%)	76 (0.19%)	0.17
Hispanic ethnicity	24,946 (21.6%)	9,182 (23.3%)	< 0.001
Unmarried	11,739 (10.2%)	4,117 (10.5%)	0.09
Education level (y)	13.4 ± 2.0	13.4 ± 2.0	0.02
3 Live births			
Variable	Vaginal only (n = 53,225)	1 Cesarean (n = 17,003)	p-Value
Subsequent ectopic pregnancy	44 (0.08%)	18 (0.11%)	0.38
Maternal age (y)	27.9 ± 3.9	28.7 ± 4.2	< 0.001
Prior ectopic pregnancy	88 (0.17%)	29 (0.17%)	0.88
Hispanic ethnicity	11,192 (21.0%)	3,884 (22.8%)	< 0.001
Unmarried	3,631 (6.8%)	1,268 (7.5%)	0.005
Education level (y)	13.5 ± 1.9	13.4 ± 1.9	0.001

Note: Data are *n* (%) or mean ± SD. *p*-values from chi-square test or Satterthwaite *t*-test, where appropriate.

Table 3

Comparison of women with prior cesarean deliveries to women with only vaginal deliveries, by number of prior cesareans

1 Live birth			
Variable	Vaginal only (n = 191,708)	1 Cesarean (n = 63,374)	p-Value
Subsequent ectopic pregnancy	383 (0.20%)	148 (0.23%)	0.11
Maternal age (y)	23.3 ± 4.4	24.7 ± 5.2	< 0.001
Prior ectopic pregnancy	290 (0.15%)	120 (0.19%)	0.04
Hispanic ethnicity	39,937 (20.8%)	14,153 (22.3%)	< 0.001
Unmarried	42,433 (22.1%)	13,840 (21.8%)	0.12
Education level (y)	13.3 ± 2.2	13.3 ± 2.2	0.43
2 Live births			
Variable	Vaginal only (n = 115,560)	2 Cesareans (n = 26,557)	p-Value
Subsequent ectopic pregnancy	140 (0.12%)	44 (0.17%)	0.07
Maternal age (y)	25.8 ± 4.2	27.1 ± 4.8	< 0.001
Prior ectopic pregnancy	185 (0.16%)	54 (0.20%)	0.12
Hispanic ethnicity	24,946 (21.6%)	6,252 (23.5%)	< 0.001
Unmarried	11,739 (10.2%)	2,783 (10.5%)	0.12
Education level (y)	13.4 ± 2.0	13.4 ± 1.9	0.002
3–4 Live births			
Variable	Vaginal only (n = 53,225)	3 Cesareans (n = 8,431)	p-Value
Subsequent ectopic pregnancy	44 (0.08%)	11 (0.13%)	0.17
Maternal age (y)	27.9 ± 3.9	28.9 ± 4.2	< 0.001
Prior ectopic pregnancy	88 (0.17%)	19 (0.23%)	0.22
Hispanic ethnicity	11,192 (21.0%)	1,971 (23.4%)	< 0.001
Unmarried	3,631 (6.8%)	569 (6.8%)	0.80
Education level (y)	13.5 ± 1.9	13.4 ± 1.8	0.006

Note: Data are *n* (%) or mean ± SD. *p*-values from chi-square test or Satterthwaite *t*-test, where appropriate.

Table 4

Multivariate logistic regression models for risks of ectopic pregnancy after 1, 2, or 3 cesarean deliveries

1 Live birth	
Variable	OR (95% CI)
Cesarean delivery for first birth	1.15 (0.94, 1.42)
2 Live births	
Variable	OR (95% CI)
Cesarean delivery for one of two births	1.42 (0.89, 2.29)
Cesarean delivery for two of two births	1.54 (1.06, 2.22)
3 Live births	
Variable	OR (95% CI)
Cesarean delivery for one of three births	0.23 (0.032, 1.66)
Cesarean delivery for two of three births	3.50 (1.49, 8.24)
Cesarean delivery for three of three births	1.99 (1.00, 3.97)

Abbreviations: CI, confidence interval; OR, odds ratio.

Note: For each model, the sample was restricted to mothers at the time of their first, second, or third live birth. The outcome analyzed was ever or never experiencing an ectopic pregnancy following a given live birth. Additional covariates in the models included maternal age at the time of the relevant live birth, Hispanic ethnicity, marital status, education level, and whether there were any previous ectopic pregnancies.