Risk Factors for Placenta Accreta: A Large Prospective Cohort

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Abstract

Objective Placenta previa and prior cesarean delivery are known risk factors for placenta accreta. However, other risk factors have not been identified. Our objective was to examine risk factors for accreta using data collected prospectively in a large multicenter cohort.

Study Design Secondary analysis of women with accreta compared to those without accreta in a large multicenter cesarean delivery cohort. Potential accreta risk factors were examined by univariate and multivariate analyses.

Results In this study, 196 of 73,257 (0.27%) cesarean deliveries were complicated by accreta. As expected, women with increasing numbers of prior cesareans were more likely to have an accreta ($p < 0.001$), as were women with previa (adjusted odds ratio [OR], 34.9; 95% confidence interval [CI], 22.4–54.3). We also considered only patients with previa and examined the following variables: maternal demographics, prior cesareans, interval between deliveries, parity, body mass index, tobacco use, and coexisting hypertension or diabetes. In this model, patients with previa and two or three prior cesarean deliveries had an adjusted OR for accreta of 4.9 (95% CI, 1.7–14.3) or 7.7 (95% CI, 2.4–24.9), respectively. However, no other variables were significantly associated with accreta.

Conclusion Patients with previa have increased risk for accreta that increases with the number of prior cesarean deliveries. However, no other maternal characteristics were associated with accreta.

Keywords
► placenta accreta
► cesarean delivery
► placenta previa
► risk factors

Placenta accreta is characterized by an abnormal adherence of the placenta to the uterine wall. It can be diagnosed clinically when there is a failure of the placenta to normally separate during the third stage of labor, or it can be diagnosed histologically.[1] The risk for placenta accreta is highest for those women with a placenta previa and prior cesarean delivery, particularly multiple prior cesarean deliveries.[2–4] Moreover, the incidence of placenta accreta has increased over the last four decades concurrent with an increased incidence of cesarean delivery.[2–5] One recent estimate for the incidence of placenta accreta is 1 in 533 pregnancies,[6] which is increased from approximately 1 in 19,000 in the 1950s and 1 in 7,000 in the 1970s.[7]

Lack of antenatal suspicion and/or attempted removal of the placenta at the time of delivery can lead to major obstetrical hemorrhage in women with placenta accreta. In turn, this often requires emergency hysterectomy and may result in massive blood transfusion, cystotomy, ureteral

injury, infection, venous thromboembolism, and prolonged hospitalization.[2] It is unclear why some women with risk factors (e.g., previa and prior cesarean) develop accreta while others do not. The identification of additional epidemiologic risk factors may help to explain the pathophysiology of accreta. Several studies have attempted to identify accreta risk factors beyond placenta previa and prior cesarean delivery.[3,6,8,9] However, these studies are generally limited by small numbers, and no additional risk factors have been consistently identified. Thus, our aim was to examine risk factors for placenta accreta in a large, prospective, multicenter cesarean delivery cohort.

Methods

We performed a secondary analysis of a de-identified dataset derived from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network' Cesarean Registry protocol. The Cesarean Registry was a prospective observational study of all women undergoing repeat cesarean section or vaginal delivery after at least one previous cesarean delivery at the participating clinical centers from 1999 through 2002. Women undergoing a primary cesarean delivery were also included during the first 2 years of enrollment. Eight centers participated throughout the study, five centers participated only during the first 2 years, and six centers participated for part of the last 2 years. To be included in the study, delivery also had to result in an infant (live or stillborn) of at least 500 g or at least 20 weeks gestation by best clinical estimate. Baseline demographic, social, medical, and obstetric data were collected through a chart review on each woman delivering by cesarean or by vaginal birth after cesarean. Information on the delivery course, type of delivery, indication for cesarean delivery, subsequent events, and neonatal data (up to 120 days) were also obtained from the medical records, usually at the time of discharge. Because of the prospective nature of the data collection, treating physicians could be approached to resolve any questions. Full details of the study design and methods have been described previously.[10]

Placenta accreta was defined as a placenta that was adherent to the uterine wall without easy separation. If a pathology report was available, this was given precedence over the clinical findings.[11] Placenta previa was identified based on the documentation in the medical record of "placenta previa." The position of the placenta within the uterus (e.g., anterior, posterior, lateral, etc.) as well as the type of previa (e.g., complete, partial, or marginal) was not recorded.[12]

For this analysis, women who had placenta accreta (cases) were identified and compared with those who did not having a placenta accreta (controls). Maternal demographic information and characteristics were compared among groups. Categorical variables were compared with χ^2 or Fisher exact test where appropriate. Continuous variables were compared with Student *t*-test.

To explore additional risk factors for the development of placenta accreta, a generalized linear model that utilized the method of generalized estimating equations was used to model the probability of placenta accreta. Such a model accounts for multiple observations for each subject. A base model was created and a separate model was considered for each variable of interest, while controlling for known risk factors for placenta accreta (i.e., placenta previa and multiple prior cesarean deliveries).

For all statistical tests, two-sided *p* values are reported, with statistical significance defined as $p < 0.05$. SAS 9.2 software (SAS Institute, Cary, NC) was used for analysis.

Results

In this study, 196 of 73,247 pregnancies (0.27%) were diagnosed with placenta accreta; 70,498 did not have a documented diagnosis regarding the presence or absence of placenta accreta; 2,553 patients (3.48%) did not have placenta accreta and comprised the control group. Demographic information and patient characteristics according to the presence or absence of placenta accreta are shown in ►**Table 1**. Overall, the cohort was 40.2% white, 29.2% African American, 25.6% Hispanic, and 5.0% other race or ethnicity. The groups were similar with regard to race/ethnicity, maternal education, smoking, pre-pregnancy body mass index (BMI), diabetes, and the interval from the prior cesarean delivery until the index cesarean delivery. Women with placenta accreta were more likely to have a placenta previa, a greater number of prior cesarean deliveries, higher parity, and were older compared with those without accreta. They also had a slightly lower delivery BMI and lower rate of chronic hypertension than controls (►**Table 1**).

►**Table 2** shows results of the logistic regression model. In this model, only placenta previa and prior cesarean delivery were significantly associated with placenta accreta. Factors such as maternal age greater than 40 years, parity, hypertension, diabetes, race, pre-pregnancy BMI, interpregnancy interval, smoking, and education were not associated with accreta. Controlling for the number of prior cesarean deliveries, patients with placenta previa were 34.9 times more likely to have placenta accreta than those patients without previa (95% confidence interval [CI], 22.4–54.3). Controlling for previa, patients with one, two, or three prior cesarean deliveries were 2.9, 4.6, and 12.6 times more likely to have an accreta, respectively.

Since placenta previa was so strongly associated with the presence of placenta accreta, we analyzed only the subset of women with placenta previa in an attempt to isolate additional risk factors for accreta. As shown in ►**Table 3**, an initial model was fit with one risk factor for placenta accreta, namely, the number of prior cesarean deliveries. A separate model was then considered for each variable of interest by adding one variable at a time to the base model. The odds ratio (OR) for placenta accreta in the presence of one, two, or three prior cesarean deliveries was 2.6 (95% CI, 0.9–7.0), 4.9 (95% CI, 1.7–14.3), and 7.7 (95% CI, 2.4–24.9), respectively. The effect of the number of prior cesarean deliveries was similar across all models (data not shown). No other variables were statistically associated with

Table 1 Clinical characteristics of women with placenta accreta compared to women without placenta accreta

Characteristics	Cases of accreta ($n = 196$)	Controls ($n = 2,553$)	p value
Age (y)	32.8 ± 5.6	28.9 ± 6.7	< 0.001[a]
Race/ethnicity			
African American	66 (33.7)	963 (37.7)	0.54[b]
White	73 (37.2)	955 (37.4)	
Hispanic	43 (21.9)	490 (19.2)	
Other	14 (7.1)	145 (5.7)	
Smoked during pregnancy			
Missing	1 (0.5)	4 (0.2)	0.50[b]
No	160 (81.6)	2,139 (83.8)	
Yes	35 (17.9)	410 (16.1)	
Pre-pregnancy BMI (kg/m^2)	28.0 ± 7.2	28.2 ± 8.4	0.76[a]
Chronic hypertension (treated)			
Missing	1 (0.5)	3 (0.1)	0.016[c]
No	191 (97.5)	2,394 (93.8)	
Yes	4 (2.0)	156 (6.1)	
Diabetes			
Missing	1 (0.5)	2 (0.1)	0.18[b]
No	178 (90.8)	2,247 (88.0)	
Yes	17 (8.7)	304 (11.9)	
Education			
Missing	78 (39.8)	887 (34.7)	0.25[b]
High school or less	70 (35.7)	1,075 (42.1)	
College	48 (24.5)	591 (23.2)	
Parity			
Missing	1 (0.5)	15 (0.6)	< 0.001[b]
0	10 (5.1)	726 (28.4)	
1	44 (22.5)	871 (34.1)	
2	58 (29.6)	466 (18.3)	
≥3	83 (42.4)	475 (18.6)	
Prior cesarean deliveries			
Missing	1 (0.5)	15 (0.6)	< 0.001[b]
0	26 (13.3)	1,126 (44.1)	
1	70 (35.7)	1,012 (39.6)	
≥2	99 (50.5)	400 (15.7)	
Prior classical hysterotomy			
No	182 (92.9)	2,470 (96.7)	0.004
Yes	14 (7.1)	83 (3.3)	
Placenta previa			
Missing	11 (5.6)	148 (5.8)	< 0.001[b]
No	94 (48.0)	2,355 (92.2)	
Yes	91 (46.4)	50 (2.0)	
Interval between delivery and last cesarean (y)	4.9 ± 4.0	4.7 ± 3.7	0.54[a]

Note: Data are presented as n (%) or mean ± standard deviation.
[a]p values from Student t-test.
[b]p values from χ^2 test.
[c]p values from Fisher exact test.

Table 2 Independent risk factors for placenta accreta identified by logistic regression

Risk factor	Odds ratio (95% CI)	p value
Prior cesarean deliveries (vs. 0)		< 0.001
1	2.86 (1.73–4.72)	< 0.001
2	4.61 (2.62–8.11)	< 0.001
≥ 3	12.57 (6.86–23.05)	< 0.001
Placenta previa	34.91 (22.42–54.34)	< 0.001

Abbreviation: CI, confidence interval.

Table 3 Independent risk factors for placenta accreta among patients with placenta previa

Risk factor	OR (95% CI)	p value
Base model		
Prior cesarean delivery (vs. 0)		0.0029
1	2.55 (0.93–6.97)	0.068
2	4.93 (1.71–14.25)	0.0032
≥ 3	7.65 (2.35–24.89)	0.0007
Additional models[a]		
Maternal age	0.98 (0.92–1.05)	0.62
Race (vs. African American)		0.59
White	1.76 (0.68–4.52)	0.24
Hispanic	1.06 (0.39–2.89)	0.91
Other	1.75 (0.37–8.35)	0.48
Smoked during pregnancy	1.13 (0.43–2.94)	0.81
Pre-pregnancy BMI (kg/m^2)	1.01 (0.93–1.10)	0.76
Chronic hypertension	2.18 (0.15–31.43)	0.57
Diabetes	0.47 (0.14–1.58)	0.22
Education (vs. elementary)		0.16
Junior high school	1.05 (0.05–21.07)	0.98
High school	0.31 (0.02–4.15)	0.38
At least some college	0.94 (0.07–13.27)	0.96
Parity (vs. nullipara)		0.43
1	0.83 (0.10–6.84)	0.86
2	1.52 (0.18–13.07)	0.70
≥ 3	0.54 (0.07–4.45)	0.57
Interval between delivery and last cesarean delivery (y)	0.95 (0.85–1.07)	0.38

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.
[a]The effects of previa and prior cesarean delivery were similar across all models, so they are not presented in each additional model.

accreta, and all were subsequently removed from the model. Thus, the final model included results for prior cesarean deliveries alone.

In addition, 147 of 196 pregnancies diagnosed with accreta resulted in hysterectomy (75%). We analyzed only the subset of patients with accreta who underwent hysterectomy and the results were unchanged (data not shown).

Discussion

Placenta previa and increasing number of prior cesarean deliveries are independent risk factors for placenta accreta. The OR for placenta accreta was 2.6, 4.9, and 7.6 for one, two, or three prior cesarean deliveries, respectively. However, after controlling for placenta previa and prior cesarean delivery, we were unable to identify any other historic or demographic risk factors that were associated with accreta. These included smoking, maternal age, parity, BMI, diabetes, and interval since last delivery.

Others also have noted increasing numbers of cesarean deliveries and previa to be major risk factors for placenta accreta.[8,9,13] This makes sense given our current concept of the pathophysiology of the condition. In cases of accreta, uterine damage or poor healing due to prior hysterotomy allows the overlying placenta to grow through an absent or damaged Nitabuch layer in the myometrium.

Usta et al noted an increased risk for accreta in women who smoked in a Lebanese cohort of women with placenta previa.[8] These investigators compared 22 women with previa and placenta accreta with 325 with previa alone.[8] The OR for accreta in smokers was 3.4 (95% CI, 1.1–10.2). This is a biologically plausible risk factor since smoking is known to impair wound healing.[14] In contrast, smoking was not associated with accreta in our cohort or in cohorts in the United Kingdom and Israel.[9,13] The United Kingdom study included 134 women with accreta and 256 controls.[13] The Israeli cohort included 130 women with accreta and almost 35,000 controls (no accreta) with cesarean deliveries.[9] Thus, the latter study was closest in design to ours.

Hypertensive disorders also were associated with accreta in the Lebanese study.[8] These conditions had an OR for accreta of 13.9 (95% CI, 2.1–91.2). The authors speculated that hypertension may lead to accreta by causing vascular endothelial damage or that accreta may lead to hypertension by causing abnormal trophoblast invasion.[8] We found no association between hypertension and accreta. In fact, there was a trend toward more hypertension in women without accreta (6.1 vs. 2.0% in women with accreta). The cohorts from the United Kingdom and Israel also found no significant association between hypertensive disorders and accreta and both noted trends toward more hypertension in women without accreta compared with women with the condition.[9,13]

Advanced maternal age was associated with accreta in the British, Lebanese, and Israeli studies.[8,9,13] The same was true in our cohort in univariate analysis. However, age was no longer associated with accreta after controlling for previa and prior cesareans. Maternal age was also no longer associated

with accreta in the Lebanese study after controlling for prior cesarean delivery,[8] and the risk was modest in the Israeli study (adjusted OR, 1.06; 95% CI, 1.03–1.09).[9] Maternal age is a known risk factor for increasing numbers of cesareans and placenta previa.[15] Thus, it is difficult to determine if it is independently associated with accreta.

Interpregnancy interval was not associated with accreta. A short interpregnancy interval is a risk factor for uterine rupture in women undergoing a trial of labor after prior cesarean[16] and may lead to suboptimal wound healing. Thus, we hypothesized that it could be associated with accreta. Fitzpatrick et al also found no association between interpregnancy interval and accreta.[13]

We also wondered if increased BMI and/or diabetes would be associated with accreta since they are also linked to poor wound healing.[17–19] However, we found no association between BMI or diabetes and accreta. Others also found no association between BMI,[13] diabetes,[9] and accreta. Recurrent pregnancy loss[9] and conception by in vitro fertilization[13] have also been associated with accreta; however, we did not have data regarding these maternal characteristics.

If placenta accreta is suspected, removal of the placenta can be avoided with a planned cesarean hysterectomy performed by experienced personnel. This strategy results in decreased hemorrhage and maternal morbidity.[20–22] Accordingly, it is desirable to identify women at risk for accreta. Unfortunately, we could not identify additional risk factors for accreta using maternal characteristics.

Strengths of our study include the large number of patients in the cohort (including a large number of patients with placenta accreta), prospective data collection by trained study nurses, and an ethnically and geographically diverse population.

Our study also had several weaknesses. First, our cohort was limited to women with cesarean delivery. Thus, we may have missed risk factors present in women with vaginal births that are not present in those with cesareans, and the results of this analysis apply only to women undergoing a cesarean delivery. Nonetheless, most women with accreta have cesarean deliveries and this is unlikely to meaningfully influence our results. Conversely, our design allowed us to control for the effect of placenta previa by analyzing only women with previa. Second, there were certain variables such as recurrent pregnancy loss that were not collected. Finally, we included women with both clinical and histologic evidence of accreta. However, this is a generally accepted definition that has been used in most studies of accreta.[1,13,21,22]

In conclusion, only placenta previa and multiple prior cesarean deliveries were shown to be significantly associated with placenta accreta. No other risk factors, including maternal age, parity, tobacco use, diabetes, hypertension, smoking, or interpregnancy interval were significant risk factors when controlling for other variables. Given the increased frequency of placenta accreta, these data are clinically relevant for all obstetric care providers. Future research should focus on imaging studies and biomarkers as predictors of placenta accreta.

Note

The title "Risk factors for the development of placenta accreta" was presented at The Society for Gynecologic Investigation 60th Annual Meeting in Orlando, FL, March 23, 2013 (Abstract #S-189).

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