Association between short interpregnancy interval and placenta accreta spectrum

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BACKGROUND: The incidence of placenta accreta spectrum is increasing in parallel with the growing number of cesarean deliveries performed. A shorter interpregnancy interval following cesarean delivery may prevent adequate scar healing, which could impact the risk of placenta accreta spectrum.

OBJECTIVE: We aimed to investigate the association between short interpregnancy intervals and placenta accreta spectrum.

STUDY DESIGN: We conducted a retrospective cohort study of patients at risk for placenta accreta spectrum at a tertiary academic center between 2002 and 2020. Our cohort was defined as pregnant individuals at risk for placenta accreta spectrum meeting the following criteria: placenta previa with previous cesarean delivery and/or uterine surgery, anterior low-lying placenta with previous cesarean delivery and/or uterine surgery, ≥3 previous cesarean deliveries, or any previous cesarean delivery with sonographic findings suspicious for placenta accreta spectrum. The primary outcome was surgically or histopathologically confirmed placenta accreta spectrum. Short interpregnancy interval was defined as <18 completed months from previous delivery and last menstrual period of the index pregnancy. Univariable analyses were performed with chi-square and Student's *t*-test, as appropriate, and Kruskal–Wallis for nonparametric variables. The unadjusted and adjusted odds ratios were calculated using multivariate logistic regression models. Covariates were selected if $P<.2$ in univariable analyses or defined a priori as clinically meaningful. The final models were derived using reverse stepwise selection of variables. We used Stata Statistical Software, version 15 (StataCorp, College Station, TX) to perform descriptive statistics.

RESULTS: Of 262 patients at risk of placenta accreta spectrum with complete records, 112 (42.7%) had placenta accreta spectrum. Pregnant individuals with short interpregnancy intervals of <18 months were no more likely than those with optimal interpregnancy intervals to have previa (58% [46/80] vs 46% [84/182]; $P=.09$) or placenta accreta spectrum (49% [39/80] vs 40% [73/182]; $P=.19$). Short interpregnancy interval of <18 months was not associated with placenta accreta spectrum (unadjusted odds ratio, 1.06; 95% confidence interval, 0.62–1.80). This association did not change when adjusting for previa and number of previous cesarean deliveries (adjusted odds ratio, 1.04; 95% confidence interval, 0.51–2.15). In a secondary analysis, an interpregnancy interval of <12 months was also not associated with placenta accreta spectrum (unadjusted odds ratio, 0.79; 95% confidence interval, 0.04–1.56; adjusted odds ratio, 0.52; 95% confidence interval, 0.21–1.27).

CONCLUSION: In patients at risk for placenta accreta spectrum, short interpregnancy intervals of <18 months or <12 months were not associated with placenta accreta spectrum, even when controlling for number of previous cesarean deliveries and previa. Short interpregnancy interval is not likely to be an important modifiable independent risk factor for placenta accreta spectrum.

Key words: cesarean delivery, maternal morbidity, placenta previa, risk factors, risk reduction

Introduction

Placenta accreta spectrum (PAS) describes the abnormal adherence of placental trophoblasts to the uterine myometrium.[1] Consequently, normal detachment of the placenta from the uterus does not occur after delivery, often leading to severe hemorrhage, with increased morbidity and even mortality for pregnant individuals and neonates.

The incidence of PAS in the United States increased from 8 per 10,000 deliveries in the 1980s to somewhere between 18 and 30 per 10,000 deliveries in the last 2 decades, which parallels the growing number of cesarean deliveries.[2–5] With each subsequent cesarean delivery, the risk of PAS increases exponentially; in patients with 4 previous cesarean deliveries and a placenta previa, the risk

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Why was this study conducted?

This study was conducted to determine if a short interpregnancy interval (IPI) is a risk factor for placenta accreta spectrum (PAS).

Key findings

Short IPI of <18 months was not associated with PAS in our cohort (unadjusted odds ratio [OR], 1.06; 95% confidence interval [CI], 0.62−1.80). This association did not change when adjusting for previa and number of previous cesarean deliveries (adjusted OR, 1.04; 95% CI, 0.51−2.15). In secondary analysis, an IPI of <12 months was also not associated with PAS (unadjusted OR, 0.79; 95% CI, 0.04−1.56; adjusted OR, 0.52; 95% CI, 0.21−1.27).

What does this add to what is known?

Short IPI does not seem to be associated with PAS. These data support the exploration of risk factors other than IPI for PAS.

of PAS exceeds 60%.[6] Advanced maternal age,[7] previous uterine surgery,[7,8] in vitro fertilization (IVF),[7,9,10] and twin gestation[11] are also associated with PAS. Understanding modifiable risk factors for PAS aids in risk assessment, targeted counseling for future pregnancies, and primary prevention.

Uterine incision during cesarean delivery leads to a defect of the endometrial−myometrial interface, preventing normal decidualization and potentially leading to trophoblast infiltration into the nearby myometrium in subsequent pregnancies.[1] The length of time between deliveries has been implicated as a risk for uterine rupture during a trial of labor after cesarean delivery.[12−15] Among patients with a previous cesarean delivery, Shipp et al[12] found that short interpregnancy interval (IPI), defined as <18 months, is a risk for uterine rupture in patients undergoing trial of labor after cesarean delivery. This suggests that short IPI may contribute to suboptimal healing of the endometrial−myometrial interface, insufficient decidualization, or weakness of the scar matrix itself, leading to greater risk of uterine rupture, dehiscence, and possibly PAS.

Previous studies have not demonstrated an association between short IPI and PAS.[7,16,17] However, limitations of these studies include inadequate sample sizes for finding clinically meaningful associations, absence of appropriate controls, and the exclusion of alternative short IPI definitions.[7,16] Previous studies also excluded vaginal birth after cesarean delivery in the calculation of IPI, instead only evaluating time from previous cesarean delivery to the pregnancy of interest.[17]

To address these concerns, we aimed to determine if an association between short IPI and PAS exists in a large retrospective cohort of pregnant individuals at high risk of PAS, which provides the appropriate comparison group for studies of PAS risk factors. We hypothesized that a short IPI is associated with increased risk of PAS.

Materials and Methods

We conducted a retrospective cohort study of patients at risk of PAS with complete records from 2002 to 2020 at a tertiary academic center that serves as a multistate regional referral center for PAS. Our cohort included pregnant individuals at risk for PAS meeting the following criteria: placenta previa at the time of delivery with previous cesarean delivery and/or uterine surgery, anterior low-lying placenta at the time of delivery with previous cesarean delivery and/or uterine surgery, ≥3 previous cesarean deliveries, or any previous cesarean deliveries with sonographic findings suspicious for PAS. These sonographic features included abnormal placental lacunae, bladder wall interruptions, increased uterovesicular or subplacental vascularity with turbulent flow, loss of retroplacental clear space, thinned or absent myometrium, placental protrusion or bulge into the bladder, or focal exophytic mass.[18,19] Pregnant individuals were excluded if they were <18 years, did not have a previous second or third-trimester delivery, if previous delivery records were unavailable, or if they did not have any of the previously described risk factors for PAS.

We queried the University of Utah Placenta Accreta Clinical Database for eligible patients with PAS or with the previously described risk factors for PAS. The database contains patients at risk for PAS at the University of Utah between 2002 and 2020. After Institutional Review Board approval, the study team abstracted data from the medical records of these patients.

Our exposure was short IPI, defined as <18 completed months between last delivery and date of last menstrual period, as determined by the patient's best estimated due date in the index pregnancy. We also planned a priori secondary analyses of IPI <12 months and <6 months.

Our primary outcome was surgically or histopathologically confirmed PAS. This was determined on the basis of descriptive findings in either the operative or pathology reports available in the medical records. Starting in 2019, surgical grading and confirmation of PAS was performed systematically using the International Federation of Gynecology and Obstetrics (FIGO) grading.[20] Before the use of FIGO grading in 2019, placentas were classified clinically by standardized definitions of placenta accreta, increta, or percreta.

Covariates included parity, maternal age, placenta previa, number of previous cesarean deliveries, previous uterine surgery, gestational age at last delivery, previous hysterotomy location and type, maternal prepregnancy or early-pregnancy−body mass index (BMI), multiple gestation in last pregnancy, IVF in current pregnancy, pregestational diabetes mellitus, smoking, and delivery mode of the preceding pregnancy.

We performed bivariate analyses using chi-square and Student's *t*-test for

categorical and continuous variables, respectively. In the case of nonparametric continuous variables, we used the Kruskal–Wallis test. We then calculated the unadjusted and adjusted odds ratios (ORs) to evaluate the association between IPI and PAS using multivariate logistic regression models. Covariates were selected if $P<.2$ in bivariate analyses or if defined a priori as clinically meaningful (eg, cesarean delivery). The final models were derived using reverse stepwise selection of variables. Covariates included in the final model were the presence of previa and the number of previous cesarean deliveries. We excluded BMI and current smoking because of missing data.

We used Stata Statistical Software, version 15 (StataCorp, College Station, TX) to perform descriptive statistics. The University of Utah Institutional Review Board approved this study.

Results

In total, there were 262 patients that met inclusion criteria. Demographic information, including maternal characteristics, obstetrical characteristics, and characteristics of last previous delivery according to optimal IPI or short IPI (<18 months) are shown in the Table. The groups were similar with regard to most characteristics, though pregnant individuals in the short IPI group were younger than those in the optimal IPI group. The mean IPI in the optimal IPI group was 46 months, compared with 11 months in the short IPI group. It should be noted that there were missing data for some variables. This was most common for BMI (n=72; 27.5%)

Of the 262 patients at risk of PAS, 112 (42.7%) had PAS. Pregnant individuals with short interpregnancy intervals of <18 months were no more likely than those with optimal interpregnancy intervals to have previa (58% [46/80] vs 46% [84/182]; $P=.09$) or placenta accreta spectrum (49% [39/80] vs 40% [73/182]; $P=.19$).

Short IPI of <18 months was not associated with PAS (unadjusted OR, 1.06; 95% confidence interval [CI], 0.62–1.80). Adjusted models initially included all covariates with $P<.20$ and previa and number of previous cesarean deliveris, as determined a priori on the basis of their clinical importance; however, all variables

TABLE
Demographic and obstetrical characteristics of the cohort

Characteristics	Optimal IPIn=182	Short IPIn=80	*P*
Maternal characteristics			
Term deliveries, median (IQR)	2 (1–3)	2.5 (1–3)	.42
Preterm deliveries, median (IQR)	0 (0–1)	0 (0–1)	.98
Pregnancy losses, median (IQR)	0.5 (0–2)	1 (0–1)	.98
Previous cesarean deliveries (total), median (IQR)	2 (1–3)	2.5 (1–3.75)	.08
Age (y), mean (95% CI)	34.1 (33.4–34.9)	31.8 (30.5–33.1)	<.001
BMI, mean (95% CI)[a]	28.8 (27.6–30.1)	26.6 (24.9–28.2)	.02
Obstetrical characteristics			
Previa, n (%)	84 (46)	46 (58)	.09
Accreta, n (%)	73 (40)	39 (49)	.19
Interpregnancy interval (mo), mean (95% CI)	46 (42–50)	11 (10–12)	<.001
Previous uterine surgery, n (%)	51 (28)	15 (19)	.11
Previous vertical or T-extension hysterotomy, n (%)[b]	19 (10)	5 (6.2)	.30
IVF, n (%)	9 (4.9)	4 (5)	.985
GA at delivery (wk), mean (95% CI)	35.4 (34.9–35.9)	35.7 (35.0–36.4)	.48
EBL at delivery (mL), mean (95% CI)	1406 (1200–1611)	1534 (1193–1875)	.51
Characteristics of previous delivery			
GA at last delivery (wk), mean (95% CI)	38.1 (37.7–38.4)	37.6 (36.8–38.4)	.11
Cesarean delivery, n (%)	172 (95)	76 (95)	.87

Displayed as median (interquartile range) or number (percentage).

BMI, body mass index; *CI*, confidence interval; *EBL*, estimated blood loss; *GA*, gestational age; *IPI*, interpregnancy interval; *IQR*, interquartile range; *IVF*, in vitro fertilization.

[a] Prepregnancy or early pregnancy BMI was not available for 27.5% (n=27) of patients; [b] History of previous vertical or T-extension hysterotomy was not available for 1.14% (n=3) of patients.

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FIGURE
Association between short interpregnancy interval and PAS

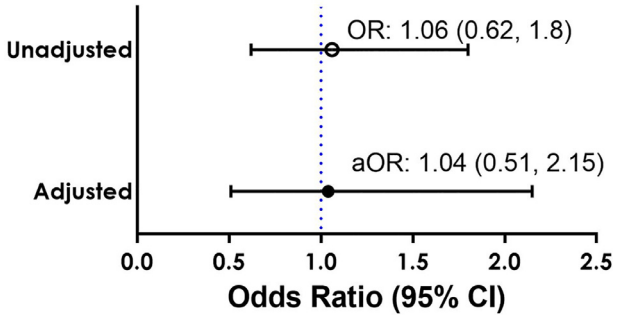

Figure displays the odds ratio and confidence interval of the association of short interpregnancy interval of <18 months and PAS (unadjusted OR, 1.06; 95% CI, 0.62−1.80). As shown, the odds ratio after adjusting for previa and number of previous cesarean deliveries did not change the association (adjusted OR, 1.04; 95% CI, 0.51−2.15).

CI, confidence interval; *OR*, odds ratio; *PAS*, placenta accreta spectrum.

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except previa and cesarean delivery were excluded during the process of reverse stepwise covariate selection. The association between short IPI and PAS did not change after adjusting for previa and number of previous cesarean deliveries (adjusted OR, 1.04; 95% CI, 0.51−2.15) (Figure). In secondary analyses using different definitions of short IPI, an IPI of <12 months was also not associated with PAS (unadjusted OR, 0.79; 95% CI, 0.04−1.56; adjusted OR, 0.52; 95% CI, 0.21−1.27). We could not evaluate short IPI as defined by <6 months because of insufficient numbers (n=10 had IPI <6 months).

Based on a known fixed sample size of n=262, with 182 in the unexposed (normal IPI) and 80 in the exposed groups (short IPI), and a 42.7% proportion of PAS, post hoc calculation of the minimal detectable effect demonstrates that we could detect a statistically significant effect as small as an 11.6% difference in PAS between the groups.

Comment

Principal findings

In patients at risk for PAS in a tertiary academic PAS referral center, short IPI was not associated with PAS, even after adjusting for number of previous cesarean deliveries and previa. Thus, short IPI is not likely to be an important modifiable independent risk factor for PAS.

Results in the context of what is known

Our findings are consistent with previous studies demonstrating that IPI is not associated with PAS. Fitzpatrick et al[7] conducted a case-control study in 2012 that identified multiple risk factors for PAS that found no association between intercesarean interval and PAS. In that study, controls were pregnant individuals who delivered immediately after the case of PAS at a particular institution and did not have PAS, indicating that they may not have had any risk factors for PAS.[7] Another secondary analysis of a cohort concluded that IPI, defined as time from last cesarean delivery to current delivery, was similar in those with and without PAS. That study also included a subgroup analysis of patients with previa, demonstrating no association between IPI and PAS.[16] Most recently, Martimucci et al[17] conducted a retrospective observational study that found no association between IPI and PAS, in which controls were matched to cases with a history of cesarean delivery on the basis of placental location. This study also defined IPI on the basis of previous cesarean delivery date.

Research implications

We currently rely heavily on the number of previous cesarean deliveries and placenta previa to identify patients at risk of PAS.[6] Some other risk factors have emerged, such as IVF and multiple gestations, but truly modifiable risk factors remain elusive. Our data suggest that IPI is unlikely to be a significant contributor to risk for PAS. Future research should examine other potential modifiable risk factors.

Strengths and limitations

There are several strengths of our study. First, this study includes a larger cohort of patients than previously published and an appropriate control population. Second, unlike previous studies, we evaluated multiple definitions of short IPI.[12] Finally, using individual medical record abstraction, we could reliably ascertain interpregnancy interval, even if the previous pregnancy was not a cesarean delivery.

Our study also has several important limitations. First, as a single-institution study at a large referral center of patients at high risk of PAS, the results of these analyses are not likely generalizable to low-risk populations. Second, because this is a retrospective observational study of a clinical dataset, we cannot exclude unmeasured confounders as a source of bias. In addition, the retrospective nature of this study limited the collection of some covariates that were not available in the electronic medical record. Third, we could not assess whether specific ultrasound findings were associated with a shorter interpregnancy interval. Finally, we were unable to perform a planned secondary analysis for an IPI of <6 months because of the small number of individuals meeting these criteria.

Conclusions

In conclusion, short interpregnancy interval was not associated with PAS. These findings build on and support those of previous studies and, when considered alongside those results, suggest that interpregnancy interval is not likely to be an important modifiable risk factor for patients at risk for PAS. ■

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