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Risk Factors and Pregnancy Outcome in Women with a History of Cesarean Section Complicated by Placenta Accreta

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Abstract

Objective: To explore the risk factors and pregnancy outcomes in women with a history of cesarean section complicated by placenta accreta (PA).

Methods: This case-control study included clinical data from singleton mothers with a history of cesarean section in 11 public tertiary hospitals in seven provinces of China between January 2017 and December 2017. According to the intraoperative findings after delivery, the study population was divided into PA and non-PA groups. We compared the pregnancy outcomes between the two groups, used multivariate logistic regression to analyze the risk factors for placental accreta.

Results: For this study we included 11,074 pregnant women with a history of cesarean section; and of these, 869 cases were in the PA group and 10,205 cases were in the non-PA group. Compared with the non-PA group, the probability of postpartum hemorrhage (236/10,205, 2.31% *vs*. 283/869, 32.57%), severe postpartum hemorrhage (89/10,205, 0.87% *vs*. 186/869, 21.75%), diffuse intravascular coagulation (3/10,205, 0.03% *vs*. 4/869, 0.46%), puerperal infection (33/10,205, 0.32% *vs*. 12/869, 1.38%), intraoperative bladder injury (1/10,205, 0.01% *vs*. 16/869, 1.84%), hysterectomy (130/10,205, 1.27% *vs*. 59/869, 6.79%), and blood transfusion (328/10,205,3.21% *vs*. 231/869,26.58%) was significantly increased in the PA group ($P < 0.05$). At the same time, the neonatal birth weight (3250.00 (2950.00–3520.00) g *vs*. 2920.00 (2530.00–3250.00) g), the probability of neonatal comorbidities (245/10,205, 2.40% *vs*. 61/869, 7.02%), and the rate of neonatal intensive care unit admission (817/10,205, 8.01% *vs*. 210/869, 24.17%) also increased significantly ($P < 0.05$). Weight (odds ratio (*OR*) = 1.03, 95% confidence interval (*CI*): 1.01–1.05)), parity (*OR* = 1.18, 95%*CI*: 1.03–1.34), number of miscarriages (*OR* = 1.31, 95%*CI*: 1.17–1.47), number of previous cesarean sections (*OR* = 2.57, 95%*CI*: 2.02–3.26), history of premature rupture of membrane (*OR* = 1.61, 95%*CI*: 1.32–1.96), previous cesarean-section transverse incisions (*OR* = 1.38, 95%*CI*: 1.12–1.69), history of placenta previa (*OR* = 2.44,95%*CI*: 1.50–3.96), and the combination of prenatal hemorrhage (*OR* = 9.95,95%*CI*: 8.42–11.75) and placenta previa (*OR* = 91.74, 95%*CI*: 74.11–113.56) were all independent risk factors for PA.

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Conclusion: There was an increased risk of adverse outcomes in pregnancies complicated by PA in women with a history of cesarean section, and this required close clinical attention. Weight before pregnancy, parity, number of miscarriages, number of previous cesarean sections, history of premature rupture of membranes, past transverse incisions in cesarean sections, a history of placenta previa, prenatal hemorrhage, and placenta previa were independent risk factors for pregnancies complicated with PA in women with a history of cesarean section. These independent risk factors showed a high value in predicting the risk for placentab accreta in pregnancies of women with a history of cesarean section.

Keywords: Placenta accreta; Risk factors; History of cesarean section; Pregnancy outcome

Introduction

Placenta accreta (PA) refers to the abnormal invasion by placental villi into the uterine wall.[1] PA has developed into a serious obstetric complication that threatens the lives of mothers and children; and has increased over the past several years.[2] In addition, it can lead to severe postpartum hemorrhage (SPPH), massive blood transfusion, intraoperative bladder injury, hysterectomy, and even deaths of mothers and children.[3] PA can cause placental separation disorder at delivery—and this can then result in SPPH, which threatens the lives of mother and child.[4] Many investigators have attempted to discern the risk factors for PA; and it has been reported that combined with placenta previa (PP)—is significantly related to the development of PA.[5] Similarly, advanced maternal age and previous cesarean sections (CSs) are also independent risk factors for PA.[6]

In the past several years, the proportion of births has risen sharply, paralleling the increase in CSs. In 2008, 29% of births in China were performed by CS,[7] and the rate of CS then increased to 36.7% in 2018.[8] Even at the lower rate, the CS rate in China remains high.[9] Since China implemented the two-child policy in 2016, the proportion of women with a scarred uterus has almost doubled, increasing from 9.8% in 2012 to 17.7% in 2016.[10] At the same time, the proportion of women delivering at an advanced maternal age and complicated with PA has also increased.[1,9,11,12]

In summary, it is particularly important to identity the predictive risk factors for PA in women with a scarred uterus in early pregnancy. In this retrospective study, we thus analyzed the clinical data from 11,074 women with a history of CS who underwent singleton pregnancies at 11 public tertiary hospitals in seven provinces of China from January 2017 to December 2017; and we identified the risk factors and outcomes for PA.

Methods

Study participants

In this case-control study, we selected 11,074 women as research subjects who had a history of CS and who underwent singleton pregnancies at 11 public tertiary hospitals in seven provinces of China between January 2017 and December 2017. According to the guidelines of Federation International of Gynecology and Obstetrics for the diagnosis and treatment of PA,[1] all cases were divided into a non-PA group (non-PA, 10,205 cases) and a PA group (PA, 869 cases) which were diagnosed based on intraoperative. Figure 1 illustrates a flow diagram of the women's inclusion and exclusion processes. This historical study was approved by the Medical Ethics Committee of Guangzhou Medical University with Medical Research No. 2016 (0406) approved on April 6, 2016. The statements on consent for participation were signed from participants and from legally authorized representatives.

Inclusion criteria

Singleton pregnancies; with a history of CS.

Exclusion criteria

Antepartum fetal death, multiple pregnancies, major fetal congenital anomalies, a scarred uterus caused by myomectomy, lack essential records—such as delivery mode or severe data loss.

Observation index

Clinical data included general patient data: age, height, weight before pregnancy, body mass index before pregnancy (BMI), ethnicity, use of assisted reproductive technology, gravida, parity, gestational weight gain (GWG), and source of pregnant women ("referral" meant that pregnant women were referred from other hospitals to tertiary hospitals. "Hospital" meant that pregnant women delivered in a tertiary hospital from the beginning); previous medical history: history of miscarriage, number of miscarriage (missed abortion, drug abortion, induced abortion; inter-val-CS (year), interval-CS (month), number of CS, previous CS, history of preterm delivery, history of postpartum hemorrhage (PPH), history of premature rupture of membranes (HPROM),

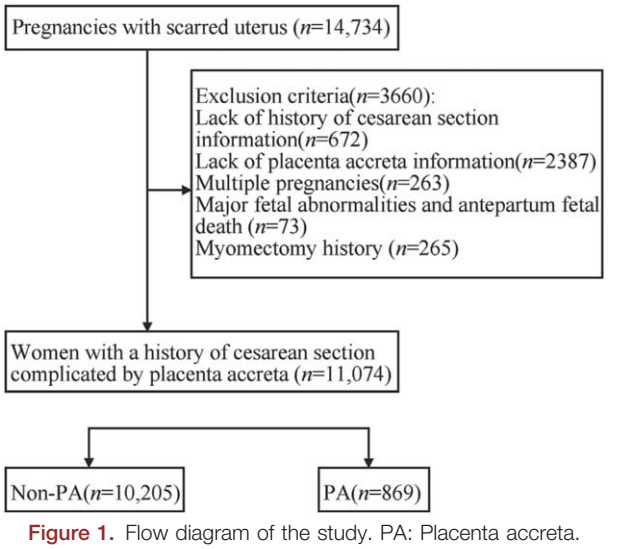

Figure 1. Flow diagram of the study. PA: Placenta accreta.

history of hysteroscopic surgery, history of uterine fibroid removal, history of endometrial injury, history of PA, history of PP, history of preeclampsia; and pregnancy outcomes: prenatal hemorrhage, PP, PPH, SPPH, uterine rupture, disseminated intravascular coagulation (DIC), puerperal infection, hysterectomy, blood transfusion, low birth weight, neonatal comorbidities, and time to neonatal intensive care unit (NICU) admission. SPPH refers to the amount of bleeding >1500 mL within 24 hours of CS.[13] Information regarding maternal and neonatal diseases were classified according to the International Classification of Diseases (ICD)-10.

Statistical analysis

We performed all of the analyses using Empower (R) (www.empowerstats.com, X&Y Solutions, Inc. Boston MA) and R (http://www.R-project.org). Means ± standard deviation were calculated for numerical and normally distributed data, while numbers and percentages were calculated for categorical data; and non-normally distributed numerical data were represented by medians (with 25% quantile and 75% quantile). For comparisons of quantitative data, we used an independent-sample *t*-test or the non-parametric Kruskal-Wallis rank-sum test. For comparisons of qualitative data, Chi-squared test or Fisher exact method was used; with the latter used when the theoretical frequency was <5. We used univariate analysis and multivariate logistic regression to analyze the risk factors. All *P*-values were two-tailed, and the differences with *P*-values of <0.05 were considered to be statistically significant.

Results

Table 1 depicts the general characteristics of all of our studied cases. We observed significant differences in ethnicity, age, weight before pregnancy, BMI before

Table 1

The general characteristics in Non-PA group and PA group.

Variables	Non-PA (*n*=10,205)	PA (*n*=869)	*P*
Source of pregnant women			<0.001
Hospital	8522 (83.51)	422 (48.56)	
Referral	1683 (16.49)	447 (51.44)	
Ethnicity			<0.001
Han Population	9971 (97.71)	864 (99.42)	
Others	234 (2.29)	5 (0.58)	
Age (years)	33.3 ± 4.3	33.0 ± 4.7	0.049
Weight before pregnancy (kg)	59.20 ± 9.54	60.51 ± 9.64	<0.001
Height (cm)	160.21 ± 4.95	160.50 ± 4.80	0.079
BMI before pregnancy (kg/m^2)	23.03 ± 3.35	23.45 ± 3.34	<0.001
GWG (kg)	13.02 ± 3.67	12.53 ± 3.24	<0.001
Gravida	3.00 (2.00–3.00)	3.00 (2.00–4.00)	<0.001
Parity	1.00 (1.00–1.00)	1.00 (1.00–2.00)	<0.001
ART	250 (2.45)	26 (2.99)	0.325
History of Miscarriage	5976 (58.56)	618 (71.12)	<0.001
Number of Miscarriage	1.00 (0.00–1.00)	1.00 (0.00–2.00)	<0.001
Missed abortion	1058 (10.37)	113 (13.00)	0.015
Drug abortion	673 (6.59)	84 (9.67)	<0.001
Induced abortion	5279 (51.73)	545 (62.72)	<0.001
Numbers of previous CS	1.07 ± 0.28	1.22 ± 0.47	<0.001
Interval-CS (year)	6.00 (4.00–9.00)	5.00 (3.00–9.00)	0.008
Interval-CS (month)	72.00 (48.00–108.00)	60.00 (36.00–108.00)	<0.001
History of preterm delivery	1920 (18.81)	155 (17.84)	0.478
HPROM	1480 (14.50)	190 (21.86)	<0.001
Previous CS transverse incision	7985 (78.25)	705 (81.13)	0.047
History of wound tear	77 (0.75)	3 (0.35)	0.212
History of wound infection	9 (0.09)	0 (0.00)	1.000
History of PPH	51 (0.50)	3 (0.35)	0.798
History of PP	117 (1.15)	33 (3.80)	<0.001
History of PA	14 (0.14)	8 (0.92)	<0.001
History of endometrial injury	227 (2.22)	42 (4.83)	<0.001
Myomectomy history	137 (1.34)	22 (2.53)	0.005
History of PE	18 (0.18)	1 (0.12)	1.000
HHS	106 (1.04)	23 (2.65)	<0.001
Combined with prenatal hemorrhage	629 (6.16)	344 (39.59)	<0.001
Complicated with PP	707 (6.93)	758 (87.23)	<0.001

Data are presented as mean ± *SD*, *n*(%), and median (*Q1*, *Q3*).

ART: Assisted reproductive technology; BMI: Body mass index before pregnancy; CS: Cesarean section; GWG: Gestational weight gain; HPROM: History of premature rupture of membranes; HHS: History of hysteroscopic surgery; PA: Placenta accreta; PP: Placenta previa; PE: Pre-eclampsia; PPH: Postpartum hemorrhage; SD: Standard deviation.

pregnancy, GWG, gravida, parity, number of miscarriages, number of CS, and source of pregnant women ($P < 0.05$). The principal source of patients with PA was referral, while the primary source of patients in the non-PA group was the outpatient service. Compared with the non-PA group, more women in the PA group had experienced miscarriage, premature rupture of membranes, transverse incision in a previous CS, PP, PA, endometrial injury, uterine fibroid removal, and/or hysteroscopic surgery. Additionally, there were also more women with prenatal hemorrhage and PP in the latter group, and the interval between the previous and current CSs was shorter ($P < 0.05$).

The pregnancy outcomes of the two groups are shown in Table 2. Compared with the non-PA group, women with PA had an increased probability of PPH, SPPH, DIC, puerperal infection, intraoperative bladder injury, hysterectomy, and blood transfusion ($P < 0.05$). In addition, the birth weight was lower and the probability of neonatal complications and the time to NICU admission were also increased significantly with PA ($P < 0.05$).

Using univariate analysis we found that Han ethnicity (odds ratio (OR) = 0.25, 95% confidence interval (CI) = 0.1–0.6), weight before pregnancy (OR = 1.01, 95%CI: 1.01–1.02), GWG (OR = 0.96, 95%CI: 0.94–0.98), BMI before pregnancy (OR = 1.04, 95%CI: 1.02–1.06), gravida (OR = 1.28, 95%CI: 1.22–1.34), parity (OR = 1.60, 95%CI: 1.42–1.79), history of miscarriage (OR = 1.74, 95%CI: 1.50–2.03), number of miscarriages (OR = 1.28, 95%CI: 1.21–1.35), history of missed abortion (OR = 1.29, 95%CI: 1.05–1.59), history of drug-induced abortion (OR = 1.52, 95%CI: 1.19–1.92), history of induced abortions (OR = 1.57, 95%CI: 1.36–1.81), number of CS (OR = 2.89, 95%CI: 2.47–3.39), interval-CS (OR = 1.00, 95%CI: 1.00–1.00), previous CS with transverse incision (OR = 1.20, 95%CI: 1.00–1.43), HPROM (OR = 1.65, 95%CI: 1.39–1.96), history of PP (OR = 3.40, 95%CI: 2.30–5.04), history of PA (OR = 6.76, 95%CI: 2.83–16.17), history of endometrial injury (OR = 2.23, 95%CI: 1.59–3.13), myomectomy history (OR = 1.91, 95%CI: 1.21–3.01), history of hysteroscopic surgery (OR = 2.59, 95%CI: 1.64–4.09), and complications with PP (OR = 91.74, 95%CI: 74.11–131.56) or prenatal hemorrhage (OR = 9.98, 95%CI: 8.52–11.68) were all risk factors related to PA in a subsequent pregnancy with a scarred uterus ($P < 0.05$). However, advanced age (OR = 0.98, 95%CI: 0.97–1.00) was not a risk factor for PA in this study.

The positive results of univariate analysis were analyzed by multivariate regression analysis. Our multivariate logistic regression model showed that weight before pregnancy (OR = 1.03, 95%CI: 1.01–1.05), parity (OR = 1.18, 95%CI: 1.03–1.34), number of miscarriages (OR = 1.31, 95%CI: 1.17–1.47), number of CS (OR = 2.57, 95%CI: 2.02–3.26), history of PROM (OR = 1.61, 95%CI: 1.32–1.96), previous CS by transverse incision (OR = 1.38, 95%CI: 1.12–1.69), history of PP (OR = 2.44, 95%CI: 1.50–3.96), history of prenatal hemorrhage (OR = 9.95, 95%CI: 8.42–11.75), and complications with PP (OR = 91.74, 95%CI: 74.11–113.56) were independent risk factors for PA. However, non-Han ethnicity (OR = 0.19, 95%CI: 0.07–0.49) was a protective factor ($P < 0.05$, Table 3).

Discussion

There are differences in the rates of CS among countries worldwide. In China, the CS rate has sharply risen in the past 30 years.[7,14,15] According to the 4th National Health Service Surveys conducted in 1993, 1998, 2003, and 2008, the national CS rate rose from 10% to 64.1% in urban areas and from 0% to 11.3% in rural areas between 1988 and 2008.[16] In addition, according to the World Health Organization global survey report conducted in 2007–2008, the CS rate in China was 46.2%, the highest in the world at the time.[17] Compared with vaginal delivery, CS exerts a negative long-term impact on future pregnancies; which increased risk for uterine rupture, PA, stillbirth, and premature delivery.[18]

PA is one of the most common complications in obstetrics, and it was reported that its increasing trends were observed in women with a history of CD (0.38%-0.45%).[2] In addition, a previous study showed that PA occurred in approximately one in 4000 deliveries in the 1970 s,[19] one in 2500 deliveries in the 1980 s,[20] and, more recently, one in 731 deliveries.[21] The principal pathologic manifestation of PA is penetration of the decidua basalis by placental villous tissue and invasion into uterine

Table 2

The pregnant outcomes in Non-PA group and PA group.

Variables	Non-PA (n = 10,205)	PA (n = 869)	P
PPH	236 (2.31)	283 (32.57)	<0.001
SPPH	89 (0.87)	189 (21.75)	<0.001
Uterine rupture	32 (0.31)	2 (0.23)	1.000
DIC	3 (0.03)	4 (0.46)	<0.001
Puerperal infection	33 (0.32)	12 (1.38)	<0.001
Intraoperative bladder injury	1 (0.01)	16 (1.84)	<0.001
Hysterectomy	130 (1.27)	59 (6.79)	<0.001
Transfusion	328 (3.21)	231 (26.58)	<0.001
Birth weight (g)	3250.00 (2950.00–3520.00)	2920.00 (2530.00–3250.00)	<0.001
Neonatal comorbidities	245 (2.40)	61 (7.02)	<0.001
Rate to NICU admission	817 (8.01)	210 (24.17)	<0.001

Data are presented as n(%), and median($Q1$, $Q3$).

DIC: Disseminated intravascular coagulation; NICU: Neonatal intensive care unit; PA: Placenta accreta; PPH: Postpartum hemorrhage; SPPH: Severe postpartum hemorrhage.

Table 3

Multivariate analysis of placental accreta in women with history of cesarean section during the second pregnancy.

Variables	*OR* (95%*CI*)	*P*
Non-Han population	0.19 (0.07–0.49)	<0.001
Weight before pregnancy (kg)	1.03 (1.01–1.05)	0.013
Parity	1.18 (1.03–1.34)	0.014
Number of miscarriage	1.31 (1.17–1.47)	<0.001
Number of previous CS	2.57 (2.02–3.26)	<0.001
Previous CS transverse incision	1.38 (1.12–1.69)	0.002
With history of PROM	1.61 (1.32–1.96)	<0.001
With history of PP	2.44 (1.50–3.96)	<0.001
Complicated with prenatal hemorrhage	9.95 (8.42–11.75)	<0.001
Complicated with PP	91.74 (74.11–113.56)	<0.001

CI: Confidence interval; CS: Cesarean section; *OR*: Odds ratio; PP: Placenta previa; PROM: Premature rupture of membranes.

muscle. During delivery it is easy to cause incomplete placental dissection and PPH. Additionally, the deep blood vessels of the uterus are destroyed after manual removal of the placenta; which can then cause massive bleeding, and even hemorrhagic shock. In order to save the lives of women or fetuses, pregnancy is then terminated early or hysterectomy is performed; which results in an increased rate of premature birth, hysterectomy, and neonatal mortality.[22,23]

Risk factors for PA

The present results revealed that risk factors for PA were pre-pregnancy weight, gravida, number of miscarriages, number of CS, history of PROM, previous transverse incisions with CS, a history of PP, and complications with prenatal hemorrhage or PP. These results are consistent with previous studies.[9–12]

The incidence ofPP in the PA group (87.23%) was much higher than that in the non-PA group (6.93%). We herein reported that the independent risk factors for PA were principally complications of PP, and this has also been reported in other studies.[24,25] However, the underlying mechanism(s) of action remains unclear. The muscle layer and decidua basalis of the lower part of the uterus are too weak in the third trimester to supply sufficient nutrients, and this may lead to PA. Thus, the placental villi may penetrate the decidua basalis in order to obtain sufficient nutrients, and this would augment the risk for PA.[26] The novelty of our study was the finding that women with a history of CS and whose pregnancy was complicated by prenatal hemorrhage had an approximately 10-fold increased risk for PA during a next pregnancy. The frequency of complicated prenatal hemorrhage in the PA group (39.59%) was higher that in the non-PAS group (6.16%). It has been reported that most prenatal hemorrhage is related to abnormal embryonic implantation, and the increase in the amount of bleeding may produce inflammation and pathologic damage to the endometrium and decidua—leading to PP.[5] Additionally, we found that PP was an independent risk factor for PA, and this might explain why prenatal hemorrhage increased PA incidence. However, the specific underlying mechanism (s) requires further clarification.

Our research also suggested that the number of CS was a risk factor for PA, which is consistent with other results.[25,27] A study has shown[14] have shown a linear increase in PA risk correlating with the number of CS, both with and without PP. This may be due to dysplasia of the decidua at the uterine scar after CS, which leads to excessive infiltration of trophoblast cells into the myometrium during the next pregnancy.[28] We also found that a history of PP was an independent risk factor for PA, consistent with the studies by Gelany.[29] Besides, the incidence of history of PP was more than twice in the PA group (3.18%) that the non-PA group (1.15%). This correlation may be due to pathologic damage to the endometrium during previous PP, resulting in insufficient vascular remodeling during the next pregnancy in women with a history of CS. In order to absorb additional nutrients the placenta extends downward, increasing the risk of PP, which is the most significant independent risk factor for PA.

The present results showed that weight before pregnancy, parity, and number of miscarriages were risk factors for PA, consistent with previous work.[22,25] Repeated abortions and deliveries might damage the endometrium and myometrium; and during the subsequent pregnancy, defects in decidual development, abnormal vascular remodeling, and reduced blood supply might lead to excessive infiltration of trophoblast cells through the endometrium, and increase the probability of PA.[10] Our results also suggested that a HPROM and previous CS with transverse incisions were independent risks for PA. However, the mechanism(s) underlying these phenomena remains unclear and requires further exploration. We hypothesize that a history of PROM is likely to cause ascending pathogen infection and endometritis, which would in turn induce endometrial damage. Moreover, decidual defects occur readily, which may lead to PA during a second pregnancy. We found that non-Han ethnicity was a protective factor. However, in this study cohort, the proportion of non-Han nationality was 2.87%, of which only 0.58% had PA. Our conclusions may be partial due to the small number of participants, and further research is needed. Previous study[6] has suggested that advanced age was a risk factor for PA, but our findings were contrary to this. We speculate that this difference may be caused by different study cohorts. Because we selected women who had a history of CS as research subjects, we guessed that under the premise of a history of CS, age did not play a role in PA.

Pregnancy outcomes with PA

PA seriously threatens the lives of mothers and children. In this study we found that the probability of PPH, SPPH, and blood transfusion in the PA group (32.57%, 21.75%, 26.58%) was much higher than that in the non-PA group (2.31%, 0.87%, 3.21%), which is consistent with previous studies.[25,30] Research by Bourgioti[31] suggested that the uterine tissue at the implantation site was too weak to maintain uterine contractions, and that residual placental tissue and blood sinusoids that could not be completely closed off would lead to uncontrollable PPH. This study also showed that the incidence of DIC in the PA group was higher (0.03% *vs.* 0.46%), which may be related to the incidence of PPH and an insufficient

endogenous supply of coagulation factors. In the present study, the incidence of puerperal infection and intraoperative bladder injury in the PA group was significantly increased (0.32% *vs.* 1.38%, 0.01% *vs.* 1.84%), which is consistent with a previous report.[32] In addition, we found that the rate of hysterectomy, low birth weight, neonatal comorbidities, and time to NICU admission in the PA group were also significantly increased (1.27% *vs.* 6.79%, 3250 g *vs.* 2920 g, 2.40% *vs.* 7.02%, 8.01% *vs.* 24.17%), which was consistent with the results of several previous investigations.[25,32,33]

Conclusions

We observed an increased risk for adverse outcomes in pregnancies complicated by PA in women with a history of CS—especially PPH, which threatens the health of mothers and children, and requires close clinical attention. Combined PP plays the most important role in the occurrence and development of PA, followed by combined prenatal hemorrhage in pregnant women with a history of CS. Obstetricians need to pay attention to pregnant women who have had multiple CSs, a history of PP, this pregnancy with PP or prenatal hemorrhage, because they have a high risk of PA. If a pregnant woman has been combined with PA before delivery, it is necessary to pay close attention to whether there is PPH which seriously threatens the life of mother and child.

The innovation of this article lies in our inclusion of variables that have not been studied previously—such as ethnicity, history of PROM, GWG, or hysteroscopic surgery. This study was a multi-center study, which effectively avoided selection and regional biases inherent in a single-center study. However, there were also several limitations—for example, this was a retrospective analysis, and lacked information on maternal living habits, the degree of invasion of PA, the surgical competency in different centers, imaging data, number of emergency cases and elective versus during pregnancy—and therefore this work requires additional investigation.

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Author Contributions

Yingyu Liang and Lizi Zhang: propose ideas, data analysis, writing, review and editing. Shilei Bi: data analysis, review and editing. Jingsi Chen: propose original questions, review and editing. Shanshan Zeng, Lijun Huang, Yulian Li, Minshan Huang and Hu Tan: investigation, data collection, and visualization. Jinping Jia, Suiwen Wen, Zhijian Wang, Yinli Cao, Shaoshuai Wang, Xiaoyan Xu, Ling Feng, Xianlan Zhao, Yangyu Zhao, Qiying Zhu, Hongbo Qi, Lanzhen Zhang and Hongtian Li: investigation, and resources. Lili Du, and Dunjin Chen: supervision, project administration, and funding acquisition.

Conflicts of Interest

None.

Editor Note

Ling Feng, Xianlan Zhao, Yangyu Zhao, Hongbo Qi are Editorial Board Members of *Maternal-Fetal Medicine*; Dunjin Chen is an Associate Editor of *Maternal-Fetal Medicine*. The article was subject to the journal's standard procedures, with peer review handled independently of these editors and their research groups.

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