Novel Risk Factors for Placenta Accreta Spectrum in Women Without Prior Cesarean Section: Insights From a Case-Control Study

Maryam Bakir Mahmood

Department of Clinical Science, College of Medicine, University of Sulaimania, Sulaimania, Kurdistan Region, Iraq

Received: Jan. 2025; Accepted: Mar. 2025

Abstract- Placenta accreta spectrum (PAS) is a significant contributor to maternal morbidity and mortality, often complicating pregnancies due to abnormal placental attachment. While cesarean section (CS) remains the most recognized risk factor, nearly one-third of PAS cases occur in women without a history of CS. Identifying risk factors in these women is critical for improving early detection and management. This study aims to investigate maternal characteristics and risk factors associated with PAS in women without a history of CS, focusing on surgical histories and other potential predictors. A case-control study was conducted at the Maternity Teaching Hospital in Sulaimania, Kurdistan Region, Iraq. The study included 120 pregnant women diagnosed with placenta previa: 60 with PAS (cases) and 60 without PAS (controls). Women with a history of CS or uterine surgery were excluded. Data on maternal age, body mass index (BMI), parity, uterine surgical history, and other clinical factors were analyzed. Univariate and multivariate logistic regression analyses were performed to identify significant risk factors. Significant risk factors for PAS included previous uterine myomectomy by laparotomy (OR 65.23, 95% CI: 7.85-541.72, $P<0.0001$), uterine septum excision (OR 9.45, 95% CI: 1.10-81.23, $P=0.022$), and a history of multiple endometrial biopsies (OR 3.92, 95% CI: 1.03-14.93, $P=0.045$). Repeated uterine curettage also emerged as a significant predictor (OR 3.78, 95% CI: 1.05-13.59, $P=0.042$). Conversely, traditional risk factors such as multiparity, gestational hypertension, and diabetes mellitus were not significantly associated with PAS in this cohort. Our study highlights uterine myomectomy, septum excision, repeated biopsies, and curettage as significant risk factors for PAS in women without a history of CS. These findings emphasize the importance of careful monitoring and risk assessment in such patients to improve early detection and management of PAS.

Acta Med Iran 2025;63(March-April):143-148.
https://doi.org/10.18502/acta.v63i2.18970

Keywords: Placenta accreta spectrum; Pregnancy complications; Risk factors; Cesarean section

Introduction

Placenta accreta spectrum (PAS) is a significant cause of maternal morbidity and mortality, contributing to severe complications during pregnancy and childbirth (1). It encompasses three distinct conditions: placenta accreta, where the placental villi attach superficially to the myometrium without invasion; placenta increta, characterized by deeper invasion of the myometrium; and placenta percreta, where the placenta invades through the uterine wall and can extend into adjacent organs such as the bladder or bowel (2-4). The spectrum of PAS has become increasingly prevalent, with global estimates suggesting an incidence of 3 to 5 cases per 1,000 pregnancies (5). This rise in PAS cases mirrors the increasing rates of cesarean sections (CS), now considered the most significant risk factor for the condition (6). Women with prior CS deliveries are at significantly higher risk of developing PAS, especially when combined with other factors such as placenta previa (7).

While cesarean delivery is the leading contributor to PAS, a considerable proportion of PAS cases, estimated at nearly one-third, occur in women who have never

Corresponding Author: M. Bakir Mahmood
Department of Clinical Science, College of Medicine, University of Sulaimania, Sulaimania, Kurdistan Region, Iraq
Tel: +9647701452627, E-mail address: maryam.mahmmod@univsul.edu.iq

undergone a CS. This subgroup of PAS patients presents a unique clinical challenge (6). The absence of a prior CS can delay suspicion and diagnosis of PAS, potentially leading to worse maternal outcomes, such as hemorrhage, hysterectomy, or even maternal death (8). As PAS is increasingly diagnosed, it is critical to identify and understand risk factors beyond cesarean delivery to guide early detection and management of the condition in these women (9).

The etiology of PAS without prior CS remains incompletely understood, but several risk factors have been proposed. These include previous uterine surgeries such as myomectomy, hysteroscopy, or curettage, all of which may alter the integrity of the uterine wall and predispose patients to abnormal placentation (10). Assisted reproductive technologies (ART), particularly in vitro fertilization (IVF), are also implicated in the pathogenesis of PAS due to their association with abnormal placental implantation. Other factors, such as advanced maternal age, high body mass index (BMI), multiparity, smoking, and the presence of uterine anomalies (e.g., fibroids or adenomyosis), may further contribute to the development of PAS (11).

Placenta previa, an independent risk factor for PAS, is another condition extensively studied in this context. Placenta previa occurs when the placenta partially or completely covers the cervical os, increasing the likelihood of abnormal placental attachment (12). Although placenta previa and prior CS are often considered together in the context of PAS, PAS can still occur in the presence of placenta previa, even in women without prior uterine surgeries (13). Therefore, understanding the interplay between placenta previa and PAS in women without previous CS is critical for improving risk prediction and management.

Management of PAS requires a multidisciplinary approach involving obstetricians, anesthesiologists, neonatologists, and surgical teams prepared for complex cases of delivery (14). In cases where PAS is suspected antenatally, planned cesarean hysterectomy may be the safest option to minimize blood loss and reduce the risk of catastrophic hemorrhage. In resource-limited settings, timely diagnosis and coordinated care are essential for reducing maternal and neonatal morbidity and mortality. Despite advancements in diagnostic imaging, such as ultrasound and MRI, which aid in the identification of PAS, early recognition remains challenging, particularly in women without prior CS (15).

There is a clear gap in the literature regarding PAS risk factors in women who have not undergone CS. Most large-scale studies focus on populations with prior cesarean deliveries, thereby limiting the generalizability of their findings to women without this surgical history (16-18). This study aims to fill this gap by investigating risk factors for PAS in women without a history of cesarean section at the Maternity Teaching Hospital in Sulaimania, Kurdistan, a tertiary referral center for high-risk obstetric patients. By controlling for placenta previa, this study seeks to uncover additional risk factors and provide a clearer understanding of PAS in this population. Such findings are crucial for enhancing antenatal care, improving clinical management strategies, and ultimately optimizing maternal and neonatal outcomes in women with PAS without prior CS.

Materials and Methods

Study design and setting

This retrospective case-control study was conducted at the Maternity Teaching Hospital in Sulaimania City, Kurdistan Region, Iraq, from August 2022 to February 2024. The study population included patients diagnosed with PAS disorders, specifically “placenta accreta,” “placenta increta,” or “placenta percreta,” presenting with antepartum hemorrhage after 24 weeks of gestation. The Maternity Teaching Hospital is a referral center for high-risk obstetric cases, including PAS, providing a suitable setting for this research.

Study population

A total of 120 women were enrolled in this study: 60 patients with a confirmed diagnosis of PAS (cases) and 60 women without PAS (controls). All participants had a diagnosis of placenta previa. To focus specifically on risk factors excluding prior CS, women with a documented history of CS were excluded. The control group consisted of women with placenta previa but no PAS or history of prior uterine surgery. Patients in both groups were selected using random sampling to minimize selection bias.

Inclusion and exclusion criteria

The study included pregnant women who:

1. Presented with antepartum hemorrhage after 24 weeks of gestation.
2. Were diagnosed with PAS disorders (placenta accreta, increta, or percreta) through clinical and imaging methods.
3. Had a coexisting diagnosis of placenta previa.

Women were excluded from the study if they:

1. Had a history of CS.
2. Had a history of other uterine surgeries such as myomectomy or hysteroscopy.
3. Were diagnosed with PAS in conjunction with any uterine scarring or surgery.

Data collection

Data was collected retrospectively from hospital records. A standardized data collection form was used to gather relevant patient information, including demographic data, obstetric history, and clinical presentations. Risk factors such as maternal age, BMI, parity, history of uterine surgery, infertility treatments, smoking status, multifetal pregnancies, and any other medical conditions were recorded. Imaging findings were obtained using transabdominal and transvaginal ultrasound to confirm the diagnosis of PAS and assess the extent of placental invasion.

Clinical management

Patients were managed according to their maternal and fetal conditions. Decisions regarding the timing and mode of delivery were based on clinical assessments, with a multidisciplinary team approach for PAS cases to ensure optimal outcomes. Any maternal complications were documented.

Statistical analysis

Data was analyzed using SPSS software version 26. Continuous variables were presented as means±standard deviations and compared using t-tests or Mann-Whitney U tests. Categorical variables were expressed as frequencies and percentages and compared using Chi-square tests or Fisher's exact tests where appropriate. Univariate and multivariate logistic regression analyses were performed to identify significant risk factors associated with PAS in women without prior CS. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. A P of <0.05 was considered statistically significant.

Results

The results showed that the average maternal age was slightly higher in the PAS group compared to the control group, but the difference was not statistically significant (P=0.133). The PAS group had a higher average pre-pregnancy BMI compared to the control group, though this difference was also not significant (P=0.217). A significantly higher proportion of multiparous women was found in the control group compared to the PAS group (P<0.001). Pregestational DM was more common in the control group than in the PAS group, with no significant difference (P=0.523). Gestational hypertension was more common in the PAS group compared to the control group, but this difference was not statistically significant (P=0.413). Only two women in the PAS group were smokers, and none in the control group. There was no significant difference in the proportion of multifetal pregnancies (P=0.154) or smoking (P=0.135) between the PAS group and the control group.

Table 2 presents the maternal risk factors in PAS without a history of CS compared to control groups. A significantly higher percentage of PAS patients had a history of laparotomy for myomectomy compared to the control group (P<0.0001). Uterine malformation correction (metroplasty) was rare, with 3.3% of PAS patients having undergone metroplasty, compared to no cases in the control group. However, the difference was not statistically significant (P=0.312). Adenomyosis was more common in the PAS group than the control group, though the difference was not statistically significant (P=0.570). Submucosal myomectomy was more frequent in the PAS group than in the control group, approaching significance (P=0.053). A significant difference between case and control groups was observed in uterine septum excision (P=0.013).

The distribution of endometrial biopsy history approached significance (P=0.062). In the PAS group, 25% had no biopsy, 53.3% had one biopsy, and 21.7% had ≥2 biopsies. In contrast, the control group had 66.7% without biopsy, 23.3% with one biopsy, and 10% with ≥2 biopsies. A significant difference was found in the history of uterine curettage (P=0.008). In the PAS group, only 28.3% had no history of curettage, while 61.7% had undergone two procedures, and 5% had ≥3 procedures. In comparison, 73.3% of the control group had no history of curettage, and only 6.7% had undergone two procedures or more.

Table 3 shows the results of the univariate and multivariate logistic regression analyses, which identified significant risk factors associated with PAS in women without prior CS. Previous uterine myomectomy by laparotomy shows the strongest association, with an OR of 72.00 (95% CI: 9.25-560.33, P<0.0001) in the univariate analysis and 65.23 (95% CI: 7.85-541.72, P<0.0001) in the multivariate analysis, indicating a highly significant risk factor.

Uterine septum excision is another significant risk factor with a univariate OR of 10.80 (95% CI: 1.25-

93.14, *P*=0.013) and a multivariate OR of 9.45 (95% CI: 1.10-81.23, *P*=0.022). Endometrial biopsy (≥2 Biopsies) and uterine curettage (≥2 Procedures) are also identified as significant risk factors in the multivariate model with ORs of 3.92 (95% CI: 1.03-14.93, *P*=0.045) and 3.78 (95% CI: 1.05-13.59, *P*=0.042), respectively.

Adenomyosis and submucosal myomectomy by hysteroscopy did not reach statistical significance in the multivariate analysis.

Table 1. Comparison of maternal characteristics between PAS and control groups

Maternal characteristics	PAS (*n* =60)	Control (*n* =60)	*P*
Maternal age at delivery (year)	32.8 ± 4.1	31.2 ± 4.2	0.133
Pre-pregnancy BMI	23.2 ± 3.0	21.5 ± 3.1	0.217
Multipara	15	40	<0.001
Gestational DM	8	18	0.654
Pregestational DM	4	10	0.523
Gestational hypertension	10	4	0.413
Smoking	2	0	0.135
Multifetal pregnancy	55	17	0.154

Table 2. Maternal risk factors in PAS without a history of CS compared to control groups

Maternal risk factors	PAS (*n* =60) (%)	Control (*n* =60) (%)	*P*
Previous uterine myomectomy by laparotomy	40 (67)	1 (1.7)	0<0001
Uterine malformation correction metroplasty	2 (3.3)	0 (0)	0.312
Adenomyosis	20 (33.3)	10 (16.7)	0.570
Submucosal myomectomy by hysteroscopy	8 (13.3)	2 (3.3)	0.053
Uterine septum excision	9 (15)	1 (1.7)	0.013
Endometrial biopsy			
0	15 (25)	40 (66.7)	0.062
1	32 (53.3)	14 (23.3)	
≥2	13 (21.7)	6 (10)	
Uterine curettage			
0	17 (28.3)	44 (73.3)	
1	3 (5)	11 (18.3)	0.008
2	37 (61.7)	4 (6.7)	
≥3	3 (5)	1 (1.7)	

Table 3. Analysis of risk factors associated with PAS in women without prior CS: A multivariate assessment

Risk Factor	Univariate OR (95% CI)	*P* (Univariate)	Multivariate OR (95% CI)	*P* (Multivariate)
Previous uterine myomectomy by laparotomy	72.00 (9.25 - 560.33)	<0.0001	65.23 (7.85 - 541.72)	<0.0001
Uterine malformation correction (metroplasty)	Not calculated	0.312	Not included	N/A
Adenomyosis	2.45 (1.02 - 5.92)	0.057	2.09 (0.84 - 5.21)	0.093
Submucosal myomectomy by hysteroscopy	4.55 (0.94 - 22.12)	0.053	4.15 (0.82 - 20.92)	0.078
Uterine septum excision	10.80 (1.25 - 93.14)	0.013	9.45 (1.10 - 81.23)	0.022
Endometrial biopsy (≥2 biopsies)	4.81 (1.23 - 18.81)	0.062	3.92 (1.03 - 14.93)	0.045
Uterine curettage (≥2 procedures)	4.43 (1.31 - 15.00)	0.008	3.78 (1.05 - 13.59)	0.042

OR: Odds Ratio; CI: Confidence Interval

Variables with *P*<0.05 were considered statistically significant and marked with a

Only significant variables in univariate analysis were included in the multivariate logistic regression model

Discussion

The present study investigated the maternal characteristics and surgical risk factors associated with PAS in women without a C history. The results indicate notable differences in certain maternal factors and surgical histories between the PAS and control groups. The average maternal age was higher in the PAS group compared to the control group, although this difference was not statistically significant. This finding aligns with previous studies, such as those by Silver *et al*., which have reported that advanced maternal age is associated with increased risks of PAS, particularly in women with a history of uterine surgeries (16).

One striking finding of this study was the significantly higher proportion of women in the PAS group with a history of laparotomy for myomectomy. This is consistent with findings from a study by Badr *et al*., which suggested that uterine surgery, particularly myomectomy, may lead to altered uterine structure and subsequent complications, increasing the risk for PAS (17). Contrary to our findings, the study by Mohr-Sasson *et al*., did not identify an increased prevalence of PAS in subsequent pregnancies following surgical myomectomy (18).

Furthermore, uterine septum excision also emerged as a significant risk factor, with an OR of 9.45 in the multivariate analysis. This finding indicates that surgical correction of uterine anomalies can increase susceptibility to abnormal placentation. The relationship between congenital uterine anomalies and PAS has been explored in prior studies, but the association with septum excision adds a new dimension to our understanding of these risks. Clinicians should consider this history during antenatal care, as it may warrant closer monitoring and potentially earlier intervention. The recent literature findings suggest uterine anomalies may predispose women to PAS (19). Also, adenomyosis was more common in the PAS group (33.3% vs. 16.7%), although the difference was not statistically significant, which is consistent with previous studies (20,21).

In this context, studies have shown mixed results regarding the association between adenomyosis and PAS, indicating that while adenomyosis can affect uterine structure, its role as a direct risk factor for PAS remains unclear (22).

The study also revealed a trend towards significance for endometrial biopsy and uterine curettage histories in the PAS group. These findings suggest that repeated uterine interventions could contribute to uterine scarring and abnormalities, aligning with previous research linking such procedures to a higher risk of abnormal placentation. These results were consistent with Baldwin's research on primiparous women in Australia (23).

Miller *et al*., cohort study demonstrated two to three times the risk for PAS in multifetal pregnancies (adjusted relative risk 2.96, 95% CI 2.23-3.93) (24).

Multiparity was unexpectedly more common in the control group than in the PAS group, with a highly significant difference. This finding contradicts previous reports that have linked higher parity with an increased risk of PAS, suggesting that other factors, such as surgical history or uterine abnormalities, may play a more dominant role in the absence of CS (25,26). Similarly, common obstetric risk factors like gestational hypertension and diabetes mellitus did not emerge as significant predictors of PAS in this cohort. This further supports the hypothesis that PAS in women without CS may be driven more by structural changes in the uterus rather than by traditional maternal comorbidities.

Our study identifies previous uterine myomectomy, septum excision, multiple endometrial biopsies, and repeated curettage as significant risk factors for PAS in women without a prior cesarean section. These findings highlight the need for heightened clinical vigilance and tailored risk assessment in this population to facilitate early detection and improve maternal outcomes. Further research is needed to explore the underlying mechanisms linking these risk factors to PAS and refine risk prediction models for clinical practice. Ultimately, a better understanding of PAS in women without CS will help to improve outcomes for this high-risk population by facilitating earlier diagnosis, timely intervention, and appropriate management strategies.

References

1. Matsuzaki S, Mandelbaum RS, Sangara RN, McCarthy LE, Vestal NL, Klar M, et al. Trends, characteristics, and outcomes of placenta accreta spectrum: a national study in the United States. Am J Obstet Gynecol 2021;225:534-e1.
2. Jauniaux E, Collins S, Burton GJ. Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. American J Obstet Gynaecol 2018;218:75-87.
3. Heller DS. The Placenta Accreta Spectrum. Benirschke's

Pathology of the Human Placenta 2022:271-80.
4. Abdelhafez MM, Ahmed KA, Mohd Daud MN, Eldiasty AM, Jeffree MS, Kadir F, et al. Placenta accreta spectrum: A current literature review. J Diagn Med Sonogr 2023;39:599-613.
5. Silveira C, Kirby A, Melov SJ, Nayyar R. Placenta accreta spectrum: We can do better. Aust N Z J Obstet Gynaecol 2022;62:376-82.
6. Ogawa K, Jwa SC, Morisaki N, Sago H. Risk factors and clinical outcomes for placenta accreta spectrum with or without placenta previa. Arch Gynecol Obstet 2022;305:607-15.
7. Imafuku H, Tanimura K, Shi Y, Uchida A, Deguchi M, Terai Y. Clinical factors associated with a placenta accreta spectrum. Placenta 2021;112:180-4.
8. Abu Hashim H, Shalaby EM, Hussien MH, El Rakhawy M. Diagnostic accuracy of the placenta accreta index for placenta accreta spectrum: A prospective study. Int J Gynecol Obstet 2022;156:71-6.
9. Morlando M, Collins S. Placenta accreta spectrum disorders: challenges, risks, and management strategies. Int J Womens Health 2020:1033-45.
10. Palacios-Jaraquemada JM, D'Antonio F. Posterior placenta Accreta Spectrum disorders: risk factors, diagnostic accuracy, and Surgical Management. Maternal-Fetal Medicine 2021;3:268-73.
11. Carusi DA, Duzyj CM, Hecht JL, Butwick AJ, Barrett J, Holt R, O'Rinn SE, Afshar Y, Gilner JB, Newton JM, Shainker SA. Knowledge gaps in placenta accreta spectrum. Am J Perinatol 2023;40:962-9.
12. El Gelany S, Mosbeh MH, Ibrahim EM, Mohammed MM, Khalifa EM, Abdelhakium AK, et al. Placenta Accreta Spectrum (PAS) disorders: incidence, risk factors and outcomes of different management strategies in a tertiary referral hospital in Minia, Egypt: a prospective study. BMC pregnancy and childbirth 2019;19:1-8.
13. Romeo V, Verde F, Sarno L, Migliorini S, Petretta M, Mainenti PP, et al. Prediction of placenta accreta spectrum in patients with placenta previa using clinical risk factors, ultrasound and magnetic resonance imaging findings. La radiologia medica 2021;126:1216-25.
14. Einerson BD, Weiniger CF. Placenta accreta spectrum disorder: updates on anesthetic and surgical management strategies. International Journal of Obstetric Anesthesia 2021;46:102975.
15. Hobson SR, Kingdom JC, Murji A, Windrim RC, Carvalho JC, Singh SS, et al. No. 383-screening, diagnosis, and management of placenta accreta spectrum disorders. J Obstet Gynaecol Can 2019;41:1035-49.
16. Silver RM, Barbour KD. Placenta accreta spectrum: accreta, increta, and percreta. Obstetrics and Gynecology Clinics. 2015;42(2):381-402.
17. Badr DA, Al Hassan J, Wehbe GS, Ramadan MK. Uterine body placenta accreta spectrum: A detailed literature review. Placenta 2020; 95:44-52.
18. Mohr-Sasson A, Timor I, Meyer R, Stockheim D, Orvieto R, Mashiach R. Placenta accreta spectrum in subsequent pregnancy following myomectomy. J Matern Fetal Neonatal Med 2022;35:4332-7.
19. Duzyj CM, Cooper A, Mhatre M, Han CS, Paidas MJ, Illuzzi JL, Sfakianaki AK. Placenta accreta: a spectrum of predictable risk, diagnosis, and morbidity. Am J Perinatol 2019;361031-8.
20. Mandelbaum RS, Melville SJ, Violette CJ, Guner JZ, Doody KA, Matsuzaki S, et al. The association between uterine adenomyosis and adverse obstetric outcomes: a propensity score-matched analysis. Acta Obstetricia et Gynecologica Scandinavica 2023;102:833-42.
21. Komatsu H, Taniguchi F, Harada T. Impact of adenomyosis on perinatal outcomes: a large cohort study (JSOG database). BMC Pregnancy and Childbirth 2023;23:579.
22. Liu X, Wang Y, Wu Y, Zeng J, Yuan X, Tong C, Qi H. What we know about placenta accreta spectrum (PAS). Eur J Obstet Gynecol Reprod Biol 2021; 259:81-9.
23. Baldwin HJ, Patterson JA, Nippita TA, Torvaldsen S, Ibiebele I, Simpson JM, Ford JB. Antecedents of abnormally invasive placenta in primiparous women: risk associated with gynecologic procedures. Obstetrics & Gynecology 2018;131:227-33.
24. Miller HE, Leonard SA, Fox KA, Carusi DA, Lyell DJ. Placenta accreta spectrum among women with twin gestations. Obstetrics & Gynecology 2021;137(1):132-8.
25. El Gelany S, Mosbeh MH, Ibrahim EM, Mohammed MM, Khalifa EM, Abdelhakium AK, et al. Placenta Accreta Spectrum (PAS) disorders: incidence, risk factors and outcomes of different management strategies in a tertiary referral hospital in Minia, Egypt: a prospective study. BMC pregnancy and childbirth 2019; 19:1-8.
26. Kılıççı Ç, Eken MK, İlhan G, Çöğendez E, Şanverdi İ, Keskin M, et al. Evaluation of Risk Factors, Incidence, Perinatal and Maternal Outcome of Placenta Previa Cases with and without Placenta Accreta Spectrum. Duzce Med J 2018;19:75-80.