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Original Article

Frequency, Risk Factors, and Pregnancy Outcomes in Cases with Placenta Accreta Spectrum Disorder: A Case-Control Study

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Abstract

Background: Placenta accreta spectrum (PAS) disorder is an important life-threatening problem. The purpose of the current study was to determine the frequency, risk factors, and pregnancy outcomes of PAS in our population.

Methods: This is a case-control study using the data from a main tertiary referral university hospital in Ahvaz, southwest of Iran. The sample included 187 cases diagnosed with placenta accreta spectrum from 2015 to 2019 and 552 controls without PAS. A multivariable logistic regression model was used to find independent risk factors with 95% confidence interval. Pregnancy outcomes were evaluated using chi-square, t-test, and Mann-Whitney U test and $p<0.05$ were considered statistically significant.

Results: The frequency of PAS during the study period was 3.7/1000 deliveries (0.37%). It was found that multiparity (≥3 deliveries, OR=2.05: 95%CI:1.21-3.47) and multigravidity (≥3 deliveries, OR=2.98: 95%CI:1.55-5.72), prior cesarean delivery (OR=52.55: 95%CI:19.73-139.96), and placenta previa (OR=27.48: 95%CI: 9.62-78.5) are the independent risk factors of PAS. Complications and morbidity associated with PAS included hysterectomy (60.4% *vs*. 0.7%, $p<0.001$), cystostomy (24.1% *vs*. 0.2%, $p<0.001$), the need for blood transfusion (73.7% *vs*. 1.4%, $p<0.001$), intensive care unit admission of mother (42.8% *vs*. 0.2%, $p<0.001$), duration of hospitalization (7.52±6.34 *vs*. 1.97±1.83, $p<0.001$), preterm birth <37 weeks (61.4% *vs*. 16.8%, $p<0.001$), and perinatal mortality (7.4% *vs*. 1.8%, $p<0.001$) which manifested statistically significant values.

Conclusion: The frequency of PAS is similar to other populations. Prior cesarean delivery, placenta previa, multigravidity, and multiparity were independent risk factors and also perinatal hysterectomy and preterm birth were the most important complications.

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Introduction

Placenta accreta spectrum (PAS) is the abnormal adhesion and penetration of the placenta into the uterine wall. According to the new FIGO guidelines (2019), it is classified into three grades based on histologic criteria: (a) grade 1, abnormally adherent placenta (placenta adher-

ent or creta); (b) grade 2, abnormally invasive placenta (Increta); and (c) grade 3, placenta percreta (1). Overall, 75% of PAS cases are accreta (creta), 18% are increta, and 7% are percreta (2). This important complication is a growing problem in recent decades, and its prevalence has been reported to be 3 per 1000 deliveries in the last decade (3).

There are several factors involved in the occurrence of PAS, which are considered as risk factors, the most important of which are the older age of the mother and the history of cesarean section (4). In the United States, the rate of cesarean section increased from 12.5% in 1982 to 23.5% in 2002, with an increase in PAS from 0.38 per 1,000 births to 1.88 per 1,000 births (5). In Iran, the rate of recurrent cesarean section has increased significantly, but unfortunately, no statistics are available regarding the prevalence of PAS and its relationship with the increase in cesarean section. Multiparity, history of termination of pregnancy with and without curettage, myomectomy and other uterine surgeries, chronic hypertension, and diabetes are other risk factors that have been mentioned in some studies. Smoking and Asherman's syndrome have also been reported as other risk factors associated with PAS (6-8). In recent years, several studies have been conducted on the association of maternal serum biochemical biomarkers in the first and second trimesters of pregnancy with PAS. A review study concluded that an increase in PAPP-A, AFP, and a decrease in B-HCG in the first and second trimesters can be associated with PAS (3), but more studies are still needed.

However, many studies have shown that about half of the cases of PAS are not diagnosed until delivery (9, 10). After delivery, pathological findings and clinical criteria (*i.e.*, any difficulty in separating the placenta or surgical procedures to remove it, and uncontrolled bleeding from placental implantation site) can be used as diagnostic criteria for placental adhesions (11, 12). Pregnancies with PAS are associated with relatively high complications before and after delivery, with more than 70% of the complications including heavy bleeding, bladder damage, uterine rupture, hysterectomy, and even maternal or fetal mortality (7). In many maternity and obstetrics centers, controlling bleeding and maintaining the uterus is one of the most important care challenges for these mothers. The purpose of this study was to comprehensively investigate the incidence, risk factors, complications, and pregnancy outcomes in cases of placenta accreta spectrum disorders in Ahvaz city in southwest of Iran.

Methods

This case-control study reports the findings of the research study which is in line with the Declaration of Helsinki and has been approved by the Medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences in Iran (Approval ID: IR.AJUMS.REC.1398.115). All information from patients' documents during the study was recorded. In this study, all medical records of mothers referring to a tertiary hospital affiliated to Ahvaz Jundishapur University of Medical Sciences for hospitalization and delivery between 2015-2019 were examined for the diagnosis and registry of abnormal placental adhesions. This hospital is the main equipped care center for high-risk mothers in southwestern Iran.

In this center, all cases of suspected abnormal placental adhesion were documented in special forms and were re-examined by a perinatologist in terms of the location of the placenta and the associated evidence, using ultrasound and color Doppler. Ultrasonographic diagnostic findings included retroplacental myometrial thickness <1 *mm*, lack of subplacental sonolucent area, placental lacuna, bulging, placental lacunar flow, subplacental vascularity, and color Doppler findings. The definitive diagnosis of PAS was based on the surgeon's confirmation during delivery and histopathological findings. Suspicious cases or cases with insufficient evidence were removed from sampling.

Data were collected using a checklist. In this checklist, in addition to demographic characteristics, obstetric characteristics and risk factors for existing problems were collected extensively.

A total of 187 definitive cases of PAS were observed, who were selected as the case group, and 552 otherwise matched women who did not have placenta accreta/increta/percreta as a control group from the same hospital. The control group included two women giving birth before the cases and one woman giving birth after each case. Of these 187 patients with PAS, 153 had placenta creta, 20 had placenta increta, and 14 had placenta percreta. The classification of PAS types is based on the new FIGO guidelines (2019), but in this paper, all types of PAS were called accrete (1). The surgical team consisted of a multidisciplinary team, including two experienced gynecologists,

two assistants, a skilled nursing team, an experienced anesthesia team, and skilled urologists. Surgical management included ultrasound mapping of placental implantation site preoperatively in order to enter the uterus without cutting the placental tissue.

The treatment strategy depended on the stage of PAS. In focal accreta, conservative management is beneficial including curettage, overseeing of the placental bed, ligation of the uterine arteries, or ligation of the anterior divisions of the internal iliac arteries. If a hysterectomy was needed, the type of hysterectomy was individualized on a case-by-case basis.

In this study, descriptive statistics including mean, standard deviation, and frequency were used. Shapiro-Wilk test was used to evaluate the normality of the data. Two-sample independent t-test and Mann-Whitney U test were used to compare the mean scores of variables according to the two groups. Univariate logistic regression models were used to determine the possible risk factors related to PAS. In the next step, the multiple logistic regression analysis, backward stepwise method (conditional), was constructed to find independent risk factors associated with placenta accrete with 95% confidence interval. The $p<0.05$ were considered statistically significant and the analysis was performed using SPSS software version 22 (IBM, USA).

Results

During the studied period, out of a total of 50037 deliveries, 187 cases (0.37%) had PAS problems, of whom 153 (81.8%) had placenta creta, 20 (10.6%) had placenta increta, and 14 (7.4%) had placenta percreta. Also, 59 (31.6%) cases of PAS were accompanied with placenta previa. Also, the antenatal diagnosis of the cases of abnormal adhesion of the placenta (80.7%) was done by imaging the location of the placenta, and in 19.3% of the cases, the problem was diagnosed during childbirth.

Table 1 shows the obstetric characteristics and risk factors associated with PAS using the univariate model. The mean age of the mothers in the two groups shows a statistically significant difference, and the increase in maternal age is associated with an increase in PAS. In the PAS group, the number of pregnancies varied from 1 to 11, with about 90% of the PAS cases having a gravidity of ≥3. Also, the number of deliveries was significantly associated with the occurrence of PAS. History of abortion and history of curettage were also significantly associated with the occurrence of PAS. The incidence of curettage was three times more likely to increase the frequency of accreta (OR=3.093:95%CI:1.87-5.90). The results also showed that previous cesarean section and the number of cesarean sections are among the high-risk factors associated with PAS so much so that more than 97% of people in the PAS group had a previous cesarean section. Only 5 patients with accreta did not have a history of previous cesarean section, whose mean age and number of pregnancies were 38.2 and 4, respectively, and 3 of them had a history of abortion in previous pregnancies. The number of people with a high rate of cesarean section (≥3) in the PAS group was two times more than that in the control group. Placenta previa is one of the important factors associated with PAS, which was significantly different between the two groups in the present study (OR=35.88:95%CI:16.1-80.4). Other associated factors of PAS in this study were a history of ectopic pregnancy and diabetes.

As shown in table 2, multiple logistic regression analysis, backward stepwise method (conditional), showed the parity of ≥3 (OR=2.05: 95% CI: 1.21-3.47) and gravidity of ≥3 (OR=2.98: 95%CI:1.55-5.72). Prior cesarean delivery (OR= 52.55:95%CI:19.73-139.96) and placenta previa (OR=27.48:95%CI:9.62-78.5) are the independent risk factors of PAS.

Table 3 shows the maternal problems and complications as well as pregnancy outcomes in the two groups. According to the findings, 60.4% of women in the PAS group underwent hysterectomy, and cystostomy was inevitable in almost a quarter (24.1%) of the PAS group. There was also a significant difference between postpartum hemorrhage and blood transfusion in the two groups. Also, about 43% of women with PAS were admitted to the intensive care unit compared to only one woman in the control group. The mean number of hospital stay in PAS group was 7.52±6.34 days, and in the control group, it was 1.97±1.83 days. In all of the above, a statistically significant difference was observed between the two groups.

Table 4 shows the perinatal characteristics and outcomes. According to this table, there is a statistically significant difference between the two groups in terms of gestational age, birth weight, first minute Apgar score and fifth minute Apgar score, neonatal intensive care hospitalization, and perinatal mortality.

Table 1. Risk factors in women with and without PAS (univariate logistic regression models)

Characteristics	Univariate					
	Class	Control (no PAS) n=552 N (%)	Case (PAS) n=187 N (%)	OR	95% CI	p-value
Maternal age (year)	Mean±SD	28.76±6.33	32.79±4.84	1.120	1.086-1.154	<0.001
Parity						
	<3	472 (85.5)	98 (52.4)	Ref	-	<0.001
	≥3	80 (14.5)	89 (47.6)	5.358	(3.69-7.77)	
Gravidity						
	<3	328 (59.4)	24 (12.8)	Ref	-	<0.001
	≥3	224 (40.6)	163 (87.2)	9.945	(6.27-15-76)	
History of abortion						
	No	446 (80.8)	133 (71.3)	Ref	-	0.006
	Yes	106 (19.2)	54 (28.9)	1.708	(1.16-2.5)	
History of curettage						
	No	515 (93.3)	153 (81.8)	Ref	-	<0.001
	Yes	37 (6.7)	34 (18.2)	3.093	(1.87-5.09)	
Prior cesarean delivery						
	No	392 (71.0)	5 (2.7)	Ref	-	<0.001
	Yes	160 (29.0)	182 (97.3)	89.1	(35.99-220.5)	
Number of cesarean deliveries						
	<3	130 (81.3)	118 (63.4)	Ref	-	<0.001
	≥3	30 (18.8)	68 (36.6)	2.49	(1.52- 4.103)	
Myomectomy						
	No	547 (99.1)	187 (100.0)	Ref	-	0.809
	Yes	5 (0.9)	0 (0.0)	0.82	(0.16-4.24)	
History of ectopic pregnancy						
	No	548 (99.3)	182 (97.3)	Ref	-	0.036
	Yes	4 (0.7)	5 (2.7)	3.764	(1.00-14)	
Infertility treatment						
	No	527 (95.5)	183 (97.9)	Ref	-	0.155
	Yes	25 (4.5)	4 (2.1)	0.461	(0.15-1.34)	
Smoking						
	No	550 (99.6)	186 (99.5)	Ref	-	0.750
	Yes	2 (0.4)	1 (0.5)	1.477	(0.13-16.39)	
History of accreta						
	No	551 (99.8)	186 (99.5)	Ref	-	0.443
	Yes	1 (0.2)	1 (0.5)	2.96	(0.18-47.59)	
History of previa						
	No	550 (99.6)	185 (98.9)	Ref	-	0.287
	Yes	2 (0.4)	2 (1.1)	2.97	(0.41-21.32)	
Multiple pregnancy						
	No	535 (96.9)	182 (97.3)	Ref	-	0.778
	Yes	17 (3.1)	5 (2.7)	0.86	(0.31-2.37)	
Hypertensive disorder						
	No	502 (90.9)	173 (92.5)	Ref	-	0.510
	Yes	50 (9.1)	14 (7.5)	0.81	(0.43-1.50)	
Diabetes						
	No	494 (89.5)	157 (84.0)	Ref	-	0.045
	Yes	58 (10.5)	30 (16.0)	1.40	(1.01-2.62)	
Previa						
	No	545 (98.7)	128 (68.4)			<0.001
	Yes	7 (1.3)	59 (31.6)	35.88	(16.01-80.4)	

Table 2. Risk factors in women with and without PAS (the multiple logistic regression analysis-backward stepwise method)

Characteristics	Class	OR	95% CI	p-value
Parity				
	<3	Ref	-	0.008
	≥3	2.05	1.21-3.47	
Gravidity				
	<3	Ref	-	0.001
	≥3	2.98	1.55-5.72	
Prior cesarean delivery				
	No	Ref	-	
	Yes	52.55	19.73-139.96	<0.001
	Yes	12.41	1.16-132.25	
Previa				
	No	Ref	-	<0.001
	Yes	27.48	9.62-78.50	

Discussion

This report is a 5-year retrospective case-control study of documented cases of placenta accreta spectrum disorders in Ahvaz, southwest of Iran. In this study, the PAS frequency was 3.7 per 1000 deliveries. Due to various designs and diagnoses in multiple studies, and the differences in the statistical populations, the reports of PAS incidence are dissimilar, all of which indicating an increase in the last two decades. The incidence has been reported to rise from 0.8 per 1000 births in the 1980s to 3 per 1000 births in the last decade (11). In this study, the biggest risk factor associated with PAS was a history of previous cesarean section, with 97.3% of PAS mothers having a previous cesarean section (OR=89.1:95%CI:35.9-220.5).

According to a previous study, the most important risk factor for placenta accreta was a history of previous cesarean section (74.8%) (7). The results of a meta-analysis showed that the risk of PAS doubled after cesarean scarring and the higher the number of cesarean sections, the greater the likelihood of PAS. The risk of PAS in women who have more than 3 scars is 10 times higher than those who have one scar (13). In our study, the risk of PAS in mothers with ≥3 cesarean sections was 2.5 times higher than that in mothers with a history of 1 or 2 cesarean sections.

Another important risk factor associated with PAS is placenta previa. In this study, 59 (31.6%) women in the PAS group had placenta previa. Particularly, if placenta previa is associated with a previous cesarean section, the risk of PAS is significantly increased. In our study, out of 59 patients with placenta previa-acreta, 54 (91%) had a previous cesarean section. The risk of placenta accreta in women with placenta previa without cesarean scarring increases by 3.3%-4% and in those with more than 3 cesarean sections, it increases by 50-67% (13).

Old age of the mother is another risk factor contributing to the increased rate of PAS. In our findings, the mean age of the mothers in the PAS and

Table 3. Complications and morbidity of women with and without PAS

Variables	Class	Case (PAS) n=187 N (%)	Control (no PAS) n=552 N (%)	p-value
Hysterectomy				
	Yes	(113) 60.4%	(4) 0.7%	<0.001
	No	74 (39.6%)	(548) 99.3%	
Cystostomy				
	Yes	(45) 24.1%	(1) 0.2%	<0.001
	No	(142) 75.9%	(551) 99.8%	
Blood transfusion				
	Yes	(138) 73.7%	(8) 1.4%	<0.001
	No	(49) 26.3%	(544) 98.6%	
Intensive care unit admission (mother)				
	Yes	(80) 42.8%	(1) 0.2%	<0.001
	No	(107) 57.2%	(551) 99.8%	
Duration of hospitalization (day)				
	Mean±SD	7.52±6.34	1.97±1.83	<0.001

Table 4. Characteristics and perinatal outcomes of women with and without PAS

Variables	Case (PAS) n=187	Control (no PAS) n=552	p–value
	Mean±SD	Mean±SD	
Gestational age (week)	34.84±4.74	37.98±3.36	<0.001
Birth weight (*kg*)	2686.17±659.52	2967.53±673.70	<0.001
Apgar score			
1 *min*	7.69±1.91	8.33±1.24	<0.001
5 *min*	8.84±1.73	9.44±1.047	
Preterm birth (<37 week)			
Yes	115 (61.4%)	93 (16.8%)	<0.001
No	72 (38.6%)	459 (83.2%)	
Perinatal mortality			
Yes	14 (7.4%)	10 (1.8%)	<0.001
No	173 (92.6%)	542 (98.2%)	

non-PAS groups was significantly different (28.76% *vs*. 32.79%; p<0.001). In previous studies, it has been reported that after the age of 20, the risk of PAS increases by 14% for each year of maternal age (14). Many studies have also shown that with advanced maternal age especially over 35, the likelihood of PSA increases (15).

As far as gravidity and parity are concerned, our findings showed that the increase in the number of pregnancies is associated with an increase in the risk of PAS. In women with parity >3, the risk of PAS increases 5-fold by delivery. Also, the higher the number of pregnancies, the higher the risk of accreta. The number of women with gravidity >3 in the PAS group was almost 2 times more than the one in the non-PAS group (87.2% *vs*. 40.6%, p<0.001). It seems that the relation between gravidity and accreta may be mostly due to scars of cesarean section. According to Gelany et al. (2019), gravidity was one of the risk factors associated with accreta (16).

In our study, the history of abortions was examined in previous pregnancies independent of the number of curettages performed, and interesting results were obtained. Abortions are 1.5 times more likely to increase the frequency of PAS. However, as far as curettage was concerned, the history of curettage is three times more likely to increase the risk of PAS. It seems that abortion with or without curettage would probably increase the rate of PAS. This increase is more pronounced especially in the case of curettage, and the manipulation of the uterus and the decidua increases the rate of PAS. Garmi et al. conducted an *in vitro* study on the decidua and confirmed that despite the later restoration of the decidua, the potential of the decidua for restoring itself and inhibiting trophoblast penetration is reduced (17). Therefore, aggressive and numerous curettages can affect the permeability and impermeability of the decidua.

In our study, the history of ectopic pregnancy was found to be 3.5 times more likely to increase the rate of PAS (OR=3.763:95%CI:1.00-14.0). In the present study, another factor associated with accreta was gestational diabetes. The indirect relationship between diabetes and accreta can be explained by the fact that diabetes increases the complications of pregnancy (macrosomia, preeclampsia, hypertension, and cardiovascular complications) and the frequency in performing obstetric interventions and cesarean section. However, the effect of hypoxia on placental vasculitis and inflammatory changes in this regard is not unlikely and needs further study. After using a multivariable logistic regression analysis, results showed that these are indeed independent risk factors for placenta accreta (Table 2).

Although several variables were significantly associated with placenta accreta in the univariate analysis, after controlling for maternal age, history of abortion and curettage, number of previous cesarean sections, history of ectopic pregnancy, and diabetes, they lost their significance as independent risk factors for placenta accreta.

Maternal complications and problems: The most important and common complication associated

with PAS is hysterectomy. According to Eshkoli et al, the most common cause of cesarean hysterectomy is related to placental adhesion, and 51.1% of emergency hysterectomies are related to PAS (7). In our study, 60.4% of the women in the PAS group underwent hysterectomy as opposed to only 0.7% in the control group. According to Farquhar et al., the rate of hysterectomy accompanied with accreta was 66.4% as opposed to only 0.4% among cases without accrete (4). In the USA and Australia, peripartum hysterectomy was the indication for 38% and 70% of peripartum hysterectomies, respectively.

Peripartum hysterectomy and emergency hysterectomy with cesarean section are among the methods of PAS control and treatment. In fact, compared with unplanned and emergency hysterectomies, scheduled hysterectomies have fewer complications with fewer ICU admissions and less blood loss (18). The decision to perform a hysterectomy depends on the mother's condition, the extent of the adhesion and its type, the severity of the bleeding, the presence or absence of placenta previa, the involvement of the bladder and its risks, and the rupture of the uterus. Of importance is also the number of children, and in our study all mothers undergoing hysterectomy already had children, and more than 87% of them had more than 3 pregnancies. Clinically, the presence and severity of bleeding throughout pregnancy can be effective in deciding on the type of delivery and controlling it.

There are several factors involved in predicting the complications and problems associated with PAS, but two are very important, namely the time of diagnosis of PAS and the treatment scenario. The earlier PAS is diagnosed in the prenatal period, the lower the risk of unforeseen complications and emergencies. According to Imtiaz et al., the rate of blood transfusion, maintaining the uterus, and ICU admissions were considerably lower in women whose PAS had been diagnosed antenatally compared with those whose PAS was diagnosed during the operation (19). In the studied center, all mothers with previous cesarean section and placenta previa were required to undergo ultrasound imaging for PAS diagnosis, and despite the 80% rate of PAS diagnosis in the antenatal stage, the treatment scenario was not based on expectant management. In PAS, the average rate of blood loss is 3-5 *liters*, and 90% of mothers need blood transfusion (20). Typically, in a hysterectomy cesarean section, the rate of blood loss is 2-5 *liters* (11). In our study, 73.7% of PAS women needed blood transfusion. The mean blood transfusion rate was 3 units. Among the maternal complications seen only in the PAS group, 3 cases of maternal disseminated intravascular coagulation (DIC) and 12 cases of postpartum hemorrhage (PPH) were observed which were not detected in the control group.

The rate of ICU admission was 80 (42.8%) cases of whom 21 were admitted to the ICU for only one day in order to be under more intensive medical attention. Farquhar et al. (2017) reported that ICU hospitalization of placenta accreta patients was 35%, which is almost identical to our findings (4). In underdeveloped and low-income countries, due to lack of access to necessary facilities, follow-up, and additional treatments, the conservative treatment approach is associated with a high risk for the mother, and the choice of peripartum hysterectomy seems safer (21). However, the studied center has recently changed its policy of treating these patients with conservative treatment.

Neonatal complications: One of the most common neonatal complications associated with PAS is preterm birth which showed a significant difference between the two groups in this study (61.4% *vs*. 16.8%, $p<0.001$). The decision to terminate pregnancy depends on several factors, such as the mother's condition, the amount of bleeding throughout pregnancy, the degree and type of adhesion, the presence of placenta previa, and the number of previous cesarean sections. In the studied center, all mothers who have a previous cesarean section will undergo another cesarean section in their next pregnancy, and vaginal delivery will not be performed in mothers already giving birth through cesarean section. This affects the age at birth because mothers with previous cesarean section terminate their pregnancy one to two weeks earlier than their estimated date of delivery. The mean age of the infant in the PAS group and the control group was 33.84 and 36.98 weeks, respectively, with a mean difference of 3.14 ($p<0.001$). Birth weight was also different in the two groups (2686.1 *vs*. 2967.5, $p<0.001$), which may be due to lower gestational age at delivery in the PAS group. Prenatal mortality was almost three times higher in the PAS group compared with the control group (7.4% *vs*. 1.8%, $p<0.001$), which is similar to the study of Eshkoli et al. (5.8% *vs*. 1.9%, $p<0.001$) (7).

Conclusion

The findings of the present study showed that the frequency of PAS is similar to other populations. Prior cesarean delivery, placenta previa, multigravidity, and multiparity were independent risk factors and also perinatal hysterectomy and preterm birth were the most important complications. The present study adds to the growing body of research by indicating that the most important factors in reducing the frequency of placenta accreta spectrum disorder are the promotion of normal childbirth, the prevention of unnecessary cesarean section, and the promotion of vaginal birth after cesarean (VBAC) which are less common in developing countries.

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Conflict of Interest

There is no conflict of interest to declare.

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