

Evaluation of the risk factors for antepartum hemorrhage in cases of placenta previa: a retrospective cohort study

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Abstract

Objective: The aim of this study was to examine the risk factors for antepartum hemorrhage (APH) in women with placenta previa.

Methods: In this retrospective cohort study, we analyzed the medical records of 233 women with singleton pregnancies presenting with placenta previa whose deliveries were performed at our hospital between January 2009 and July 2018.

Results: Of the 233 women included in this study, 130 (55.8%) had APH. In the APH group, the gestational age and neonatal birth weight were significantly lower compared with the no hemorrhage group. Maternal age <30 years and multiparity were identified as significant risk factors for APH in both the univariate and multivariate analyses. Focusing on the previous route of delivery in multiparous women, the risk of APH was significantly higher in multiparous women who had experienced at least one vaginal delivery compared with nulliparous women (adjusted odds ratio (OR): 3.42 [95% confidence interval: 1.83–6.38]).

Conclusion: We showed that women with placenta previa who were under 30 years old and who had a history of vaginal delivery may be at significant risk of experiencing APH.

Keywords

Antepartum hemorrhage, cesarean delivery, parity, placenta previa, preterm birth, vaginal delivery

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Introduction

The prevalence of placenta previa is approximately 4 per 1000 births.^{1,2} Placental bleeding is a major adverse sequela of placenta previa, and placenta previa is associated with an increased risk of antepartum (relative risk (RR): 9.8), intrapartum (RR: 2.5), and postpartum (RR: 1.9) hemorrhage.³ Thus, patients with placenta previa (vs. without, respectively) are more likely to receive blood transfusion (12% vs. 0.8%),⁴ postpartum hysterectomy (5.3% vs. 0.04%),⁵ uterine/iliac artery ligation, or embolization of the pelvic vessels to control bleeding (2.5% vs. 0%).⁴ In cases of placenta previa, antepartum hemorrhage (APH) is associated with a higher incidence of preterm delivery and a greater risk of neonatal morbidity and mortality compared with cases without placenta previa.⁶ A systematic review and meta-analysis revealed that women with placenta previa have a greater risk of preterm delivery at <37 weeks (RR: 5.32; 95% confidence interval (CI): 4.39–6.45), neonatal intensive care unit (NICU) admission (RR: 4.09; 95% CI: 2.80–5.97), neonatal death (RR: 5.44; 95% CI: 3.03–9.78), and perinatal death (RR: 3.01; 95% CI: 1.41–6.43) compared with women without placenta previa.⁷

More than half of the women with placenta previa experience APH.⁸ The initial bleeding episode occurs prior to 30 weeks' gestation in approximately one-third of women with placenta previa. This group is more likely to require blood transfusion and shows a higher rate of preterm delivery and perinatal mortality compared with cases in which bleeding begins later in gestation.^{9–11} The number of episodes of APH and the need for blood transfusion are independent predictors of emergency cesarean delivery.¹²

For an individual pregnant woman with placenta previa, it is not possible to

accurately predict whether spontaneous bleeding will occur, the gestational age at which it will occur, or the volume or frequency of bleeding. Anterior placenta previa is more likely to be associated with APH than posterior or lateral previa.^{13,14} Sonographic features, such as thick placental edge,¹⁵ short cervical length,^{16,17} and decreased cervical length in the third trimester^{18,19} are associated with a higher likelihood of antepartum bleeding. However, few studies have focused on this issue. Therefore, we examined the risk factors for APH in women with placenta previa.

Methods

Participants

In this retrospective cohort study, we consecutively analyzed the medical records of women whose deliveries were conducted at Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan, between January 2009 and July 2018. Among these women, we selected those who delivered with placenta previa and excluded cases involving multiple pregnancy, delivery before 22 weeks' gestation, stillbirth, or low-lying placenta. We divided the women into two groups, the APH group and the no hemorrhage (NH) group, according to the presence or absence of APH during pregnancy.

This investigation conformed to the principles outlined in the Declaration of Helsinki (1964). This study was approved by the Ethics Committee of the Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Nagoya, Japan (approval number: 2018-115). We compiled and analyzed the data in such a way that each patient's personal information could not be identified. Therefore, the Ethics Committee waived the need to obtain patient consent. The reporting of this

study conforms to the STROBE guidelines.²⁰

Data collection and definition

We obtained maternal and perinatal data from the patients' medical records. Maternal data (age, parity, type of placenta previa, placental position, infertility treatment, blood loss volume at cesarean delivery, hysterectomy, and blood transfusion) and neonatal data (gestational age at delivery, birth weight, Apgar scores, and NICU admission) were extracted. The diagnosis of placenta previa was made according to ultrasonography and/or magnetic resonance imaging (MRI) within 1 week of cesarean delivery. Placenta previa includes both marginal (the placenta extends to the edge of the cervix), partial (some of the cervical opening is covered by the placenta), and complete types (the cervical opening is completely covered by the placenta).² We usually manage women with placenta previa as outpatients; however, patients with APH are admitted to hospital and managed as inpatients. There were no cases of premature rupture of membranes (PROM) in this study. Infertility treatment included artificial insemination and *in vitro* fertilization. APH was defined as painless genital bleeding from the placenta during pregnancy.

Statistical analysis

Clinical data were extracted from the medical records and entered into a computerized spreadsheet (Excel; Microsoft Japan Co., Ltd., Tokyo, Japan). The EZR software program (version 1.38; Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used to perform all statistical analyses. Estimating the APH rate at 30% to 50%, the power calculation (80% power and 5% alpha) demonstrated that 206 women were required in this study.

After using the Shapiro–Wilk test to assess the normality of the data, we used the Mann–Whitney *U* test to compare continuous variables between the groups, and Student's *t*-test was used as appropriate. The chi-square test was used to compare categorical variables. A logistic regression model that included maternal age, parity, infertility treatment, placental position, and type of placenta previa was used to develop a prediction model for APH. We calculated the crude rates of APH in placenta previa and expressed the association between these variables and APH as odds ratios (ORs) [95% confidence intervals (CIs)]. Adjusted ORs were then derived from logistic regression models after controlling for the influence of these variables. *P* values <0.05 were considered statistically significant.

Results

Patients' background characteristics

Of the 14,791 deliveries during the study period, 309 involved placenta previa. After excluding multiple pregnancy, deliveries before 22 weeks' gestation, stillbirth, and low-lying placenta, 233 cases were analyzed. One hundred thirty of the 233 (55.8%) women included in this study had APH, and 103 (44.2%) had NH (Figure 1). The perinatal outcomes in each group are shown in Table 1. In the APH group, the gestational age and neonatal birth weight were significantly lower compared with the NH group ($P < 0.01$); however, after adjustment for gestational age, the difference in neonatal birth weight was no longer significant (OR: 1.00 [0.99–1.01]). There were no significant differences between the groups regarding blood loss at cesarean delivery, or the rates of blood transfusion and hysterectomy. Six patients in the APH group and three patients in the NH group received hysterectomy. Of the six cases in the APH

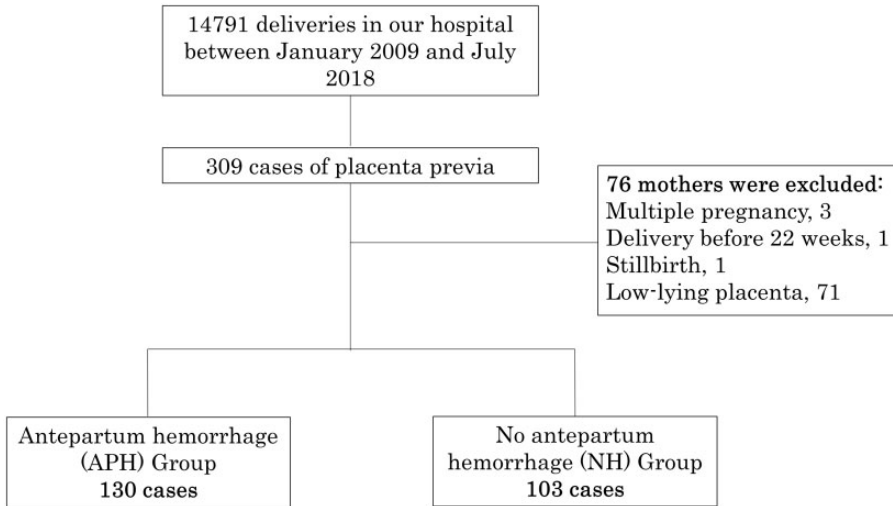


Figure 1 Study flowchart of patient enrollment.

Table 1. Perinatal outcomes in the APH and NH groups.

Outcome	APH (n = 130)	NH (n = 103)	P-value
Gestational age at delivery, weeks	34.0 ± 2.6	36.3 ± 1.6	<0.01
Blood loss at CS, grams	1532 ± 962	1500 ± 1012	0.88
Blood transfusion	10/130 (7.7%)	4/103 (3.1%)	0.28
Placenta accreta spectrum	4/130 (3.1%)	2/103 (1.9%)	0.70
Hysterectomy	6/130 (4.6%)	3/103 (2.9%)	0.74
Neonatal birth weight, grams	2186.4 ± 553	2620.7 ± 441	<0.01
Apgar score at 1 minute	6.6 ± 2.0	7.3 ± 1.7	<0.01
Apgar score at 5 minutes	7.9 ± 1.6	8.4 ± 1.4	<0.01
NICU admission	98/130 (75.4%)	45/103 (43.7%)	<0.01
Hospitalization, days	21.3 ± 25.5	6.1 ± 17.6	<0.01

APH, antepartum hemorrhage; NH, no antepartum hemorrhage; CS, cesarean section; NICU, neonatal intensive care unit. Data are presented as the mean ± standard deviation.

group, four patients experienced placenta accreta spectrum (PAS) and two experienced massive postpartum hemorrhage. Of the three cases in the NH group receiving hysterectomy, two experienced PAS and one experienced massive postpartum hemorrhage. The maternal characteristics in each group are shown in Table 2. Maternal age, infertility treatment, placental position, and type of previa did not differ significantly between the groups; however, parity was a significant factor.

In the APH group, the rate of nulliparity was significantly lower than that in the NH group ($P < 0.01$), and the percentage of multiparous women who had experienced at least one vaginal delivery was significantly higher in the APH group.

Risk factors for APH in placenta previa

The results of the univariate and multivariate analyses to identify the risk factors for APH in placenta previa are shown

Table 2. Maternal characteristics.

Characteristic	APH (n = 130)	NH (n = 103)	P-value
Maternal age			0.16
<30 years	31/130 (23.8%)	16/103 (15.5%)	
≥30 years	99/130 (76.2%)	87/103 (84.5%)	
Parity			<0.01
Nulliparous	46/130 (35.4%)	63/103 (61.2%)	
Multiparous (CS only)	16/130 (12.3%)	12/103 (11.7%)	
Multiparous (≥1 VD)	68/130 (52.3%)	28/103 (27.2%)	
Infertility treatment	22/130 (16.9%)	23/103 (22.3%)	0.38
Placental position			0.07
Anterior	34/130 (26.2%)	16/103 (15.5%)	
Posterior	96/130 (73.8%)	87/103 (84.5%)	
Placenta type			0.33
Complete	59/130 (45.4%)	44/103 (42.7%)	
Partial	17/130 (13.1%)	8/103 (7.8%)	
Marginal	54/130 (41.5%)	51/103 (49.5%)	

APH, antepartum hemorrhage; NH, no antepartum hemorrhage; CS, Cesarean section; VD, vaginal delivery.

in Table 3. Maternal age <30 years and multiparity were identified as significant risk factors for APH in the multivariate analyses. In particular, multiparity was associated with the highest risk of APH (adjusted OR: 2.87 [1.61–5.14]; $P < 0.001$). Anterior placenta was a significant risk factor for APH in the univariate analysis but not in the multivariate analysis.

History of vaginal delivery was a significant risk factor for APH

We found that multiparity was associated with the highest risk of APH. Therefore, we focused on the previous route of delivery in the multiparous women who were included in this study. We divided the multiparous women into two groups: those who had experienced at least one vaginal delivery, and those who had experienced only cesarean delivery. Of the 126 multiparous women, 96 experienced at least one vaginal delivery while 28 experienced only cesarean deliveries. Next, to evaluate the effect of maternal age as a risk factor for APH, we divided maternal age into three

groups: <25 years, 25 to 30 years, and ≥30 years. The analysis showed that the risk of APH in multiparous women who experienced at least one vaginal delivery was significantly higher than that in nulliparous women (adjusted OR: 3.42 [1.83–6.38]; $P < 0.001$). However, the risk of APH in multiparous women who had experienced only cesarean delivery and the risk in nulliparous women did not differ significantly (adjusted OR: 1.69 [0.68–4.17]) (Table 4). In contrast, after stratifying for maternal age, the younger group tended to have a higher risk of APH; however, the difference was not statistically significant. We also performed a multivariate analysis (stepwise regression) to calculate the adjusted ORs for APH. The results showed that multiparity with at least one vaginal delivery was the only significant factor (adjusted OR: 3.33 [1.86–5.95]; $P < 0.001$). We also calculated the ORs for APH according to maternal age and parity (Table 5) and found that women who were <30 years old with a history of vaginal delivery had a higher risk of APH compared with nulliparous women >30 years old (OR: 8.12 [2.18–30.3]; $P < 0.001$).

Table 3. Univariate and multivariate analysis of the risk factors for antepartum hemorrhage in women with placenta previa.

	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Maternal age (<30 years)	1.70	0.87–3.32	0.119	2.08	1.01–4.28	0.048
Multiparous	2.88	1.68–4.91	<0.001	2.87	1.61–5.14	<0.001
Infertility treatment	0.71	0.37–1.36	0.300	1.20	0.58–2.48	0.614
Anterior placenta	1.93	1.04–3.87	0.039	1.72	0.85–3.49	0.131
Marginal previa	1.00			1.00		
Partial previa	2.01	0.80–5.05	0.827	1.71	0.65–4.47	0.278
Complete previa	1.27	0.73–2.19	0.898	1.04	0.58–1.86	0.893

OR, odds ratio; CI, confidence interval.

Table 4. Multivariate analysis of the risk factors for antepartum hemorrhage in women with placenta previa according to a history of vaginal delivery.

Risk factor	Adjusted OR	95% CI	P-value
Maternal age (≥ 30 years)	1.00		
Maternal age (25–30 years)	1.90	0.86–4.18	0.110
Maternal age (<25 years)	2.92	0.68–12.5	0.150
Nulliparous	1.00		
Multiparous (≥ 1 VD)	3.42	1.83–6.38	<0.001
Multiparous (CS only)	1.69	0.68–4.17	0.258
Infertility treatment	1.26	0.61–2.59	0.539
Anterior placenta	1.87	0.90–3.88	0.091
Marginal previa	1.00		
Partial previa	1.56	0.59–4.16	0.372
Complete previa	1.04	0.58–1.87	0.883

OR, odds ratio; CI, confidence interval; VD, vaginal delivery; CS, cesarean section.

Table 5. Odds ratios for the risk of antepartum hemorrhage according to maternal age and parity.

	APH rate	OR	95% CI	P-value
Maternal age (≥ 30 years)				
Nulliparous	25/84 (38.1%)	1		
Multiparous (≥ 1 VD)	52/78 (66.7%)	3.25	1.71–6.19	<0.001
Multiparous (CS only)	15/24 (62.5%)	2.71	1.06–6.91	0.037
Maternal age (<30 years)				
Nulliparous	14/25 (56%)	2.07	0.84–5.11	0.120
Multiparous (≥ 1 VD)	15/18 (83.3%)	8.12	2.18–30.3	<0.001
Multiparous (CS only)	2/4 (50%)	1.62	0.22–12.1	0.640

APH, antepartum hemorrhage; OR, odds ratio; CI, confidence interval; VD, vaginal delivery; CS, cesarean section.

Discussion

This study revealed two important findings. First, APH affected perinatal outcomes because it led to preterm delivery. Second, women who were younger than 30 years old with a history of vaginal delivery had the greatest risk of experiencing APH.

Placenta previa is a known risk factor for preterm delivery. In particular, APH in cases of placenta previa can be associated with preterm delivery, which is correlated with neonatal morbidity and mortality.⁶ In a US population-based cohort, 27.5% of women with placenta previa delivered at 34 to 37 weeks' gestation, and 16.9% of women delivered before 34 weeks' gestation.^{21,22} Bahar *et al.* showed that APH was associated with preterm delivery in cases of placenta previa (OR: 14.9 [4.9–45.1]; $P < 0.001$).²³ However, in the APH and NH groups in this study, there were no significant differences in blood loss at cesarean delivery or in the blood transfusion rate. APH in placenta previa can affect neonatal outcomes but not maternal outcomes.

Women with anterior placenta previa are more likely to develop APH;^{13,14} however, we did not identify this association in our study population. In the present study, the only significant risk factors for APH were maternal age < 30 years and multiparity. Conflicting data exist regarding the association between APH and parity in placenta previa. Fan *et al.* showed a positive correlation between multiparity and the prevalence of APH ($r = 0.534$; $P = 0.027$) and a negative correlation between the survey year and the prevalence of APH ($r = -0.400$; $P = 0.031$) in a meta-analysis that included 29 articles.⁸ Our results were similar to the results of Fan *et al.*'s study; however, other small studies showed no significant association between parity and APH. Nur Azurah *et al.* showed no difference in the incidence of APH between 56

primigravida and 187 nonprimigravida women.²⁴ Interestingly, we found that multiparity and younger age (< 30 years) were both significant risk factors for APH. Moreover, we divided multiparous women into two groups: those with a history of vaginal delivery and those without a history of vaginal delivery. We demonstrated that multiparity with a history of vaginal delivery was the only significant risk factor for APH. This is the first report regarding this issue. In Japan, the average maternal age at delivery was 30.7 years in 2018; thus, we defined the cutoff value for maternal age as 30 years. However, after stratification according to maternal age, the younger group tended to have a high risk of APH; therefore, it is necessary to be aware of APH in women in this age group.

The mechanism of APH has not been fully elucidated.²⁵ Oyelese and Smulian reported that contractions and cervical effacement and dilatation result in placental separation, leading to small amounts of bleeding.²⁶ Goto *et al.* showed that early opening (before 25 weeks) of the uterine isthmus was associated with a higher risk of emergency cesarean section owing to bleeding compared with late opening (after 25 weeks) of the uterine isthmus (OR: 2.7 [1.1–6.2]; $P = 0.023$).²⁷ In accordance with these results, we hypothesized that cervical and lower uterine segment elasticity is important. Empirically, the cervix and lower uterine segment are soft in younger women and in multiparous women. Therefore, it is reasonable that younger women are more likely to experience APH. Interestingly, a significant risk of APH was observed only in multiparous women with a history of vaginal delivery and not in women who had delivered only by cesarean section. This finding supports our hypothesis. To further test this hypothesis, a future study should investigate whether cesarean section was performed before the onset of labor (when the cervix

was almost closed) or after the onset of labor (when the cervix was already dilated) in the previous cesarean delivery(ies).

The strength of this study is that we focused on parity, especially on the route of delivery. Obtaining information, such as the patient's reproductive history and maternal age, may be useful for predicting the risk of APH in placenta previa. Unfortunately, we could not obtain information about whether previous cesarean sections were elective or emergent, or whether the cervix was dilated at that time. Additionally, the present study has limitations, namely its retrospective design and the relatively low number of patients with cesarean deliveries in both groups. Of the 126 multiparous women, 96 experienced at least one vaginal delivery while 28 experienced only cesarean deliveries. This proportion may have caused bias; therefore, careful attention is needed when interpreting the conclusion of this study. Next, data regarding a history of abortion, smoking, hypertension, and time interval between pregnancies were not included in this study. Further studies are necessary. It is currently impossible to accurately predict the gestational age, volume, or frequency of bleeding in individual pregnant women with placenta previa who experience APH. We hope that these issues can be elucidated in the future. Sonographic features, such as thick placental edge,¹⁵ short cervical length,^{16,17} and decreased cervical length in the third trimester^{18,19} are associated with a higher likelihood of experiencing APH. In the future, the risk of APH may be estimated according to maternal age, parity, and these sonographic findings.

In conclusion, we showed that women with placenta previa who are under 30 years old and who have a history of vaginal delivery may have a significant risk of experiencing APH. We believe that the findings of the present study will be useful in the

management of women with placenta previa.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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