Maternal and neonatal outcomes of repeated antepartum bleeding in 493 placenta previa cases: a retrospective study

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Abstract

Background Placenta previa (PP) is a serious complication of late pregnancy. Exploring the effect of antepartum bleeding caused by PP on pregnancy outcomes is very important.

Methods We retrospectively analyzed 493 women complicated with PP. Patients were divided into antepartum repeated bleeding and non-bleeding groups. Maternal characteristics and pregnancy outcomes were compared.

Results The risk of antepartum hemorrhage was 2.038 times higher when gravidity was 5 (95% CI 1.104 ~ 3.760, *P* = 0.023). Pregnant women with a history of more than three intrauterine procedures had a 1.968 times higher risk of antepartum hemorrhage (95% CI 1.135 ~ 3,412, P = 0.016) compared to pregnant women without any intrauterine procedures. The risk of antepartum bleeding was found to be decreasing with the pregnancy advancing; When the placenta edge was noted to be over cervival os, the risk of antepartum bleeding was 4.385-fold than the low-lying plcaenta cases (95%CI2.454□8.372,P = 0.000). In the respect of maternal outcomes, the repeated bleeding group, the risk of emergency surgery was 7.213 times higher than elective surgery (95% CI 4.402□11.817, *P* = 0.000). As for the neonatal outcomes, the risk of asphyxia was 2.970 times and the risk of NICU admission was 2.542-fold higher in repeated bleeding group compared to non-bleeding group, respectively.

Conclusions Obstetricians should be aware of the increased risk of antepartum bleeding especially for ≤ 34 weeks and placenta edge over cervical os PP patients, they have a higher risk of antepartum bleeding. These women have higher possibility of emergency c-section and need preterm newborn resuscitation.

Background

Placenta previa (PP) is a serious complication of late pregnancy and represents one of the most common acute and severe obstetric emergencies. The prevalence of this complication has been estimated to be roughly 0.5% of all pregnancies [1]. The most common manifestation of PP is painless prenatal bleeding in late pregnancy, often causing patient anxiety. PP is closely related to maternal and fetal morbidity and mortality, which is the main cause of prenatal, peripartum and postpartum hemorrhage [2].

Advanced maternal age, smoking, *in vitro* fertilization technology, prior cesarean section, and multiparty have been found to increase the risk of PP [3–5]. Interestingly, previous cesarean delivery was found to be the most important risk factor for the development of placenta previa [6]. Studies have demonstrated a dose-response relationship between the risk of previa and previous cesarean deliveries. The relative risk compared to no history of cesarean section was 4.5-fold for one, 7.4-fold for two, 6.5 -fold for three, and 44.9-fold for four or more prior cesarean sections [7].

Studies have reported that complete previa patients are more likely to have prenatal hemorrhage, blood transfusions, placenta acceta and hysterectomy [4]. Patients and doctors become especially worried about the prenatal massive hemorrhage. Furthermore, obstetricians are often confused about the proper

timing of pregnancy termination to reduce the damage to mothers and babies, yet the subject has rarely been studied. To this end, the clinical characteristics of 493 placenta previa cases treated between 2010 and 2017 at the First Affiliated Hospital of Nanjing Medical University were retrospectively analyzed to explore the relationship between antepartum hemorrhage and pregnancy outcomes.

Methods:

General Information:

A total of 29,520 deliveries from Jiangsu Province Hospital registered between October 2010 - December 2017 were analyzed, of which there were 493 cases of placenta previa representing an overall incidence of 1.67%. The gestational ages of these 493 patients were confirmed based on records of last menstruation and prenatal ultrasound. Within this case series there were 143 cases of marginal placenta previa, 21cases of partial placenta previa, and 329 cases of central placental previa. Interestingly, there were 11 vaginal deliveries, 10 of these cases had marginal placenta previa with one case of partial placenta previa; 482 cases of delivery by cesarean section; 46 cases of twin pregnancy and 447 cases of single pregnancy.

Methods:

In this retrospective analysis of patients with placenta previa, clinical data from the prenatal period were collected and is divided into three parts: obstetrical risk factors (age, gravidity, parity,number of intrauterine procedures, number of fetuses in the current pregnancy,gestational age when the pregnancy was terminated,times of c-section,proportion of multipara type of placenta previa); maternal outcome (operation type, postpartum hemorrhage, use of blood products, hysterectomy); neonatal outcome (neonatal gender, birth weight, Apgar score, fetal position, neonatal asphyxia, and NICU admission). The number of intrauterine procedures refers to total number of intrauterine operations, such as artificial abortion, hysteroscopy and other related procedures, ever undergone by the patient. The data was collected by three physician independently.

Diagnostic criteria:

Prenatal diagnosis was made using the most recent ultrasound examination the distance(millimeters) that placenta extends over the internal cervical os: placenta previa was indicative of a placenta completely covering the endocervical opening; when the placental edge is < 2 cm from internal os, marked as low-lying placenta. Diagnostic criteria were mainly based on the results of the last transvaginal ultrasound. In cases where a diagnosis could not be reached by ultrasound or ultrasound was not performed, final diagnosis of placenta previa were based on intraoperative processes or postpartum diagnosis.

Inclusion criteria for antepartum hemorrhage included vaginal bleeding caused by placenta previa at gestational age after 20 weeks, and gestational age at delivery ≥ 28 weeks. Exclusion criteria included patients with vaginal bleeding due to vaginitis, cervicitis, cervical polyps, spontaneous abortion or

placental abruption. Patients were divided into two groups based on antepartum hemorrhage caused by placenta previa: *1.* Repeated bleeding group defined as those patients with repeated vaginal bleeding during pregnancy were included. Antepartum hemorrhage was assessed based on the weighing method to calculate the accumulated amount of bleeding, and then accumulated. *2.* Non-bleeding group was defined as patients having pregnancy (Gestational week more than 20 weeks) without bleeding or a very small amount of bleeding (less than 5 ml), and no vaginal bleeding in later pregnancy. Postpartum hemorrhage refers to total blood loss ≥ 500 ml after 24 hours of post normal delivery or blood loss ≥ 1000 ml after cesarean section. Antepartum hemorrhage blood loss was calculated using the following formula: blood loss (ml) = (blood clothing or sanitary napkins - dry clothes or sanitary napkins) / 1.05.

Ethical approval:

The study was approved by the Ethical Board of the First Affiliated Hospital of Nanjing Medical University (Ethics Committee 2020-SR-256).As this is observational prospective study, no intervention were done to these patients.

Statistical methods:

Data were analyzed using the statistical software SPSS 22.0. Numerical data for the two groups were obtained by t test analyses. The risk ratio between the two groups were tested using binary logistic regression; $P < 0.05$ was considered statistically significant.

Results:

Clinical Features of non-bleeding and repeated bleeding groups
Age, gravidity, parity, number of intrauterine procedures, gestational age when pregnancy is terminated were each analyzed using t test. General clinical data demonstrated: no significant difference in maternal age, gravidity, parity and times of c-sections ($P > 0.05$). The non-bleeding group had a significantly higher gestational age when pregnancy was terminated compared to the repeated bleeding group, 36.91 ± 2.04 weeks vs.34.50 ± 2.56 weeks, $P = 0.003$. The number of intrauterine procedures was higher in repeated bleeding group than that in non-bleeding group, $P = 0.043$. (See Table 1).

Table 1
Clinical Features of non-bleeding and repeated bleeding groups

Clinical Features (means ± SD)	**Non-bleeding(n = 282)**	**Repeated bleeding (n = 211)**	**t value**	***P***
Age(years)	31.47 ± 4.81	31.04 ± 5.44	0.902	0.056
Gravidity	2.91 ± 1.62	3.24 ± 1.68	-2.161	0.476
Parity	1.47 ± 0.60	1.64 ± 0.68	-2.543	0.091
Uterine surgery procedures	1.30 ± 1.35	1.57 ± 1.46	-2.073	0.043*
Times of CS	0.78 ± 0.77	0.70 ± 0.78	1.071	0.450
GA termination(weeks)	36.91 ± 2.04	34.50 ± 2.56	11.615	0.003*
CS = cesarean section; GA = gestational age				

Analysis of obstetrical risk factors for antepartum hemorrhage in placenta previa

With a total of 493 cases of placenta previa, the non-bleeding group accounted for 57.2% of total patients, and repeated bleeding group accounted for 42.8%. Our results showed that the age of mothers, times of c-section, number of fetuses,Placental location, and Placenta accreta were not associated with risk of antepartum bleeding. The risk of antepartum hemorrhage was 2.038 times higher when gravidity was 5 (95% CI 1.104 ~ 3.760, *P* = 0.023). Pregnant women with a history of more than three intrauterine procedures had a 1.968 times higher risk of antepartum hemorrhage (95% CI 1.135 ~ 3,412, P = 0.016) compared to pregnant women without any intrauterine procedures. After stratified analysis of gestational age we found that with an increase in gestational age, the risk of antepartum hemorrhage decreases. When gestational age is 34-36.9 weeks, the risk of antepartum hemorrhage was found to be 0.280-fold compared to a gestational age of < = 33.9 weeks (95%CI 0.162–0.483, *P* = 0.000). At > = 37 weeks gestational age, the risk of antepartum hemorrhage was 0.064-fold compared to a gestational age of < 37 weeks (95%CI 0.035–0.117,*P* = 0.000). When the placenta edge was noted to be over os, the risk of antepartum bleeding was over 4.385-fold than the low-lying plcaenta cases (95%CI2.454–8.372，P = 0.000) (See Table 2). Moreover, when analyzed the 4 significant items in Table2 together, the regression equation for predicting prenatal hemorrhage is calcutaled with the four clinical characters the Four items including: gravidity(≥ 5), Uterine surgery procedures(≥ 3), GA termination(34–36.9weeks)or GA termination，≥37 weeks, Placenta edge over OS, with their regression coefficient β 1.712,1.785,-1.488,-2.886, and 1.164,respectively (See Table 3).

Table 2
Analysis of obstetric risk factors for antepartum bleeding in PAS

Group N (%)	No bleeding (282,%)	Repeated bleeding (211,%)	OR(95%CI)	*P*
Age(years) <35	199 (70.6)	150 (71.1)		
≥35	83(29.4)	61(28.9)	1.026(0.693–1.519)	0.900
Gravidity 1	58(20.6)	34(16.1)		
2	74(26.2)	40(19.0)	0.922(0.520–1.634)	0.781
3	59(20.9)	57(27.0)	1.648(0.943–2.880)	0.079
4	55(19.5)	37(17.5)	1.148(0.643–2.079)	0.650
≥ 5	36(12.8)	43(20.4)	2.038(1.104–3.760)	0.023*
Uterine surgery procedures 0	85(30.1)	58(27.5)		
1	95(33.7)	55(26.1)	0.848(0.530–1.359)	0.494
2	67(23.8)	51(24.2)	1.116(0.681–1.828)	0.664
≥3	35(12.4)	47(22.3)	1.968(1.135–3.412)	0.016*
Times of CS 0	121(42.9)	104 (49.3)		
1	103(36.5)	66 (31.3)	0.746(0.497–1.118)	0.155
≥2	58(20.6)	41 (19.4)	0.822(0.510–1.327)	0.423
No.of fetuses 1	276(97.9%)	206 (97.6%)		
≥2	6(2.1%)	5 (2.4%)	1.117(0.336–3.709)	0.857
GA termination(weeks) –33.9	22(7.8%)	75 (35.5%)		
34–36.9	107(37.9%)	103 (48.8%)	0.282(0.163–0.488)	0.000*

CS = cesarean section; GA = gestational age

Group N (%)	No bleeding (282,%)	Repeated bleeding (211,%)	OR(95%CI)	*P*
≥37	153(54.3%)	33 (15.6%)	0.063(0.035–0.116)	0.000*
Placental location Posterior	132(46.8%)	97(46%)		
Anterior	150(53.2%)	114(54%)	1.041(0.728–1.489)	0.825
Distance placenta extend over os < 2 cm	106(37.6%)	37 (17.5%)		
Over os	176(62.4%)	174 (82.5%)	4.385(2.454–8.372)	0.000*
Placenta increta No	186(66.0%)	152 (71.1%)		
yes	96(34.0%)	59 (27.9%)	0.752 (0.510–1.109)	0.151
CS = cesarean section; GA = gestational age				

Table 3
Analysis of obstetric risk factors for antepartum bleeding in PAS

Obstetric risk factors	B	OR(95%CI)	*P*
Gravidity ≥ 5	1.712	5.539(1.306–23.502)	0.020*
Uterine surgery procedures ≥ 3	1.785	5.959(1.586–22.398)	0.008*
GA termination(weeks)			
34–36.9	-1.488	0.226(0.125–0.407)	0.000*
≥37	-2.886	0.056(0.029–0.108)	0.000*
Placenta edge over os	1.164	3.204(1.601–6.414)	0.001*
GA = gestational age			

Analysis of the relationship between antepartum bleeding and maternal outcomes

From our patient series of 493 cases of placenta previa, there were 11 cases of normal delivery and 482 cases of cesarean section. In the non-bleeding group, there were 11 cases normal delivery and 271 cases

of cesarean Sect. 25 cases required emergency surgery, which were caused by unsatisfactory prenatal fetal heart rate monitoring and suspected fetal distress surgery.

There were a total of 211 patients in the repeated bleeding group, of which emergency surgery was performed in 87 cases and elective surgery in 124 cases. In the repeated bleeding group, the risk of emergency surgery was 7.213 times higher than elective surgery (95% CI 4.402–11.817, $P = 0.000$). However, there was no significant difference between the two groups in terms of blood product transfusion, postpartum hemorrhage and hysterectomy ($P > 0.05$, respectively)(See Table 4).

Table 4
Analysis of the relationship between antepartum bleeding and maternal outcomes

Group	**Non-bleeding**	**Repeated bleeding**	**OR(95%CI)**	***P***
N (%)	**(282,%)**	**(211,%)**		
Operation type	257(91.1)	124(58.8)		
Elective				
Emergency	25(8.9)	87(41.2)	7.213(4.402–11.817)	0.000*
PPH	144(51.1)	113(53.6)		
No				
Yes	138(48.9)	98(46.4)	0.905(0.633–1.294)	0.584
Blood Transfusion	144(51.1)	103(48.8)		
No				
Yes	138(48.9)	108(51.2)	1.094(0.766–1.563)	0.621
Hysterectomy	270(95.7)	197(93.4)		
No				
Yes	12(4.3)	14(6.6)	1.599(0.724–3.532)	0.246
PPH:Postpartum hemorrhage.				

Analysis of the relationship between antepartum bleeding and neonatal outcomes

There was no correlation found between fetal gender or fetal position with risk of antepartum hemorrhage. The patient group with repeated bleeding had an increased risk of delivering lower weight neonates than non-bleeding group, 2955.04 ± 587.63 g vs.2476.59 ± 617.77 g,$P < 0.05$. The 1 min and 5 min Apgar score in non-bleeding group were 9.37 ± 1.31 and 9.77 ± 0.76, which were significantly higher than that of the repeated bleeding group, $P < 0.05$. Similarly, the risk of asphyxia was 2.970 times higher in the repeated bleeding group compared to non-bleeding group (95% CI 1.676–5.265; $P < 0.05$). Finally, the risk of NICU admission was 2.542-fold higher in repeated bleeding group compared to non-bleeding group (95% CI 1.685–3.835, $P < 0.05$) (See Table 5).

Table 5
Analysis of the relationship between antepartum hemorrhage and neonatal outcomes

Group means ± SD, N(%)	No bleeding (282,%)	Repeated bleeding (211,%)	OR(95%CI)or *t*	*P*
Gender Male	140(49.6)	117(55.5)		
Female	142(50.4)	94(44.5)	0.792(0.554–1.133)	0.202
Birth weight, g	2955.04 ± 587.63	2476.59 ± 617.77	8.687	0.000*
Fetal Presentation Head	196(69.5)	141(66.8)		
Breech	57(20.2)	38(18.0)	0.927 (0.583–1.474)	0.748
Transverse	29(10.3)	32(15.2)	1.534 (0.888–2.651)	0.125
APGAR 1*	9.37 ± 1.31	8.57 ± 2.06	5.247	0.000*
APGAR 5*	9.77 ± 0.76	9.29 ± 1.40	4.834	0.000*
Asphyxia No	262(92.9)	172(81.5)		
Yes	20(7.1)	39(18.5)	2.970(1.676–5.265)	0.000*
NICU admission No	230(81.6)	134(63.5)		
Yes	52(18.4)	77(36.5)	2.542(1.685–3.835)	0.000*

Neonatal gender, birth weight, fetal presentation, fetal asphyxia, NICU admission data were analyzed using binary logistic regression statistical analysis. *: Apgar score data were analyzed using t test. $P < 0.05$ was considered statistically significant.

Discussion

Risk factors for PP include previous cesarean delivery, advanced age, multiparity, history pregnancy with placenta previa, multiple abortion, and smoking ,et al [8]. Antepartum hemorrhage is an important cause of perinatal mortality and maternal morbidity in pregnant women with PP in the world [9]. The doctors are always confused about the proper time for pregnany termination to reduce the bad effect of blood transfusion, hysterectomy, fetal blood loss, *etc*. So the patients were devided into two groups, non-bleeding and repeated bleeding group, to survey the risk factors of antepartum bleeding in placenta previa cases and study the pregnancy outcomes.

Antepartum repeated bleeding patients have more intrauterine procedures than non-bleeding ones. Binary logistic regression indicated that higher number of gravidity and intrauterine procedures increased the risk of antepartum hemorrhage. This study found that when gravidity ≥ 5 and the patient history of three uterine cavity procedures, the risk of antepartum bleeding was 2.038 and 1.968 times higher, respectively. Such a finding may be associated with damage caused by cesarean section, multiple number of pregnancies, abortion, delivery and other injuries to the endometrium or uterine muscle, causing inflammatory or atrophic lesions, affecting endometrial growth, and eventually leading to increased bleeding risk of PP[10].

Binary logistic regression analysis also indicated that pregnancy termination week, distance placenta extend over os and placenta accreta are closely related with the risk of antepartum bleeding. The results of this study suggest that non-bleeding patients with PP can continue a pregnancy to near term delivery (36.91weeks), however, the repeated bleeding group have a greater chance of preterm birth at an average of about 34.5 weeks. Interesting, the risk of antepartum bleeding was reduced with an increase in gestational age. The results showed that the risk of bleeding was highest at ≤ 33.9 weeks gestation. Specifically, a gestational age of 34–36.9 weeks and ≥ 37 weeks had 0.280, 0.064-fold likelihood of suffering antepartum bleeding compared with a gestational age of ≤ 33.9 weeks. Clinical observation also found that antepartum bleeding are more easily to occur during 28–34 weeks gestation in pregnant women with placenta previa. This change may be caused by faster growth of uterine in 28–34 weeks' gestational age, leading to placenta and uterine muscle wall capillary rupture. When the placenta edge was noted to be over os, the risk of antepartum bleeding was over 4.385-fold than the low-lying plcaenta cases. So the doctors should be aware of the prenatal bleeding especially when the placenta was over os and ≤ 34 weeks.This study also found that these is no relationship between placental accreta and antepartum bleeding. It has been proposed that placenta often yields very solid adherence with the uterine wall and it is therefore difficult to separate causing bleeding before placenta removal.

Furthermore, previous cesarean delivery did not increase the risk of antepartum bleeding in pregnancies complicated with placenta previa, but the risk of peripartum and postpartum hemorrhage was high due to an increased risk of placental implantation, particularly pernicious placenta previa of the anterior uterine wall. Studies have reported that anterior wall placenta previa increased the risk of perioperative bleeding, blood transfusion, and hysterectomy [11, 12]. However, our study found there was no relationship between the placenta location and antepartum bleeding.

The risk of emergency surgery was significantly increased in the repeated bleeding group, which was 7.213 times higher than that of the non-bleeding group. A large amount of vaginal bleeding often causes great anxiety for patients and doctors, and such vaginal bleeding often occurs at midnight. Obstetricians often worry about hemorrhagic shock caused by large amount of vaginal hemorrhage, so there is a high probability of emergency surgery. Luangruangrong's study had revealed the higher risks of preterm birth, emergency CS, blood transfusion, and low birth weight in antepartum hemorrhage group than the control group[13]. The study also found that antepartum hemorrhage does not increase the risk of postpartum hemorrhage and hysterectomy. There are several possible explanations for this. In the past two years, the

implementation of interventional-guided cesarean section, pre-operative ultrasound, MRI to assess placenta accreta, and elective surgery has reduced the risk of emergency surgery. Additionally, interventional-guided cesarean section has greatly, reduced the risk of hysterectomy and postpartum hemorrhage. In the postpartum follow-up process we did not find significant abnormalities. In this study, there were total of 26 cases of hysterectomy, 20 of which occurred more than 4 years ago. Additionally, our hospital has immediate prevention and treatment methods for postpartum hemorrhage during surgery, including: uterus contractions drugs, B-lynch procedures, uterine gauze and packing, uterine artery ligation and other effective measures.

In 2003, Ananth et al. reported the birth weight of 61,711 neonates born to mothers with placenta previa in the United States and found that neonates of gestational age 28–36 weeks were about 210 g lower than neonates with normal placental position [14].In this study, pregnant women with antepartum bleeding had an increased risk of delivering neonates with low birth weights. Neonatal asphyxia and NICU admission risk were also increased. Fetal birth weight was also lower in the repeated bleeding group. Possible explanations include: pregnant women in the repeated bleeding group suffered anemia that affected fetal growth and development; and pregnancies were terminated in the repeated bleeding group at an early period. Our results also demonstrate that the non-bleeding group could maintain pregnancy until gestational age > 36 weeks while only 40 pregnant women in the repeated bleeding group were maintained to > 36 weeks.

Some limitations of this study should be acknowledged. The main limitation is the present study was a single-center, retrospective study. We need to do a multi-center study in the future. In conclusion, the clinical significance of this study was firstly to strengthen prenatal education and prevent the occurrence of placenta previa and antepartum hemorrhage by reducing the number of abortions and the rate of cesarean section. Next, we demonstrated that active treatment of pregnancy complications could reduce the risk of antepartum hemorrhage, anemia correction. Active preparation for antepartum, peripartum and postpartum hemorrhage prevention and treatment remains an important part of medical care for mothers and neonates.

Conclusions

In conclusion,the significance of this study is to remind the obstetricians to be aware of the increased risk of antepartum bleeding especially for ≤ 34 weeks and placenta edge over cervical os PP patients, they have a higher risk of antepartum bleeding. These women have higher possibility of emergency c-section and need preterm newborn resuscitation.

Abbreviations

Placenta previa (PP)

the neonatal intensive care unit (NICU)

GA(gestational age)

CS(C-section)

Declarations

Ethics approval and consent to participate :The study was approved by the Ethical Board of the First Affiliated Hospital of Nanjing Medical University (Ethics Committee 2020-SR-256). Informed consent process was waived given in the retrospective study.
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Authors' contributions：SY Huang and Q Zuo : data collection , manuscript writing ZP Ge and HM Lu and X Zhou: data collection; TJ Wang, XT Tang: chart making; ZY Jiang: data analysis, provide financial support and examine and verify the manuscript. All authors have read and approved the manuscript.

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