Original Article

# Hemorrhagic Morbidity in Nulliparous Patients with Placenta Previa without Placenta Accrete Spectrum Disorders

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ABSTRACT

**Background:** Placental adhesion spectrum (PAS) is a disease in which the trophoblast invades the myometrium, and is a well-known high-risk condition associated with placental previa. **Aim:** The morbidity of nulliparous women with placenta previa without PAS disorders is unknown. **Patients and Methods:** The data from nulliparous women who underwent cesarean delivery were collected retrospectively. The women were dichotomized into malpresentation (MP) and placenta previa groups. The placenta previa group was categorized into previa (PS) and low-lying (LL) groups. When the placenta covers the internal cervical os, it is called placenta previa, when the placenta is near the cervical os, it is called the low-lying placenta. Their maternal hemorrhagic morbidity and neonatal outcomes were analyzed and adjusted using multivariate analysis based on univariate analysis. **Results:** A total of 1269 women were enrolled**:** 781 women in the MP group and 488 women in the PP-LL group. Regarding packed red blood cell transfusion, PP and LL had adjusted odds ratio (aOR) of 14.7 (95% confidence interval (CI): 6.6 – 32.5), and 11.3 (95% CI: 4.9 – 26) during admission, and 51.2 (95% CI: 22.1 – 122.7) and 10.3 (95% CI: 3.9 – 26.6) during operation, respectively. For intensive care unit admission, PS and LL had aOR of 15.9 (95% CI: 6.5 – 39.1) and 3.5 (95% CI: 1.1 – 10.9), respectively. No women had cesarean hysterectomy, major surgical complications, or maternal death. **Conclusion:** Despite placenta previa without PAS disorders, maternal hemorrhagic morbidity was significantly increased. Thus, our results highlight the need for resources for those women with evidence of placenta previa including a low-lying placenta, even if those women do not meet PAS disorder criteria. In addition, placenta previa without PAS disorder was not associated with critical maternal complications.

**Keywords:** *Low-lying placenta, neonatal outcome, placenta accrete spectrum, placenta previa, postpartum hemorrhage, pregnancy, prognosis*

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## Introduction

Placenta previa is categorized into previa and low-lying groups. When the placenta covers the internal cervical os, it is called placenta previa, when the placenta is near the cervical os, it is called the low-lying placenta. It requires cesarean delivery, and its incidence rate is about 0.4% to 1.3%,[1,2] and is gradually increasing.[3] Placenta previa is related to advanced maternal age, maternal smoking, the use of assisted reproductive technology, and the rate of cesarean delivery.[4,5] Placenta previa causes antenatal and postpartum hemorrhaging and increases maternal and neonatal morbidity. About 22% of women with placenta previa experience postpartum hemorrhages,[6] which can result in massive transfusion, disseminated intravascular coagulation, hysterectomy, and maternal death.

Placental adhesion spectrum (PAS) is a disease in which the trophoblast invades the myometrium. Multiple studies revealed that when placenta previa is accompanied by placenta accrete spectrum (PAS), the risk of hemorrhage increases.[7,8] For this reason, most studies on the outcomes of previa have mainly focused on its relationship with PAS. PAS is present in about 3% to 67% of women with placenta previa.[9] PAS risk depends on the number of prior cesarean deliveries. On the other hand, of the women with placenta previa, 17% were reported to be nulliparous, and 37% to 55% of women had no previous cesarean delivery.[9,10] Since relevant studies concentrated on the previa group with PAS, the risk of simple placenta previa without PAS is unknown due to few studies.

Thus, in this study, we identified the morbidity of nulliparous women with placenta previa without PAS.

## Patients and Methods

This was a retrospective study that employed the electronic medical record systems of seven tertiary care centers under the College of Medicine, the Catholic University of Korea, from January 2009 to March 2021. This study was approved to use registry data and documentation of informed consent was waived by our Institutional Review Board (XC20WIDI0103/2020-2158-0020). The study subjects were nulliparous women who had a medical record of cesarean delivery. Patients were dichotomized into malpresentation (MP) and placenta previa (PP-LL) groups. The PP-LL group was categorized into previa (PP) and low-lying (LL) groups. To divide the PP and the LL groups from the PP-LL group, women whose placenta covered the internal cervical os were categorized into the PP group and when the placental edge was <20 mm from, but not over, the internal os, women were categorized into the LL group. Exempting criteria included multiple gestations, <20 weeks of gestational age delivery, <500 grams of birth weight, maternal hematologic disease, maternal autoimmune disease, prior myomectomy history, history of uterine surgery, preeclampsia, eclampsia, gestational hypertension, fetal major congenital anomaly, intrauterine fetal death, myomectomy in a cesarean operation, PAS diagnosis in the hospital record, and abruptio placenta. In addition, patients with previously diagnosed hypertension without evidence of preeclampsia were included in this study. Regarding fetal growth restriction, cases with a definite diagnosis after delivery were included.

Statistical analyses were conducted using R software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). The study data are presented as means ± standard deviations (SD) or absolute values (proportions), as appropriate. All variables were analyzed using parametric or nonparametric tests as appropriate, followed by the Kolmogorov–Smirnov test to determine the normal distribution of each value. Continuous variables were analyzed using analysis of variance (ANOVA) or the Kruskal–Wallis test, and categorical variables were analyzed using the Chi-squared or Fisher's exact test to compare the three groups with a *post hoc* Bonferroni correction. Multivariate binary logistic regression was performed to calculate odds ratios (OR) for variables significant in univariate analyses. All *P* values were two-sided, and a *P* value <0.05 was considered statistically significant.

## Results

### General characteristics

Of the 33,720 deliveries, nulliparous women numbered were 17,816. A total of 1,269 women met the inclusion criteria and were enrolled in this study. There were 781 women in the MP group and 488 women in the PP-LL group, among whom the PP group numbered 304 and the LL group numbered 184 [Figure 1]. The general characteristics of the study population are presented in Table 1. The PP-LL group showed significantly higher maternal ages (31.7 ± 4.4 vs 33.0 ± 4.4 years, $P < 0.001$), history of abortion (25.6% vs 34.2%, $P = 0.001$), and gestational age at delivery (36.9 ± 3.1 *vs* 37.2 ± 2.2 weeks, $P = 0.040$), and significantly lower values for diabetes mellitus (9.7% vs 6.4%, $P = 0.030$) and hemoglobin (Hb, 12.1 ± 1.2 vs 11.7 ± 1.3, $P < 0.001$) in the third trimester and hemoglobin (12.0 ± 1.2 vs 11.9 ± 1.2, $P = 0.028$) at admission. Regarding neonatal outcomes, the MP group showed significantly lower birth weights (2.7 ± 0.6 kg

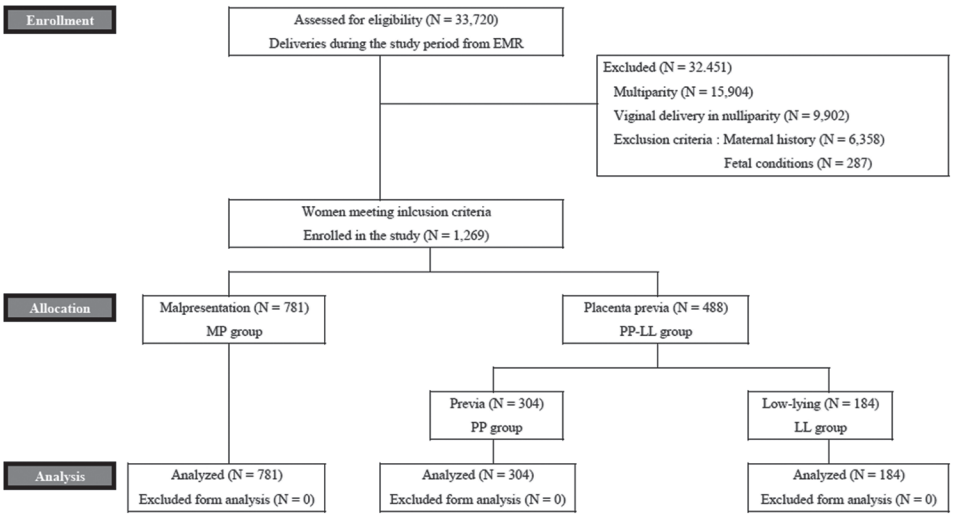


**Figure 1:** Flowchart of this study

**Table 1: General characteristics of the study population**

| | MP (*n*=781) | PP-LL (*n*=488) | *P* |
|---|---|---|---|
| Maternal factors | | | |
| Maternal age (years) | 31.7±4.4 | 33.0±4.4 | <0.001 |
| Abortion history, *n* (%) | 200(25.6) | 167(34.2) | 0.001 |
| Tabacco use, *n* (%) | 66(8.5) | 43(8.8) | 0.340 |
| Alcohol use, *n* (%) | 54(6.9) | 28(5.7) | 0.400 |
| BMI | | | |
| Pre-conception | 21.0±3.4 | 21.2±3.2 | 0.310 |
| Delivery | 25.8±3.8 | 26.2±3.6 | 0.920 |
| Hypertension, *n* (%) | 32(4.1) | 17(3.5) | 0.340 |
| DM, *n* (%) | 76(9.7) | 31(6.4) | 0.030 |
| Hb (g/dL) | | | |
| 3rd trimester | 12.1±1.2 | 11.7±1.3 | <0.001 |
| Admission | 12.0±1.2 | 11.9±1.2 | 0.028 |
| Fetal factors | | | |
| Gestational age (wks) | 36.9±3.1 | 37.2±2.2 | 0.040 |
| Birth weight (Kg) | 2.7±0.6 | 2.8±0.5 | <0.001 |
| Gender, male, *n* (%) | 369(47.2) | 259(53.1) | 0.040 |
| Growth restriction, *n* (%) | 70(9.0) | 21(4.3) | 0.002 |

Values are presented as mean±standard deviation and numbers (proportions) as appropriate. BMI, body mass index; DM, diabetes mellitus; Hb, hemoglobin

vs 2.8 ± 0.5 kg, $P < 0.001$) and more fetal growth restriction (9.0% vs 4.3%, $P = 0.002$).

## Maternal and neonatal outcomes

Estimated blood loss and transfused pRBC during surgery, admission for outcomes related to hemorrhage, ICU admission, and intrauterine balloon tamponade treatment for the outcomes related to surgical complications were statistically and significantly different among the three groups [Table 2]. The PP group had the highest occurrence, whereas the MP group had the lowest. Women admitted to the ICU after surgery stayed for an average of 1.2 ± 1.3 days, which was not different among the three groups. The PP and LL groups were administered pRBC more often than the MP, and the PP group was administered pRBC more than the LL during both surgery and admission. Uterine artery embolization was performed significantly more frequently in the PP group (1.5%) than the other groups (the LL 0.5% and the MP 0.0%; $P = 0.004$). Peripartum fever occurred significantly more frequently in the PP group (5.6%) than in the MP group (2.0%, $P = 0.017$). However, there was no statistical difference between the LL and PP groups for peripartum fever occurrence. Regarding Hb levels on the first day after surgery, the LL and PP groups had lower levels than the MT group ($P < 0.001$). The length of hospital stay and cesarean deliveries taking 2 h and longer were not different among the three groups ($P = 0.170$ and $P = 0.550$, respectively). There were no cesarean hysterectomies or maternal deaths for critical maternal hemorrhagic morbidity. In addition, there were no major surgical complications, such as bowel injury, bladder injury, or ureter injury in any of the three groups. Regarding neonatal outcomes, the MP group had a greater incidence of below 5 points on the 1-min and 5-min Apgar tests than the LL and the PP groups ($P = 0.030$ and $P = 0.020$, respectively). The incidences of respiratory distress syndrome and neonatal jaundice were not different among the three groups ($P = 0.140$ and $P = 0.970$, respectively).

## Adjusted factors for maternal hemorrhagic morbidity and ICU admission

Maternal outcomes related to hemorrhage were evaluated in multivariate binary logistic regression adjusted by maternal age, history of abortion, Hb levels in the third trimester, and admission. Adjusted odd ratios (aORs) were calculated and compared to those of the MP group [Table 3]. Regarding pRBC transfusion

**Table 2: Maternal and fetal outcomes in nulliparous women without placenta accrete spectrum disorders**

| | MP (*n*=781) | PP-LL (*n*=488) | | *P*[a] |
|---|---|---|---|---|
| | | LL (*n*=184) | PP (*n*=304) | |
| Maternal factors | | | | |
| Accreta, *n* (%) | 5(0.6) | 15(8.2)* | 48(15.8)*† | <0.001 |
| Hospital stay (d) | 6.2±6.0 | 6.5±5.9 | 7.0±6.3 | 0.170 |
| Operation >2 h, *n* (%) | 2(0.3) | 1(0.5) | 2(0.7) | 0.550 |
| Peripartum fever, *n* (%) | 16(2.0) | 8(4.3) | 17(5.6)* | 0.017 |
| ICU admission, *n* (%) | 7(0.9) | 10(5.4)* | 44(14.5)*† | <0.001 |
| Hemorrhagic complications related | | | | |
| Hb, 3rd trimester (g/dL) | 12.1±1.2 | 11.8±1.4 | 11.6±1.2* | <0.001 |
| Hb, postoperation 1 d (g/dL) | 11.2±1.3 | 10.7±1.4* | 10.6±1.4* | <0.001 |
| Estimated blood loss (ml) | 430±227.7 | 539±333.0* | 745.4±536.9*† | <0.001 |
| Transfusion, pRBC, operation, *n* (%) | 7(0.9) | 22(12.0)* | 105(34.5)*† | <0.001 |
| Transfusion, pRBC, admission, *n* (%) | 15(1.9) | 34(18.5)* | 130(42.8)*† | <0.001 |
| Transfusion, pRBC >4 units, operation, *n* (%) | 0(0) | 0(0) | 8(2.6)*† | <0.001 |
| Transfusion, pRBC >4 units, admission, *n* (%) | 1(0.1) | 7(3.8)* | 11(3.6)* | <0.001 |
| Operation complications related | | | | |
| Cesarean hysterectomy, *n* (%) | 0(0) | 0(0) | 0(0) | N/A |
| Uterine artery embolization, *n* (%) | 0(0) | 1(0.5) | 5(1.6)* | 0.004 |
| Intrauterine balloon tamponade, *n* (%) | 3(0.4) | 14(7.6)* | 51(16.8)*† | <0.001 |
| Fetal factors | | | | |
| Apgar score | | | | |
| <5 pts in 1 min, *n* (%) | 84(10.8) | 13(7.0)* | 25(8.2) | 0.030 |
| <5 pts in 5 min, *n* (%) | 25(3.2) | 2(1.1) | 2(0.7)* | 0.020 |
| pH<7.2, cord blood, *n* (%) | 10(1.3) | 6(3.3) | 7(2.3) | 0.230 |
| RDS, *n* (%) | 90(11.5) | 17(9.2) | 38(12.5) | 0.140 |
| Jaundice, *n* (%) | 16(2) | 4 (2.2) | 7 (2.3) | 0.970 |

ICU, intensive care unit; RDS, respiratory distress syndrome; Hb, hemoglobin; d, day; pRBC, packed red blood cell. [a]*P* values have resulted from analysis of variance (ANOVA) and Chi-squared test or Fisher's exact test as appropriate. **P*<0.05 versus MP and †*P*<0.05 versus LL. with *post hoc* Bonferroni correction

**Table 3: Multivariate binary logistic regression analysis for adjusted odds ratio to predict maternal hemorrhage-related complications and ICU admission after surgery**

| | PP | | | LL | | |
|---|---|---|---|---|---|---|
| | aOR | 95% CI | *P* | aOR | 95% CI | *P* |
| Transfusion, pRBC, operation | 52.2 | 22.1–122.7 | <0.001 | 10.3 | 3.9–26.6 | <0.001 |
| Transfusion, pRBC, admission | 14.7 | 6.6–32.5 | <0.001 | 11.3 | 4.9–26.0 | <0.001 |
| Intrauterine balloon tamponade | 56.9 | 13.4–240.3 | <0.001 | 18.0 | 3.9–83.2 | <0.001 |
| ICU admission | 15.9 | 6.5–39.1 | <0.001 | 3.5 | 1.1–10.9 | 0.008 |

aOR, adjusted odds ratio; CI, confidence interval; Hb, hemoglobin; ICU, intensive care unit; pRBC, packed red blood cell. Adjusted by maternal age, accrete, history of abortion, Hb at 3rd trimester, and Hb at admission

during operation, the PP group had an aOR of 52.2 (95% CI: 22.1 – 122.7) and the LL group had an aOR of 10.3 (95% CI: 3.9 – 26.6). Regarding pRBC transfusions during admission, the PP group had an aOR of 14.7 (95% CI: 6.6 – 32.5) and the LL group had an aOR of 11.3 (95% CI: 4.9 – 26). The PP group had a 5.1- and 1.3-fold higher risk for pRBC transfusion than the LL group during operation and admission, respectively. Regarding intrauterine balloon tamponade, the PP and LL groups had aORs of 56.9 (95% CI: 13.4 – 240.3) and 18.0 (95% CI: 3.9 – 83.2), respectively, and the PP group had a 3.2-fold higher risk than the LL group. Regarding ICU admission, the PP group had an aOR of 15.9 (95% CI: 6.5 – 39.1) and the LL group had an aOR of 3.5 (95% CI: 1.1 – 10.9). The PP group had a 4.5-fold higher risk for ICU admission than the LL group. Consequently, both the PP and the LL groups showed significantly higher aORs than the MP group, and the PP group had a higher risk than the LL group for outcomes related to maternal hemorrhage and ICU admission.

## Discussion

This study was conducted in women with placenta previa who did not detect PAS disorders. Most studies to

date have concentrated on women with placenta previa detecting PAS disorders. In a previously published study, in women with primary cesarean deliveries and no PAS, hemorrhagic morbidity was increased by previa.[11] pRBC transfusion (relative risk (RR) of 3.8 (95% CI: 2.51 – 5.74) and hysterectomy (RR of 5.14 (95% CI: 1.53 – 17.28)) were more common in previa cases, but ICU admission was not different. The authors also reported no maternal death.[11] In our study, we calculated aORs from multivariate binary logistic regression to evaluate the risk of women with previa detecting no PAS after adjusting for factors that could be affected by previa or low-lying placenta. The PP group had a 14.7-fold (95% CI: 6.6 – 32.5) greater risk than the MP group and a 1.3-fold greater risk than the LL group. Regarding ICU admission, the PP group had a 15.9-fold (95% CI: 6.5 – 39.1) greater risk than the MP group and a 4.5-fold greater risk than the LL group. The LL group also showed a 3.5-fold greater risk than the MP group. Women with previa and low-lying placenta without PAS disorders were associated with maternal hemorrhagic morbidity. These results consistently support the results of a previous study,[11] but the risks calculated in our study were higher. We suggest the reason lies in the control group because our control group was limited to primary cesarean deliveries with MP, while the previous study included women with a variety of conditions. In this respect, the criteria for the MP group as a control group could have helped obtain more accurate results regarding the risk of women with previa and low-lying placenta.

With respect to critical maternal complications such as severe hemorrhagic events and major surgical complications, studies have reported the following incidences of critical maternal complications in women with PAS disorders: 5% to 40% massive blood transfusion, 1% to 7 maternal death, 2% to 4% bowel injury, 5% to 40% bladder injury, and 0% to 18% ureter injury.[12] In our results, women with previa detecting no PAS disorders experienced no cesarean hysterectomies, maternal death, or major surgical complications, such as bowel injury, bladder injury, and ureter injury. Thus, these results indicate that nulliparous women with previa without PAS disorders have a low probability of severe hemorrhagic or major surgical complications.

A few studies analyzed whether previa was related to adverse neonatal outcomes such as fetal growth restriction.[13,14] In our results, the MP group as the control group showed fewer weeks of gestational age at delivery and lower weight than the PP-LL group. In addition, the MP group had more fetal growth restriction. The hospitals participating in this study were tertiary care centers. Even if the women in the PP-LL group had no other accompanying diseases, their risk level could have resulted in a transfer to tertiary care centers. In the case of MP, more transfers to tertiary care centers occurred when accompanied by other diseases. Therefore, the results for neonatal outcomes may be biased for these reasons.

The strength of our study is that although it is a big dataset study, it has the advantage of checking detailed medical records such as surgical records and provides realistic estimates by analyzing relatively recent data (January 2009 to March 2021). This study also has some limitations. First, our study was retrospective and there were missing data. Second, the results of neonatal outcomes would be influenced by Berkson's bias due to our institute being a tertiary care center that received referred patients with various medical conditions from other nearby hospitals. Third, we compared pregnant women who underwent cesarean delivery with MP rather than with cesarean delivery without any other conditions, due to cesarean delivery being the secondary alternative to vaginal delivery. Thus, we decided to include women with MP for the control group with the expectation of maternal complications after surgery. However, we cannot exclude the possibility of maternal complications by MP.

Women with placenta previa without PAS disorders had an increased risk of maternal hemorrhagic morbidity. Our results highlight the need for resources such as blood transfusion, expert surgeons, expert intervention radiologists, and ICU admission for women with evidence of placenta previa including a low-lying placenta, even if those women do not meet the definition for PAS disorders. Furthermore, placenta previa without PAS disorder was not associated with critical maternal or major surgical complications such as cesarean hysterectomy or maternal death. The results of this study could be useful as objective data for counseling patients with previa and their families as well as for offering preoperative preparation to physicians.

## Ethical approval

This study was approved by our Institutional Review Board (XC20WIDI0103/2020-2158-0020).

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## Conflicts of interest

There are no conflicts of interest.

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