

Pregnancy Outcomes of Placenta Previa with or without Antepartum Hemorrhage

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Objective: To compare pregnancy outcomes between antepartum hemorrhage (APH) and no APH in women with a diagnosis of placenta previa (PP).

Material and Method: A retrospective cohort study was conducted in 60 gravidas diagnosed with PP. The study group (n = 30) consisted of women with APH while the control group (n = 30) comprised those without. The pregnancy outcomes were compared between the two groups. They included preterm birth, emergency cesarean section (CS), peripartum hysterectomy, requirement for blood transfusion, low birth weight (LBW), and birth asphyxia. Uni- and multivariable analyses were used for statistical analysis.

Results: Data of all 60 women were obtained. In univariable analysis, the study group had significantly higher risks of early, late, and overall preterm birth, emergency CS, blood transfusion, and LBW than the control group; odds ratio (95% confidence intervals) = 6.1 (1.5-25.0), 3.9 (1.1-21.2), 4.3 (1.6-11.2), 5.2 (2.3-11.7), 2.6 (1.4-4.6) and 3.7 (1.1-11.8) respectively. When multivariable analysis adjusted for potential confounders, these risks remained in the study group. The highest risk was an emergency CS with an adjusted odds ratio of 30.5 (4.1-227.3).

Conclusion: Women with PP complicated by APH had significantly higher risks of adverse pregnancy outcomes than women without APH.

Keywords: Antepartum hemorrhage, Placenta previa, Pregnancy outcomes

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Placenta previa (PP), a condition in which the placenta lies over or close to the internal os, is found in 0.3 to 0.9% of all pregnancies worldwide⁽¹⁻⁴⁾. This condition poses a number of risks to both the mother and her infant, such as obstetric hemorrhage, fetal growth restriction, preterm birth, emergency cesarean section (CS), peripartum hysterectomy, or even death⁽⁴⁻⁸⁾. The exact cause of PP is currently unknown. However, there is evidence that it associates with several factors including advanced maternal age, high parity, multiple gestation, previous CS or abortion, smoking, and Asian ethnicity⁽⁸⁻¹⁰⁾.

Focusing on the antenatal period, vaginal bleeding is a very common complication of PP, with reported incidence of 40.7 to 78.3%^(4,10,11). From the practical viewpoint, knowing the course of disease or prognosis of PP with antepartum hemorrhage (APH) would be beneficial because appropriate management,

for example, antenatal corticosteroids use, maternal-fetal transfer to a resource-adequate setting, or timely delivery would be applied to improve the pregnancy outcomes. Currently, the findings from previous studies remained conflicting. Some authors found a significant increase in maternal and neonatal morbidities in gravidas with PP who bled compared to those without bleeding⁽⁴⁾. On the contrary, others failed to show a relationship between APH and adverse perinatal outcomes⁽¹¹⁾.

Taking into consideration that the prevalence of PP in Asian gravidas is relatively high^(9,12), this would plausibly cause an increase number of women being at risk of PP-related complications especially vaginal bleeding before delivery. At present, data on the impact of PP complicated by APH on the risk of maternal and neonatal morbidities are scarce. Among these, only one study was conducted in an Asian population⁽⁴⁾. Thus, more research on this topic is needed. The aim of this study was to investigate whether APH in association with PP would increase risks of adverse pregnancy outcomes in Thai or other Southeast Asian populations.

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Material and Method

A retrospective cohort study was conducted after approval of the Vajira Institutional Review Board (Registered Number 019/55). Eligibility criteria were singleton pregnant women with a diagnosis of PP, who presented for antenatal care and delivered at Vajira hospital between January 1, 2008 and December 31, 2011. The study subjects were those with APH while the control subjects were those without. Each group of women was selected in sequence from records of the operating room until the sample size was attained.

The control subjects were selected in a row until the sample size was attained. Then, the study subjects were selected by using computer generated numbers.

The authors considered preterm birth to be the primary outcome measure since it brings various health and developmental problems to the neonates as well as considerable emotional and economic impacts to families. Based on the findings of 54.5% and 11.1% preterm birth rates in women with and without APH, respectively from a pilot investigation of 20 women with a diagnosis of PP, the sample size was then calculated using 5% type I error and 20% type II error. The authors added 25% to the number calculated in the event that any case was excluded. This resulted in a total of 30 study subjects and 30 controls needed. Exclusion criteria were women who had underlying disease that may affect pregnancy outcomes (e.g., chronic hypertension, renal disease, or overt diabetes mellitus), major fetal malformation, stillbirth, and incomplete clinical data.

Data of the women were collected from the hospital's computer file and obstetric charts. These included maternal age, parity, body mass index (BMI), history of preterm birth, prior abortion, CS or other uterine operations that involve in part of myometrium and/or endometrium such as myomectomy, smoking status, baseline hematocrit value, gestational age (GA) at diagnosis of PP, type of PP (major or minor types), presence or absence of APH, GA at delivery, operative blood loss, infant birth weight, and maternal and neonatal morbidities. The diagnosis of PP was established on screening ultrasound findings (either transabdominal or transvaginal examination as appropriate) that placenta tissue/edge covered, touched or lay close to the internal os⁽¹³⁾, which was confirmed by repeated ultrasound within a week prior to delivery. Major PP was diagnosed when the placenta partly or totally covered the cervix while minor PP was considered when the placental edge touched (but did

not cover) or implanted close to the os⁽¹⁴⁾. APH was defined as at least one episode of vaginal bleeding during the antenatal period. The primary outcome of interest was preterm birth and the secondary outcome measures were emergency CS, peripartum hysterectomy, requirement for blood transfusion, low birth weight (LBW) and birth asphyxia. Preterm birth was a delivery prior to the completion of 37 weeks of gestation. Infants born between 34^{0/7} and 36^{6/7} weeks were considered late preterm births and those born before 34 weeks of gestation were considered early preterm deliveries⁽¹⁵⁾. LBW was defined as neonatal birth weight less than 2,500 g. Birth asphyxia referred to 1-minute Apgar score below 7⁽¹⁶⁾.

Statistical analysis was performed with the SPSS software package version 11.5 (SPSS Inc., Chicago, IL, USA). Continuous variables were compared by the Student t-test while categorical variables were compared by χ^2 test or Fisher's exact test as appropriate. The odds ratio (ORs) with 95% confidence intervals (95% CIs) of the primary and secondary outcomes in the APH group were analyzed by multivariable analysis adjusted for potential confounders. P-value <0.05 was considered statistically significant.

Results

There were 10,360 deliveries during the study period: 92% were Thai and 8% were other Southeast Asians. Out of these 10,360 gravidas, 86 (0.8%) were diagnosed as having PP (83 = live born singleton 2 = twin pregnancy and 1 = DFIU). Most of the affected women (54/86 or 62.8%) had APH. Data of all 60 women (30 study and 30 control subjects) who were recruited into the present study were totally obtained. Their mean GA when PP was surely diagnosed by late second- or third-trimester sonographic examinations was 30.4±4.1 weeks and most of them (60%) had major PP. All of these women underwent a CS.

The demographic and clinical characteristics of the study and control groups were compared. Both groups had similar characteristics of mean age, BMI, antenatal hematocrit level, rates of primipara, smoking and major PP. The proportions of women with a history of preterm birth, abortion, prior CS, or uterine operation between the two groups were also comparable. Details of the characteristic features of all women, women with and without APH are presented in Table 1.

Table 2 compared maternal outcomes between the study and control groups. The authors found that

women with APH had significantly lower mean GA at delivery but higher rates of emergency CS, postpartum and all blood transfusion than those without APH. On the other hand, mean operative blood loss and rate of peripartum hysterectomy were not significantly different between both groups.

With regard to the neonatal outcomes (Table 3), the authors observed a significantly increased rate of early (data not shown) and overall preterm birth but lower mean birth weight in the APH group as compared to the non-APH group. Likewise, the infants

of women with APH had higher rate of birth asphyxia than the infants of those with no bleeding. However, this increased rate did not reach statistical significance.

The risks of adverse pregnancy outcomes of the study subjects were determined using the control subjects as the reference group (Table 4). In univariable analysis, the APH group had significantly higher risks of early, late, and overall preterm birth, emergency CS, postpartum and all blood transfusion, and LBW than the non-APH group. When multivariable analysis was adjusted for some potential confounders including age,

Table 1. Demographic and clinical characteristics of the study population (n = 60)

Characteristic	Overall (n = 60)	APH (n = 30)	No APH (n = 30)	p-value
Age (years)	32.7 (4.8)	32.4 (5.8)	33.0 (5.6)	0.59*
Primipara	34.0 (56.7)	21.0 (70.0)	13.0 (43.3)	0.28**
BMI (kg/m ²)	22.9 (4.9)	23.7 (4.9)	22.1 (4.8)	0.22*
History of preterm birth	2.0 (3.3)	2.0 (6.7)	0 (0)	0.16***
History of abortion	19.0 (31.7)	7.0 (23.3)	12.0 (40.0)	0.17**
Prior CS	14.0 (23.3)	9.0 (30.0)	5.0 (16.7)	0.22**
Prior uterine operation	15.0 (25.0)	5.0 (16.7)	10.0 (33.3)	0.14**
Current smoking	2.0 (3.3)	0 (0)	2.0 (6.7)	0.15***
Antenatal hematocrit (%)	33.9 (2.8)	33.5 (2.8)	34.4 (2.7)	0.22*
Major PP	36.0 (60.0)	19.0 (63.3)	17.0 (56.7)	0.60**

Data are mean (SD) or n (%)

APH = antepartum hemorrhage; BMI = body mass index; CS = cesarean section; GA = gestational age; n = number; PP = placenta previa; SD = standard deviation

* Student t-test, ** χ^2 test, *** Fisher's exact test

Table 2. Comparison of maternal outcomes between the study and control groups

Outcome	Overall (n = 60)	APH (n = 30)	No APH (n = 30)	p-value
GA at delivery (weeks)	36.5 (2.4)	35.4 (2.7)	37.6 (1.3)	<0.001*
Emergency CS	31 (51.6)	26 (86.7)	5 (16.7)	<0.001**
Indication for emergency CS [#]				
Vaginal bleeding	24/31 (77.4)	24/26 (92.3)	0/5 (0)	<0.001***
In labor and/or PROM	17/31 (54.8)	13/26 (50.0)	4/5 (80.0)	0.22***
Preeclampsia	1/31 (3.2)	0/26 (0)	1/5 (20)	0.02***
Operative blood loss (mL)	1,000 (600-1,575)	1,100 (800-2,025)	904 (500-1,425)	0.05****
Peripartum hysterectomy	4 (6.7)	3 (10.0)	1 (3.3)	0.30***
Blood transfusion				
Antepartum	2 (3.3)	2 (6.7)	0 (0)	0.15***
Postpartum	31 (51.7)	22 (73.3)	9 (30.0)	0.001**
All	32 (53.3)	23 (76.7)	9 (30.0)	<0.001**

Data are mean (SD) or n (%), except data of operative blood loss are median (interquartile range)

APH = antepartum hemorrhage; CS = cesarean section; GA = gestational age; n = number; NA = no appropriate; PROM = premature rupture of the membranes; SD = standard deviation

[#] Eleven women had both vaginal bleeding and labor pain

* Student t-test, ** χ^2 test, *** Fisher's exact test, **** Mann-Whitney test

Table 3. Comparison of neonatal outcomes between the study and control groups

Outcome	Overall (n = 60)	APH (n = 30)	No APH (n = 30)	p-value
Preterm birth	21 (35.0)	17 (56.7)	4 (13.3)	<0.001**
Birth weight (g)	2,967.9 (550.6)	2,728.2 (654.6)	3,007.5 (384.6)	0.04***
LBW	14 (23.3)	11 (36.7)	3 (10.0)	0.15**
Birth asphyxia	14 (23.3)	10 (33.0)	4 (13.3)	0.06**

Data are mean (SD) or n (%)

APH = antepartum hemorrhage; LBW = low birth weight; n = number; NICU = neonatal intensive care unit; SD = standard deviation

* χ^2 test, ** Fisher's exact test, *** Student t-test

Table 4. Univariable and multivariable analyses to determine the risk of adverse outcomes in the study group

Adverse outcome	APH (n = 30)	No APH (n = 30)	Crude OR (95% CI)	Adjusted OR# (95% CI)
Primary outcome				
Preterm birth (vs. term birth)*				
Early	10 (33.3)	2 (6.7)	6.1 (1.5-25.0)	6.8 (1.3-30.6)
Late	7 (23.3)	2 (6.7)	3.9 (1.1-21.2)	4.7 (0.8-40.5)
All	17 (56.7)	4 (13.3)	4.3 (1.6-11.2)	5.6 (1.1-27.8)
Secondary outcome				
Emergency CS (vs. elective CS)*	26 (86.7)	5 (16.7)	5.2 (2.3-11.7)	30.5 (4.1-227.3)
Peripartum hysterectomy (vs. no hysterectomy)*	3 (10.0)	1 (3.3)	3.0 (0.3-27.2)	2.4 (0.1-75.5)
Blood transfusion (vs. no blood transfusion)*				
Postpartum	22 (73.3)	9 (30.0)	2.4 (1.4-4.4)	5.4 (1.1-30.7)
All	23 (76.7)	9 (30.0)	2.6 (1.4-4.6)	6.6 (1.2-36.8)
LBW (vs. no LBW)*	11 (36.7)	3 (10.0)	3.7 (1.1-11.8)	3.4 (1.1-16.7)
Birth asphyxia (vs. no asphyxia)*	10 (33.0)	4 (13.3)	2.5 (0.9-7.1)	2.7 (0.7-10.8)

Adjusted for age, parity, BMI, smoking status, previous preterm delivery, and the other variable in the Table

* Reference group

APH = antepartum hemorrhage; BMI = body mass index; CI = confidence interval; CS = cesarean section; LBW = low birth weight; n = number; OR = odds ratio; SD = standard deviation

parity, BMI, smoking status, previous preterm delivery, and the other variables in Table 4 was performed, these risks, except for late preterm birth, remained in the APH group. The highest risk was an emergency CS, with an adjusted odds ratio of 30.5 (95% CI, 4.1-227.3). No maternal or neonatal mortality was observed in the study population.

Discussion

The incidence of PP in the present study was 0.8%, which was in the upper end of the 0.3-0.9% range reported in the literatures^(1-4,9). The observed high incidence of PP among Thai or other Southeast Asians supported the findings of Kim et al⁽⁹⁾ and Taylor et al⁽¹²⁾ who reported the highest rate of PP in Asian ethnicity compared with other ethnic groups. Although the underlying mechanism for the association of ethnicity with PP development is still poorly defined,

data from Kim et al⁽⁹⁾, Taylor et al⁽¹²⁾ and the present study suggest that obstetricians must have awareness or high index of suspicion for PP in Asian gravidas unless a detailed ultrasound scan is done to rule out an abnormal site of placenta.

It is well accepted that PP is a risk factor for several maternal and neonatal complications; one of which is APH^(1-4,9). The finding of a 62.8% rate of APH in the current study was similar to the study of Lam et al⁽⁴⁾ that showed a 65.4% APH rate in a cohort of Hong Kong Chinese women who were diagnosed with PP. Aside from PP itself, the effects of APH on pregnancy outcomes have been investigated, but the results from previous studies were inconsistent^(4,11). Paying attention to the primary outcome of the present study, the authors observed a 5.6-fold risk for overall preterm birth and a 6.8-fold risk specifically for early preterm birth in gravidas with PP and APH compared

with those without bleeding. Similarly, Lam et al⁽⁴⁾ identified RRs of 17.1 and 12.6 for overall and early preterm birth, respectively in women with PP who had APH. Although the degrees of RRs between Lam et al⁽⁴⁾ and the present study were quite different, the results from both studies indicated that risk of preterm birth, especially delivery at or before 34 weeks, was significantly higher in the APH group. Given that preterm birth is the leading cause of neonatal death, knowing the characteristics associated with preterm delivery in women with PP and APH will provide insight into the efficient evaluation and surveillance. One recent study found that second trimester vaginal bleeding (adjusted odds ratio [aOR] = 4.2; 95% CI, 1.3-13.7) and the presence of uterine contractions on admission (aOR = 4.0; 95% CI, 1.6-10.2) were independent risk factors for delivery at or before 36 weeks in PP gravidas with APH⁽¹⁷⁾. Unfortunately, the authors failed to confirm such findings upon further analysis. This might result from inadequate power due to a small number of the women. Nevertheless, the authors found that bleeding before 32 gestational weeks was an independent risk factor for early preterm birth (aOR = 3.1; 95% CI, 1.4-19.8; $p < 0.01$). Future research with larger sample size is needed to verify the result.

Other than preterm birth, the authors observed a significantly higher rate of LBW in the APH women than the non-APH gravidas. This increased risk was undoubtedly due to an increased rate of preterm birth. Unlike the study of Lam et al⁽⁴⁾, the authors were unable to show an association of APH with birth asphyxia. As the sample size in the present study was calculated based on the primary outcome measure, it might yield insufficient power to assess the secondary outcome.

Concerning maternal outcomes, the authors found that women with APH were at significantly increased risk of emergency CS compared with non-APH gravidas. This finding was in agreement with previous studies^(4,11), and could be explained by uncontrollable vaginal bleeding or uterine contractions⁽⁷⁾. In the current study, the rates of antepartum blood transfusion between the two groups were not different. The main reason is probably because the majority of the APH women did not have massive antenatal bleeding and their hematocrit levels declined slightly so blood transfusion was unnecessary. In contrast, the authors observed a significantly increased risk of postpartum blood transfusion in the APH group. Since blood transfusion in the postpartum period is related to both intrapartum and postpartum hemorrhage in consequence of several factors,

such as uterine atony, placenta adherens, peripartum hysterectomy, operative technique and skill, these variables are therefore the possible factors contributing to the result. Similar to the study of Lam et al⁽⁴⁾, the authors did not find an impact of APH on the risk of peripartum hysterectomy. In fact, there are many potential confounders that may be associated with obstetric hysterectomy, e.g., uterine atony, placenta adherens, ruptured uterus, etc.^(18,19). In addition, a small sample size in the present study might not allow adequate power to determine this pregnancy outcome.

The strength of the present study was that all of the women underwent repeated ultrasound within a week before delivery, therefore, information on the diagnosis of PP was considered accurate. At the same time, some limitations existed in the current study. As it was a retrospective design, data on other potential risk factors for the outcomes being studied were not obtainable, e.g., bleeding pattern, cervical length, ultrasound scan demonstrating vascular lacunae within the placenta, etc. However, the authors adjusted for known potential confounders by using multivariable analysis. Moreover, the authors were aware of the limited number of the study population. Hence, one could not draw a conclusion until more studies with larger sample size further validate the authors' results.

The present findings indicated that pregnancy outcomes of PP with APH were significantly worse than those without APH. Significant maternal morbidity included emergency CS and postpartum blood transfusion while major neonatal morbidity comprised early preterm birth and LBW. The potential life-threatening consequence of PP with APH necessitates its management in tertiary care centers, where appropriate counseling, multidisciplinary team approach, and blood donor should be available at all times. Because various studies have shown that aggressive expectant management of PP with APH, including tocolytic therapy, use of antenatal corticosteroids, and repeated blood transfusion could improve neonatal outcomes^(17,20,21), future research is warranted to identify suitable women who might benefit from such management.

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Potential conflicts of interest

None.

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ผลลัพธ์ของการตั้งครุฑที่มีรกเกาะต่ำร่วมกับการมีหรือไม่มีภาวะตกเลือดก่อนคลอด

พรทิพย์ เหลืองเรืองรอง, เด่นนพพร สุดใจ, บุษบา วิริยะสิริเวช, ชาดากานต์ ผลไธประการ

วัตถุประสงค์: เพื่อเปรียบเทียบผลลัพธ์ของการตั้งครุฑระหว่างหญิงตั้งครุฑที่มีรกเกาะต่ำร่วมกับภาวะตกเลือดก่อนคลอดและไม่มีภาวะตกเลือดก่อนคลอด

วัสดุและวิธีการ: การศึกษาทางระบาดวิทยาแบบย้อนหลังในหญิงตั้งครุฑที่ได้รับการวินิจฉัยเป็นรกเกาะต่ำจำนวน 60 ราย กลุ่มศึกษา (จำนวน 30 ราย) เป็นสตรีที่มีภาวะตกเลือดก่อนคลอด ในขณะที่กลุ่มควบคุม (จำนวน 30 ราย) ไม่มีภาวะตกเลือดก่อนคลอด โดยเปรียบเทียบผลลัพธ์ของการตั้งครุฑระหว่างสองกลุ่ม ได้แก่ คลอดก่อนกำหนด ผ่าตัดคลอดฉุกเฉิน การตัดมดลูกหลังคลอด ความต้องการได้รับเลือด น้ำหนักทารกแรกคลอดน้อย และภาวะขาดออกซิเจนในเลือดตั้งแต่แรกเกิด การวิเคราะห์ข้อมูลทางสถิติทำโดยใช้สถิติการวิเคราะห์ตัวแปรเดี่ยว และหลายตัวแปร

ผลการศึกษา: ข้อมูลจากหญิงตั้งครุฑทั้งหมด 60 ราย ถูกรวบรวมจากสถิติการวิเคราะห์ตัวแปรเดี่ยว พบว่ากลุ่มศึกษามีอัตราเสี่ยงของการคลอดก่อนกำหนดในระยะแรก ระยะท้าย และโดยรวม การผ่าตัดคลอดฉุกเฉิน การได้รับเลือด และน้ำหนักแรกคลอดน้อยสูงกว่าในกลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ โดยมีค่าความเสี่ยงสัมพัทธ์ (ช่วงความเชื่อมั่นร้อยละ 95) เท่ากับ 4.3 (1.6-11.2), 3.9 (1.1-21.2), 6.1 (1.5-25.0), 5.2 (2.3-11.7), 2.6 (1.4-4.6) และ 3.7 (1.1-11.8) ตามลำดับ เมื่อใช้สถิติการวิเคราะห์ข้อมูลหลายตัวแปรเพื่อควบคุมตัวแปรกวนพบว่าค่าความเสี่ยงสัมพัทธ์ยังคงสูงอย่างมีนัยสำคัญทางสถิติในกลุ่มศึกษา โดยพบว่าการผ่าตัดคลอดฉุกเฉินมีค่าความเสี่ยงสัมพัทธ์สูงสุด (ช่วงความเชื่อมั่นร้อยละ 95) เท่ากับ 30.5 (4.1-227.3)

สรุป: หญิงตั้งครุฑที่มีรกเกาะต่ำร่วมกับภาวะตกเลือดก่อนคลอดมีความเสี่ยงของการเกิดผลลัพธ์ที่ไม่ดีของการตั้งครุฑสูงกว่าหญิงตั้งครุฑที่มีรกเกาะต่ำร่วมกับการไม่มีภาวะตกเลือดก่อนคลอดอย่างมีนัยสำคัญทางสถิติ
