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Relationship Between Placenta Previa and Premature Preterm Rupture of Membranes: Case-Cohort Study

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Abstract

Objective

This study aimed to evaluate whether the prevalence of premature preterm rupture of membranes (PPROM) is higher among patients with placenta previa.

Material And Method

A retrospective screening was conducted on a total of 59,567 pregnant women who delivered at our hospital between 2016 and 2021. Among the patients, 1,721 pregnant women meeting the inclusion criteria with PPROM were identified. The participants were divided into two groups: PPROM without placenta previa (control group, n=1,698) and PPROM with placenta previa (n=23). The data were analyzed subsequently.

Results

The birth week of PPROMs with placenta previa was found to be earlier (p = 0.028). The time between diagnosis and birth was shorter in PPROMs with placenta previa than in the second group (p<0.001), and there was a higher frequency of clinical chorioamnionitis in these patients (p=0.037). The prevalence of PPROM with placenta previa was 8.4%, compared to 2.88% for PPROM without placenta previa, demonstrating a statistically significant difference (p<0.001).

Conclusion

Our study found a significantly higher prevalence of PPROM in patients with placenta previa compared to those without placenta previa. Moreover, the interval from diagnosis to delivery was shorter, and clinical chorioamnionitis was more common in patients with PPROM and placenta previa.

Keywords: Chorioamnionitis, placenta previa, premature preterm rupture of membranes, PPROM

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Introduction

Placenta previa is a placental implantation disorder that occurs in approximately 0.5% of all pregnancies and can cause peripartum hemorrhage (1, 2). This condition, diagnosed by second trimester ultrasound findings and vaginal bleeding, is associated with maternal and fetal morbidities. These include maternal morbidities such as cesarean section, sepsis, postpartum hysterectomy, blood transfusion, placenta acreata, and fetal morbidities such as preterm birth, low birth weight, and infections (3, 4).

PPROM can lead to fetal morbidity and mortality, prematurity, hemorrhage, abruptio placenta, fetal infections, oligohydramnios, fetal cord complications, which occur in approximately 3% of all pregnancies (5). This condition is known to occur secondary to inflammation due to ascending infection (6). Premature births have also been known to occur due to inflammation and infection at placenta previa (7). However, it is not known whether fetal and neonatal outcomes differ in PPROM in the presence of placenta previa. Premature preterm rupture of membranes (PPROM) refers to the rupture of membranes before 37 weeks of gestation in the absence of active labor.

PPROM has been established as an exclusion criterion in many studies. The association between PPROM and placenta previa. is not clear in the literature. The association between placenta previa. and pregnancy diseases such as chorioamnionitis or PPROM has been reported in very few studies (8). Some authors suggest that ascending infection is less common in the presence of a placenta located in the lower segment (8), and some studies have reported that histological chorioamnionitis increases in the presence of placenta previa (9). Considering that PPROM is not a local infection but the result of subclinical inflammation of the entire placental unit, the association between a low-lying placenta and PPROM is significant.

This study's primary goal is to ascertain whether placenta previa has a greater prevalence of PPROM. Our secondary objective is to investigate whether low-lying placentas negatively affect fetal and neonatal outcomes compared with normally located placentas.

Material and Method

We designed our study as follows: In the presence of placenta previa, ascending infection may penetrate more easily into the choriodecidua, the chorionic plate, amnion, and/or umbilical cord respectively, due to the pathological location of the placenta, and the likelihood of chorioamnionitis and PPROM may increase. PPROM is not a local infection. It is a more subclinical process affecting the entire placental unit. Evidence of increased PPROM in women with placenta previa supports this hypothesis. Placental placement in placenta previa may increase susceptibility to all of this condition.

Pregnant women diagnosed with PPROM between 2016 and 2021 who delivered at our hospital were divided into two groups: those with and those without placenta previa. Nonviable gestational weeks (< 22 weeks), multiple pregnancies, and pregnancies with major fetal anomalies were excluded from the study. During the years in question, a total of 59.567 pregnant women were delivered at our hospital, and a total of 1721 pregnant women with PPROM who met our criteria were found. Of these, 1698 were PPROM without placenta previa (control group) and 23 were PPROM with placenta previa.

The diagnosis of PPROM was made on the basis of clinical history and vaginal amniotic drainage by the physician and/or the AmniSure ROM test (Qiagen Sciences LLC, Germantown, MD, USA) (based on the determination of placental alpha-microglobulin-1 in vaginal fluid) performed in patients with suspected PPROM. In our clinic, all pregnant women with PPROM receive a single dose of betamethasone (6 mg intramuscularly every 24 hours for two doses, Celestone Chronodoses®, Schering Corp) and antibiotics (1 g azithromycin (Azro®) orally and an additional 2 g ampicillin (Penbisin®) intravenously four times daily for two days, followed by 2 g ampicillin orally four times daily for five days) as a treatment protocol. Many signs are used to diagnose clinical chorioamnionitis, including fever, maternal or fetal tachycardia, foul/purulent amniotic fluid, uterine discomfort, and maternal leukocytosis.

Data were obtained from individual medical and laboratory records via the hospital's digital registration system. Maternal demographic data and maternal and perinatal outcomes were examined.

Statistical Analysis

The statistical analyses of the investigation were conducted utilizing the SPSS 23.0 software. Mean and standard deviation are provided as descriptive statistics for the categorical variables in the data set, while median, minimum, and maximum values are provided as descriptive statistics for the continuous variables. The Shapiro-Wilk test was used to determine if the continuous variables agreed with

the normal distribution. For two-group comparisons of variables that were not normally distributed, the Mann-Whitney U test was employed. p-values less than 0.05 were deemed statistically significant.

Results

Between January 2022 and December 2022, a total of 59567 deliveries were performed in our hospital. 23 of the deliveries were placenta previa + PPROM and 1698 were placenta previa without PPROM. While the prevalence of PPROM+ placenta previa was 8.4%, the prevalence of PPROM without placenta previa was 2.88%, and there was a significant difference between them (p< 0.001).

Table 1 shows the demographic characteristics of the two groups. In either group, there was no significant difference in interventional procedures, BMI, smoking, or assisted reproductive techniques during pregnancy. The age difference between the two groups was significant (p= 0.003) and group 1 patients were older. Significant differences were observed between the two groups in the frequency of more than two births (p = 0.001), previous cesarean deliveries (p = 0.001), early pregnancy bleeding lasting longer than one week (p = 0.005), and more than two miscarriages in prior pregnancies (p = 0.026).

Table 2 shows that there was no significant difference in weeks of gestation at the time of diagnosis (p=

Table 1 Demographic and clinical characteristics of the study population

	PPROM and placenta previa (n:23)	PPROM without placenta previa (n:1698)	p
Age(year)	31.8 ± 3.7	27.4 ± 7.2	**0.003**
Parity			
0	5 (21.7 %)	951 (56 %)	**0.002**
1	5 (21.7 %)	439 (25.9 %)	0.835
>2	13 (56.5 %)	308 (18.1 %)	**< 0.001**
Miscarriage			
0	13 (56.5 %)	1193 (70.3 %)	0.230
1	6 (26.1 %)	422 (24.9 %)	1
>2	4 (17.4 %)	83 (4.9 %)	**0.026**
Previous cesarean			
0	8 (34.8 %)	1275 (75.1 %)	**< 0.001**
>1	15 (65.2 %)	423 (24.9 %)	
BMI (kg/m²)	28.3 ± 5.5	26.6 ± 6.1	0.257
Assisted reproduction	1 (4.3 %)	141 (8.3 %)	1
Smoking	6 (26.1 %)	635 (37.3 %)	0.370
Bleeding in early pregnancy lasting longer than one week	5 (22.7 %)	83 (4.9 %)	**0.005**
Invasive testing in the current pregnancy	1 (4.3 %)	47 (2.8 %)	0.480

Mann Whitney U Test was performed.
BMI, body mass index; kg/m2, kilograms per square meter.
Data are expressed as mean± standard deviation, or frequency (percentage) where appropriate. A p-value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

0.257). The first group had a shorter week of birth, and there was a significant difference in weeks of delivery between the two groups (p=0.028). The duration of the delivery interval was shorter in the first group of patients than in the second group (p 0.001). Whereas there were 5 (21.7%) patients with prenatal clinical chorioamnionitis in group 1, there were 138 (8.1%) in group 2, with a significant difference (p= 0.037).

Significant differences were found between the two groups in terms of hysterectomy at the time of delivery (p= 0.002), and the number of patients undergoing hysterectomy was higher in the second group. In addition, 4 (17.3%) of our PPROM+ placenta previa patients were confirmed to have PAS after surgery. There was no significant difference in fetal outcomes (birth weight, fetal loss, sepsis, retinopathy of prematurity, respiratory distress syndrome, bronchopulmonary dysplasia) between the two groups.

Discussion

In this study, the prevalance of PPROM was found to be significantly higher in patients with placenta previa than in patients without placenta previa. The interval from diagnosis to delivery was shorter, and clinical chorioamnionitis occurred more frequently

Table 2 Comparison of maternal and fetal outcomes between groups

	PPROM and placenta previa (n:23)	PPROM without placenta previa (n:1698)	p
Prevalence of disease in the cohort	23 (8.4 %)	1698 (2.88 %)	**< 0.001**
Maternal outcomes			
Gestational age at diagnosis (weeks)	29.5 ± 4.1	30.3 ± 3.4	0.257
Gestational age at delivery (weeks)	31.0 ± 4.1	32.5 ± 3.4	**0.028**
Interval from diagnosis to delivery (days)	10.1 ± 18.2	15.4 ± 12.6	**<0.001**
Anhydramnios diagnosed during the follow-up	3 (13 %)	566 (33.3 %)	0.067
Clinical chorioamnionitis diagnosed before delivery	5 (21.7 %)	138 (8.1 %)	**0.037**
Surgically confirmed PAS	4 (17.3 %)	-	**-**
Hysterectomy	3 (14.3 %)	17 (1.0 %)	**0.002**
Fetal outcomes			
Neonatal birth weight			
Mean ± SD	1700 ± 726	2070 ± 672	**0.023**
< 10th percentile	2 (8.7 %)	84 (4.9 %)	0.321
NICU admission	14 (60.9 %)	935 (55.1%)	0.730
Perinatal death	1 (4.3 %)	13 (0.8 %)	0.172
Sepsis	2 (8.7 %)	68 (4.0 %)	0.240
ROP	5 (21.7 %)	241 (14.2 %)	0.361
BPD	3 (13 %)	189 (11.1 %)	0.736
RDS	5 (21.7 %)	164 (9.7 %)	0.067

Mann Whitney U Test was performed.
PAS, placenta accreta spectrum; NICU, neonatal intensive care unit; ROP, Retinopathy of prematurity; BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome.
Data are expressed as mean±standard deviation or frequency (percentage) where appropriate. A p-value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

in patients with PPROM and placenta previa. In addition, anhydramnios was less frequent in patients with PPROM and placenta previa.

Placenta previa is one of the most common causes of third trimester hemorrhage and is associated with severe maternal complications, including bleeding requiring blood transfusions, disseminated intravascular coagulation, and emergency hysterectomy (10). There are many mechanisms for the transmission of microorganisms in the occurrence of intrauterine infections in pregnancy. The ascending infection route is the most common from the vagina to the uterus (11). Romero et al. found that histologic chorioamnionitis in patients with twin births was more common in the firstborn twin than in the second twin because the membranes of the first twin were generally adjacent to the cervix, suggesting ascending intrauterine infection associated with preterm labor (11). We think that the higher prevalence of chorioamnionitis in the firstborn twin in this study is similar to the higher prevalence of chorioamnionitis in women with PPROM and placenta previa found in our study compared to PPROM without placenta previa due to the proximity of the placental membranes.

PPROM and intra-amniotic infection/inflammation were discussed at most studies but the cases with with placenta previa were excluded because of heterogeneous clinical features compared with cases without placenta previa. Therefore, the number of studies that have investigated the presence of intrauterine infection and inflammation in patients with placenta previa is very limited in the literature, and there is some inconsistency between the results of these few studies. Yonn et al showed that, the incidance of intraamniotic infection was 10%, intraamniotic inflammation was found in 32% of cases, and 53% of placentas available for analysis had histologic chorioamnionitis in patients with spontaneous preterm birth and intact membranes without placenta previa (7). Park et al. found that intra-amniotic inflammation was present in 16.7%, proven amniotic fluid infection in 4.9%, and histologic chorioamnionitis in 19.0% of patients with placenta previa and preterm labor and intact membranes. Also, all cases with histological chorioamnionitis had inflammation in the choriodecidua exposed to the cervical canal at placenta previa, but inflammation of the chorionic plaque was present in 63%. Compared to the results of the study by Yonn et al, these authors interpreted the low rates in patients with placenta previa in their study to mean that the placenta may play a protective role against ascending infections in contrast to our current study. On the other hand ,in their study, the time interval to delivery was shorter associated with intraamniotic inflammation in patients with placenta previa and preterm labor with intact membranes, similar to our study (9).

Idiopathic vaginal bleeding is associated with intra-amniotic infection in 14% of patients (12). Additionally, antepartum decidual hemorrhage is an important risk factor for PPROM, which can occur even in the presence of placenta previa. Madan et al showed that intraamniotic infection was present in 5.7% and intraamniotic infection and/or inflammation in 17.9% in patients with placenta previa who had vaginal bleeding. In addition, they found that intra-amniotic infection and/or inflammation was a risk factor for preterm delivery within 48 hours in the group (8). This finding suggests that vaginal bleeding in a subset of patients with placenta previa may also reflect microbial invasion. In this study, we found that vaginal bleeding which had longer than 1 week in early pregnancy was higher and the interval from diagnosis to delivery was shorter, and clinical chorioamnionitis occurred more frequently in patients with PPROM and placenta previa.

In the study by Kim et al, defective placentation, defined as failure of physiological transformation of the myometrial segment of the spiral artery, was frequently found in PPROM and the mean number of spiral arteries with failed physiological transformation of the myometrial segment was significantly higher in patients with PPROM and preeclampsia than in normal pregnant women (13). The finding that patients with PPROM also have a higher rate of vascular lesions in the villous tree and basal plate suggests that vascular disease may play a role in the pathogenesis of PPROM (14, 15). We also think that the increase in the prevalance of PPROM development in placenta previa patients in our study is due to this pathogenesis. Several explanations can be suggested for the shorter interval from diagnosis to delivery in patients with placenta previa and PPROM. First of all, active bleeding in placenta previa is an obstetric emergency, if vaginal bleeding occurs in the presence of PPROM with placenta previa, in this case, it may not be possible to distinguish whether the bleeding is due to previa or placental abruption and it may be considered bleeding requiring delivery. Another important situation is clinical chorioamnionitis was more common in PPROM with placenta previa, and the interval from diagnosis to delivery may have been shorter because chorioamnionitis is one of the conditions under which delivery should be performed. Lastly, considering the close correlation between placenta previa and placenta accreta spectrum (PAS), it is advisable to

rule out PAS in any patient with placenta previa. In the presence of PAS spectrum suspicion, the timing of delivery is earlier or due to a lower threshold for the decision to deliver.

Because the clinical approach was standardized, all patients received the same care from the same clinical personnel and according to the same protocol, which is the strength of our study. The weaknesses of the study are that it was obtained from a relatively small cohort over a period of only 4 years and that all data were obtained from an electronic database because of the retrospective design. In addition, we based the study on the evaluation of clinical chorioamnionitis, not histological chorioamnionitis for the same reason.

Conclusion

Our study showed the prevalence of PPROM was found to be significantly higher in patients with placenta previa than in patients without placenta previa and a higher incidance of chorioamnionitis in women with PPROM and placenta previa than in PPROM without placenta previa. The interval from diagnosis to delivery was shorter in these patients. In this regard, more data is needed and further pathological, morphological investigations will be necessary to clarify placenta previa, especially in the presence of PPROM. Our findings suggest that in patients with placenta previa, the extension of the placenta beyond the internal os may heighten the risk of ascending infection and PPROM development.

Conflict of Interest Statement
The authors declare no conflicts of interest.

Ethical Approval
The study was approved by the Etlik Zubeyde Hanım Women's Health Training and Research Hospital's ethics committee (Approval number: 19/11/2021/13). All procedures were performed in accordance with the Declaration of Helsinki.

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Availability of Data and Materials
Individual level data (excluding identifiers) will be made available on request.

Authors Contributions
SYE: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft, Project administration;

BS: Data curation; Formal analysis

YAR: Investigation

SS: Formal analysis

COU: Resources

MB: Investigation

ZS: Visualization

GK: Writing-original draft

BTC: Data curation

GA: Validation

IO: Writing-original draft

CTI: Supervision; Methodology; Writing-original draft. Writing-review & editing.

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