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Journal of the Chinese Medical Association 80 (2017) 657−661

www.jcma-online.com

Original Article

Third trimester preterm and term premature rupture of membranes: Is there any difference in maternal characteristics and pregnancy outcomes?

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Received July 30, 2016; accepted December 20, 2016

Abstract

Background: The clinical significance and management of preterm premature rupture of membranes (PPROM) remains a topic of a controversy. Although PROM is associated with a low rate of complications, PPROM may lead to significant neonatal and maternal morbidity.
Methods: We performed a retrospective study of 714 women who presented to Jiangsu Province Hospital with third trimester PPROM or PROM between January and December 2015. The data were analyzed by SPSS; the significance of maternal characteristics, and maternal and neonatal outcomes were tested using Student's t test and the χ^2 test. A two-sided p value < 0.05 was considered statistically significant.
Results: There were 714 women included in this analysis. We identified 577 (80.8%) women with PROM and 137 (19.2%) with PPROM. In the PPROM group, we further divided the women into 28^{+0}−31^{+6} weeks ($n = 21$) and 32^{+0}−36^{+6} weeks ($n = 116$) of gestational age. PPROM was associated with a significantly lower gestational age, and patients in this group showed higher C-reactive protein and body temperature when admitted to the hospital ($p < 0.05$). Breech presentation and history of previous cesarean section were associated with occurrence of PPROM compared with PROM ($p < 0.05$). The PPROM group showed a significantly longer latency period compared with the PROM group, in which the latency period increased with the lower gestational age (28^{+0}−31^{+6} weeks). Significantly higher neonatal intensive care unit (NICU) admission rate was shown in the PPROM group as compared with the PROM group, and gestational age 28^{+0}−31^{+6} weeks yielded a significantly higher rate of NICU admission than 32^{+0}−36^{+6} weeks did ($p < 0.05$).
Conclusion: Higher C-reactive protein and body temperature in the PPROM group suggest an asymptomatic infection that requires close monitoring to prevent any adverse effect on pregnancy outcome. Longer latency period in PPROM group is predictable in order to minimize perinatal morbidity and mortality because of prematurity itself. Therefore, an increase in gestational age plays an important role that can affect a clinician's decision making regarding whether to transfer to the NICU.

Keywords: pregnancy outcomes; premature rupture of membranes prematurity; preterm premature rupture of membranes

1. Introduction

Premature rupture of membranes (PROM) is the rupture of the fetal membranes before the onset of labor. The incidence of PROM is 2.7−7% in China and 5−15% in America.[1] In most cases, this occurs near term; however, when membrane rupture occurs before 37 weeks' gestation, it is known as preterm PROM (PPROM). PPROM is one of the clinical subtypes of preterm birth, and occurs in ~3% of pregnancies, resulting in one-third of preterm births. It remains the leading cause of preterm deliveries and neonatal mortality and morbidity.[2] Preterm births can be subdivided according to gestational age: about 5% of preterm births occur at < 28 weeks (extreme prematurity), ~15% at 28−31 weeks (severe prematurity), ~20% at 32−33 weeks (moderate prematurity), and 60−70% at 34−36 weeks (near term).[3]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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http://dx.doi.org/10.1016/j.jcma.2016.12.006

Factors associated with PPROM include lower socioeconomic status, prior preterm delivery, previous PROM, sexually transmitted diseases, vaginal bleeding, connective tissue disorders, smoking, and overdistension of the uterus. However, there are cases when recognizable causes of PROM are absent. Clinical significance and management of PPROM is still controversial. Although PROM is associated with a low rate of complications, PPROM may lead to significant neonatal and maternal morbidity.[4] The purpose of this retrospective study was to evaluate maternal characteristics and pregnancy outcomes in different gestational ages in patients with third trimester cases of PPROM or PROM.

2. Methods

This was an observational retrospective study, and approval was obtained from the Institutional Review Board of our hospital. A manual search was performed through electronic medical records, and annual reports of Jiangsu Province Hospital from January 2015 to December 2015. There were 897 women who presented to Jiangsu Province Hospital with PPROM or PROM between January and December 2015. We only included pregnant women in this study in third trimester, which was defined as 28^{+0}–42^{+0} weeks' gestation. We divided the women into PROM and PPROM groups. We further divided the PPROM group into 28^{+0}–31^{+6} weeks' gestational age, and 32^{+0}–36^{+6} weeks' gestational age. Recognizable risk factors for PPROM and PROM were already excluded: history of sexually transmitted diseases, uterine distension (e.g., polyhydramnios and multifetal pregnancy), systemic lupus erythematosus, cervical incompetence, fever, uterine morphology abnormality, or procedures that may result in PROM or PPROM (e.g., cerclage). Additionally, women who did not deliver in our hospital and who had missing data files were also excluded. The first complete blood count (CBC) and C-reactive protein (CRP) level were recorded when pregnant women presented to the hospital with the above-referenced symptoms.

The diagnosis of PROM and PPROM was based on taking of patient history, physical examination, and laboratory studies. Gestational age was determined from the date of last menstrual period when reliable and sonographic confirmation was obtained during the first 20 weeks' gestation and/or the first trimester sonographic measurement of crown lump length. Patients often report a sudden gush of fluid with continued leakage. Physical examination included: (1) sterile speculum examination to see if fluid was pooling in the vagina; (2) nitrazine paper turned blue; and (3) fern test. Fern test was performed when nitrazine test was negative. We included the cases if at least two of these examinations were positive.

2.1. Statistical analysis

The data were collected using Microsoft Excel 2007 (Window XP; Microsoft Corp., Redmond, WA, USA) and analyzed using statistical software package SPSS version 20.0 (SPSS Inc.). Data were expressed as the mean ± standard deviation or rate (%) and were tested for significance using Student's t test and the χ^2 test. A two-sided p value < 0.05 was considered statistically significant.

3. Results

Among 897 women admitted to Jiangsu Province Hospital with PROM from January 2015 to December 2015, there were 183 who did not meet our study criteria. Only 714 women were included in this analysis. We identified 577 (80.8%) women with PROM and 137 (19.2%) women with PPROM.

Comparison of maternal characteristics and comorbidity between PROM and PPROM groups are shown in Table 1. The maternal characteristics were similar, with no significant difference in maternal age, parity, time since last delivery, systolic blood pressure, diastolic blood pressure, and body mass index ($p > 0.05$). There were significant differences between the two groups in terms of gestational age when rupture of the membrane occurred (39 ± 1.5 weeks vs. 34.3 ± 2.0 weeks, $p < 0.05$), gravidity (1.92 ± 1.16 vs. 2.18 ± 1.34, $p < 0.05$), CRP (6.43 ± 5.63 vs. 7.76 ± 6.59 mg/L, $p < 0.05$), and body temperature when admitted (36.67 ± 0.31 vs. 36.76 ± 0.34, $p < 0.05$). Regarding maternal comorbidity, there were no significant differences between patients who had hypertensive disorders, gestational diabetes mellitus, placenta previa, fetal factors, and carriers of hepatitis B virus ($p > 0.05$). The rates of patients with a history of cesarean section and patients with breech presentation were significantly higher in the PPROM group compared with the PROM group (14.6% vs. 4.7% and 9.5% vs. 1.9%, $p < 0.05$).

Table 1
Maternal characteristics and comorbidity between PROM and PPROM group.

	PROM (n = 577)	PPROM (n = 137)	p
Maternal characteristics (mean ± SD)			
Age (y)	29.16 ± 4.50	28.69 ± 4.91	0.27
Gravidity	1.92 ± 1.16	2.18 ± 1.34	0.02
Parity	0.26 ± 0.45	0.31 ± 0.5	0.33
Last delivery (y)	1.74 ± 3.71	1.93 ± 3.85	0.60
Gestational age (wk)	39.0 ± 1.50	34.30 ± 2.0	0.0
SBP (mmHg)	119.66 ± 10.74	120.54 ± 10.63	0.38
DBP (mmHg)	76.05 ± 7.73	75.48 ± 8.37	0.45
BMI (kg/m^2)	27.09 ± 3.15	27.22 ± 3.83	0.67
CRP	6.43 ± 65.63	7.76 ± 6.59	0.01
Temperature when admitted (°C)	36.67 ± 0.31	36.76 ± 0.34	0.0
Maternal comorbidity, n (%)			
Hypertensive disorder[a]	10 (1.7)	6 (4.4)	0.06
GDM	121 (21)	26 (19)	0.60
Previous CS	27 (4.7)	20 (14.6)	0.0
Breech presentation	11 (1.9)	13 (9.5)	0.0
Placenta previa	1 (0.2)	0 (0.0)	0.62
Hepatitis B carrier	11 (1.9)	6 (4.4)	0.08
Fetal factors[b]	12 (2.1)	4 (2.9)	0.55

BMI = body mass index; CRP = C-reactive protein; CS = cesarean section; DBP = diastolic blood pressure; GDM = gestational diabetes mellitus; PPROM = preterm premature rupture of membranes; SBP = systolic blood pressure; SD = standard deviation.

[a] Gestational hypertension, preeclampsia.

[b] Fetal distress, fetal congenital anomaly.

Table 2
Maternal characteristics and comorbidity between gestational age 28^{+0}–31^{+6} weeks and 32^{+0}–36^{+6} weeks.

	28^{+0}–31^{+6} (n = 21)	32^{+0}–36^{+6} (n = 116)	p
Maternal characteristics (mean ± SD)			
Age (y)	28.33 ± 5.46	28.75 ± 4.83	0.72
Gravidity	2.38 ± 1.39	2.15 ± 1.33	0.46
Parity	0.43 ± 0.59	0.28 ± 0.49	0.23
Last delivery (y)	2.57 ± 4.33	1.81 ± 3.77	0.40
Gestational age (wk)	30.80 ± 1.10	35.0 ± 1.40	0.00
SBP (mmHg)	123.33 ± 9.99	120.03 ± 10.71	0.19
DBP (mmHg)	75.76 ± 11.69	75.43 ± 7.69	0.86
BMI (kg/m^2)	27.50 ± 5.31	27.17 ± 3.52	0.72
CRP	8.52 ± 7.16	7.62 ± 6.51	0.56
Temperature when admitted (°C)	36.85 ± 0.34	36.74 ± 0.34	0.16
Maternal comorbidity, n (%)			
Hypertensive disorder[a]	1 (4.8)	5 (4.3)	0.92
GDM	3 (14.3)	23 (19.8)	0.55
Previous CS	6 (28.6)	14 (12.1)	0.04
Breech presentation	4(19)	9(7.8)	0.35
Placenta previa	0(0)	0(0)	-
Hepatitis B carrier	2 (9.5)	4 (3.4)	0.21
Fetal factors[b]	1 (4.8)	3 (2.6)	0.58

BMI = body mass index; CS = cesarean section; DBP = diastolic blood pressure; GDM = gestational diabetes mellitus; SBP = systolic blood pressure; SD = standard deviation.
[a] Gestational hypertension, preeclampsia.
[b] Fetal distress, fetal congenital anomaly.

After subgrouping (Table 2), there was almost no significant difference in maternal characteristics between the two groups except for a difference in gestational age when PROM occurred (30.80 ± 1.10 vs. 35.0 ± 1.40, $p< 0.05$). From the aspect of maternal comorbidity, this study showed that rates of patients with previous cesarean section were significantly higher in earlier gestational age (28.6% vs. 12.1%, $p < 0.05$).

Regarding maternal outcomes (Table 3), there were no significant differences between the PROM and PPROM groups in terms of mode of delivery and postpartum hemorrhage ($p > 0.05$), but the PPROM group had a significantly longer duration of latency before termination of pregnancy (43.29 ± 50.33 hours vs. 18.94 ±17.11 hours, $p < 0.05$). From the aspect of neonatal outcomes (Table 3), infants in the PROM group had a significantly higher birth weight (3389.17 ± 453.88 vs. 2468.25 ± 551.63, $p < 0.05$), meconium staining rates (10.6% vs. 3.6%, $p < 0.05$), APGAR score at 1 minute (9.94 ± 0.41 9 vs. 9.44 ± 1.21, $p < 0.05$), and APGAR score at 5 minutes (9.98 ± 0.22 vs. 9.71 ± 0.91, $p < 0.05$). NICU admission rates were significantly higher in the PPROM group than the PROM group (65.7% vs. 11.8%, $p < 0.05$).

Table 3
Maternal and neonatal outcomes between PROM and PPROM group.

	PROM (n = 577)	PPROM (n = 137)	p
Maternal outcomes, mean ± SD or n (%)			
Latency (h)	18.94 ± 17.11	43.29 ± 50.33	0.0
Mode of delivery			
Normal	431 (74.70)	96 (70.10)	0.26
Cesarean section	146 (25.30)	41 (29.90)	
PPH	44 (7.60)	6 (4.40)	0.18
Neonatal outcomes, mean ± SD or n (%)			
Birth weight (g)	3389.17 ± 453.88	2468.25 ± 551.63	0.0
Meconium staining	61 (10.60)	5 (3.60)	0.01
APGAR score 1 min	9.94 ± 0.41	9.44 ± 1.21	0.0
APGAR score 5 min	9.98 ± 0.22	9.71 ± 90.91	0.0
NICU admission	68 (11.80)	90 (65.70%)	0.0

NICU = neonatal intensive care unit; PPH = postpartum hemorrhage; PPROM = preterm premature rupture of membranes; SD = standard deviation.

Table 4
Maternal and neonatal outcomes between gestational age 28^{+0}–31^{+6} weeks and 32^{+0}–36^{+6} weeks.

	28^{+0}–31^{+6} (n = 21)	32^{+0}–36^{+6} (n = 116)	p
Maternal outcomes, mean ± SD or n (%)			
Latency (h)	91.52 ± 56.94	34.56 ± 43.94	0.0
Mode of delivery			
Normal	13 (61.9%)	83(71.6%)	0.37
Cesarean section	8 (38.1%)	33(28.4%)	
PPH	2 (9.5%)	4 (3.4%)	0.21
Neonatal outcomes, mean ± SD or n (%)			
Birth weight, g	1716.67 ± 367.19	2604.3 ± 463.23	0.07
Meconium staining	2(9.5%)	3 (2.6%)	0.11
APGAR score 1 min	8.67 ± 1.82	9.58 ± 1.02	0.0
APGAR score 5 min	9.43 ± 0.81	9.76 ± 0.92	0.19
NICU admission	21 (100%)	70 (60.3%)	0.0

NICU = neonatal intensive care unit; PPH = postpartum hemorrhage; SD = standard deviation.

After subgrouping (Table 4), there were also no significant differences between the two groups in terms of mode of delivery and postpartum hemorrhage ($p > 0.05$), but the latency period was significantly longer at earlier gestational age (91.52 ± 56.94 hours vs. 34.56 ± 43.94 hours, $p < 0.05$). Neonatal infants at gestational age of 32^{+0}–36^{+6} weeks had a significantly higher APGAR score at 1 minute (9.58 ± 1.02 vs. 8.67 ± 1.82, $p < 0.05$), but NICU admission rates were significantly higher at gestational age of 28^{+0}–31^{+6} weeks (100% vs. 60.3%, $p < 0.05$). There were no differences in birth weight, meconium staining and APGAR score at 5 minutes between these groups ($p > 0.05$).

4. Discussion

We collected data for pregnant women with PPROM and PROM, and demonstrated that 80.8% of 714 pregnant women had PROM, and the remainder had PPROM (19.2%). PPROM (i.e, rupture of the membranes before the onset of labor) occurs in 20% of all births and 40% of all preterm births.[5] Intrauterine infection is a frequent and important mechanism leading to preterm birth. The mechanisms by which intrauterine infections lead to preterm labor are related to activation of the innate immune system, which reflect four major pathogenic processes: (1) activation of the maternal or fetal hypothalamic–pituitary–adrenal axis; (2) decidual–chorioamniotic or systemic inflammation; (3) decidual hemorrhage; and (4) pathological distention of the uterus. They each

converge on a final common biochemical pathway involving myometrial activation and stimulation and enhanced genital tract protease activity promoting PROM and cervical change.[3,6] Well-known biomarkers of inflammation such as CRP in maternal blood have been routinely used in clinical practice to identify risks for preterm delivery in patients with PPROM.[7]

According to our study, women in the PPROM group had significantly higher CRP and body temperature compared with the PROM group ($p < 0.05$). It is well known that CRP is released by the body in response to acute injury, infection, or other inflammatory stimuli, and is a leading blood marker of systemic (or body-wide) inflammation. Its value is as a general indicator. A high or increasing amount of CRP in the blood suggests the presence of inflammation, but will not identify its location or the condition causing it. Proinflammatory cytokine interleukin-6 is suggested to play a critical role in fever induction and in the synthesis of CRP by hepatocytes.[8]

We did not perform cervical culture routinely in patients with PPROM, so these findings suggest that asymptomatic infection and systemic inflammation might be underlying factors in occurrence of PPROM that could lead to preterm birth. Our finding was consistent with the one reported by Min-A Kim et al.[7] After subgrouping, women of earlier gestational age had higher CRP and body temperature, although it was not statistically significant.

Our study showed that patients in the PPROM group were more likely to have breech presentation compared with PROM group (9.5% vs. 1.9%, $p < 0.05$). Our findings were consistent with the study conducted by Demol et al.[9] After subgrouping, there were no differences in fetal presentation with prevalence of PPROM. Previous studies showed strong correlation between breech presentation and low gestational age. Cammu et al[10] performed a population based cohort study of 28,059 women who had delivered in breech presentation and concluded that the earlier the gestational age, the higher the prevalence of breech presentation. Another study of 4024 patients at a gestational age of $\geq$ 28 weeks by Hill et al[11] showed that the prevalence of breech presentation at 28 weeks was 24.4%, and had decreased to 3.7% by 37 weeks. We hypothesized that the lower the gestational age, the higher the probability of breech presentation. The natural correlation between breech presentation and low gestational age combined with PPROM explains why we found significant correlation between PPROM and breech presentation.

In this study we also showed that a history of previous cesarean section significantly correlated with PPROM rather than PROM (14.6% vs. 4.7%, $p < 0.05$). After subgrouping, earlier gestational age had significantly higher rate of previous caesarean section history (28.6% vs. 12.1%, $p < 0.05$). Unfortunately, we were not able to explain the correlation between previous cesarean section with PPROM. It may be that these results were affected by our study sample, which was not sufficiently large.

Regarding maternal outcomes, the PPROM group had significant longer duration of latency than the PROM group had. After subgrouping, duration of latency was significantly longer with gestational age 28^{+0}–31^{+6} weeks than 32^{+0}–36^{+6} weeks. The main concern for PPROM is prematurity; hence, the latency period influences the maternal and fetal outcomes. A study of 1596 patients with PPROM by Drassinower et al[12] demonstrated that prolonged latency in the setting of PPROM was associated with a decreased risk for neonatal sepsis and that infants delivered soon after PPROM were at the highest risk. Periventricular leukomalacia is neonatal white matter damage of the brain of preterm infants that often leads to cerebral palsy. The prevalence of cerebral palsy at age 3 years is 21 per 1000 for those born between 28 weeks and 30 weeks, and 0.6 per 1000 for those delivered at term.[13] So, when appropriate, expectant management is usually advised in the absence of labor or complications necessitating delivery in order to minimize perinatal morbidity and mortality.

After hospitalization, in the absence of an indication for immediate delivery, all women were managed expectantly in the standardized protocol. This comprised a close follow-up of the maternal status, intermittent fetal heart rate monitoring, and blood analysis. In the setting of PPROM, tocolysis and antenatal steroid administration are the usual practice. In our hospital, pregnant women who presented with PPROM received dexamethasone therapy and two doses of 6 mg were given intramuscularly 12 hours apart for 2 days. Besides this, antibiotic prophylaxis was given. Tocolytic therapy suppresses uterine contractions and permits steroid and antibiotic administration. The decision whether to terminate pregnancy with cesarean section or normal delivery is based on maternal and fetal status. Cesarean section is mainly indicated in cases of pregnancy complication, for example, maternal fever, presence of clinical chorioamniocitis, nonreassuring fetal status and fetal death, and placental abruption.

Regarding neonatal outcomes, as expected, infants in the PROM group had a significantly higher birth weight, and APGAR score at 1 minute and 5 minutes ($p < 0.05$). Meconium staining amniotic fluid rate was also significantly higher in the PROM group than PPROM group ($p < 0.05$). Meconium is a common finding in amniotic fluid and placental specimens, particularly in term or post-term pregnancy. The physiological propensity of the fetus to pass the meconium increases with gestational age. Our findings were consistent with this theory.[14] Our findings, however, were contradicted by the study of Wallenstein et al,[15] who showed that meconium staining of amniotic fluid was associated with prematurity and PPROM, although their patients were neonatal infants with gastroschisis. NICU admission rates were significantly higher in the PPROM group than in the PROM group ($p < 0.05$). After subgrouping, there were no differences in birth weight, meconium staining rate and APGAR score at 5 minutes ($p > 0.05$), but the APGAR score at 1 minute was higher at later gestational age. We found a significantly higher NICU admission rate at gestational age of 28^{+0}–31^{+6} weeks compared with 32^{+0}–36^{+6} weeks (100% vs. 60.3%, $p < 0.05$). This showed that even though both subgroups had not reached term, an increase in gestational age plays an important role that might affect decision making whether to transfer to the NICU.

One limitation of this study was that we did not perform cervical culture routinely in our patients, which is one of the crucial tests to detect presence of intrauterine infection. The other limitation was the retrospective nature of the study, and our findings should be confirmed with larger prospective studies.

In conclusion, higher CRP and body temperature in the PPROM group compared with PROM group suggest an asymptomatic infection that needs close monitoring to prevent an adverse pregnancy outcome. Patients with a history of previous cesarean section and breech presentation are strongly correlated with occurrence of PPROM compared with PROM, in which history of previous cesarean section remains correlated with lower gestational age (28^{+0}–31^{+6} weeks). Longer latency period in the PPROM group compared with PROM group is predictable in order to minimize perinatal morbidity and mortality because of prematurity itself. An increase in gestational age plays an important role that can affect decision making whether to transfer to the NICU.

Acknowledgments

The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors would like to thank Dr. Bai Jin for the comment on the draft manuscripts.

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