Perinatal outcomes following immediate delivery or expectant management of preterm premature rupture of membranes during the late preterm period

Hayan Kwon
Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Severance Hospital, Institute of Women's Life Medical Science, Yonsei University College of Medicine, Seoul,

Suk Ho Kang
Department of Obstetrics and Gynecology, Ilsan CHA General Hospital, Goyang, Republic

Hyun Sun Ko
Department of Obstetrics and Gynecology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul

Ja Young Kwon
Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Severance Hospital, Institute of Women's Life Medical Science, Yonsei University College of Medicine, Seoul,

Han-sung Kwon
Department of Obstetrics and Gynecology, Konkuk University School of Medicine, Seoul

Kyung Joon Oh
Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam

Minkyung Oh
Department of Pharmacology, Inje University College of Medicine, Busan

Soo-young Oh
Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul

Mi-Young Lee
Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul

Soo Ran Choi
Department of Obstetrics and Gynecology, Inha University Hospital, Inha University College of Medicine, Incheon

You Jung Han
Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, Seoul

Ah-Ram Sul
National Evidence-based Healthcare Collaborating Agency, Seoul

Youjin Jung
National Evidence-based Healthcare Collaborating Agency, Seoul
Jimin Kim
National Evidence-based Healthcare Collaborating Agency, Seoul
Ji Jeong Park
National Evidence-based Healthcare Collaborating Agency, Seoul
Jayoun Lee
National Evidence-based Healthcare Collaborating Agency, Seoul
Young Nam Kim (ob.youngnam@gmail.com)
Department of Obstetrics and Gynecology, Busan Paik Hospital, College of Medicine, Inje University, Busan
Jeong In Yang (yangji@ajou.ac.kr)
Department of Obstetrics and Gynecology, Ajou University School of Medicine, Suwon

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Research Article

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Abstract

The aim of this study is to evaluate maternal and neonatal outcomes following immediate delivery or expectant management of preterm premature rupture of membranes (PPROM) during the late preterm period at 34^{+0}–36^{+6} weeks of pregnancy. We conducted a retrospective study on singleton pregnancies with PPROM during the late preterm period using medical records at twelve tertiary medical centres in Korea from January 2007 to December 2016. Data on demographic characteristics and outcome measures were collected. The primary outcomes were maternal sepsis for maternal outcome and neonatal sepsis and neonatal death for neonatal outcomes. Of the 1,072 women, 782 cases (72.9%) were assigned to the immediate delivery group, and 290 cases (27.1%) were categorized into the expectant management group. There was a significant difference in the rate of clinical neonatal sepsis (immediate delivery, 3.8% *vs* expectant management, 15.8%; $p < 0.0001$), however, no differences in maternal sepsis ($p = 0.5424$), culture-proven neonatal sepsis ($p = 0.2108$), or neonatal death ($p = 0.3899$) were observed. In conclusion, expectant management in women with PPROM during the late preterm period does not increase the risk of severe maternal and neonatal morbidities and mortality; however, careful monitoring for chorioamnionitis or fetal compromise should be considered during expectant management.

Introduction

Preterm premature rupture of membranes (PPROM) is the rupture of amniotic membranes prior to the onset of labor before 37 weeks of gestation. PPROM occurs in 2–3% of all pregnancies and one-third of preterm births [1,2]. The mother exposed to PPROM might be at higher risk for preterm labor resulting in preterm delivery, potential intra-amniotic infection, placental abruption, and cord prolapse during the latent period. Neonates exposed to PPROM show an increased risk of sepsis, pulmonary hypoplasia, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and neonatal death due to prematurity and decreased amniotic fluid [3–5]. Some clinical guidelines recommend that immediate delivery should be considered for women with PPROM on the basis of the following conclusions: “delivery should be considered at 32 gestational weeks if fetal lung maturity can be documented or at 34 weeks of gestation because prolonged latent period exposes the fetus to intra-amniotic infection, retroplacental hematoma or fetal distress.” [3,6,7]. However, prolonged latent period in women with PPROM without overt signs of infection or fetal compromise can lower neonatal morbidities due to prematurity and lessen the economic burden of premature infants in neonatal intensive care units (NICU). Recent randomised controlled trials demonstrated that expectant management of PPROM during the late preterm period provided good neonatal outcomes without significant risk to neonates [8–10]. Therefore, optimal timing for delivery in women with PPROM during the late preterm period remains controversial because both reducing fetal prematurity at birth and avoiding complications including intra-amniotic infection during the latent period should be regarded. In addition, it is now clear that neonates born at 34–37 weeks of gestation are physiologically immature and are associated with a substantial short-and

long-term health burden such as RDS, sepsis work-ups, phototherapy for hyperbilirubinemia, significantly increased use of intensive care, longer hospitalization, and concomitant increased hospital charges. [8,11].

Hence, we aimed to evaluate maternal and neonatal outcomes following immediate delivery or expectant management of PPROM during the late preterm period at 34^{+0}–36^{+6} weeks of gestation to establish the optimal management and time for delivery. This investigation of current management status can help clinicians in counselling affected women and assist decision making process for optimal timing of delivery.

Methods

Study design

We conducted a retrospective study of singleton pregnancies complicated by PPROM during the late preterm period using medical records at twelve tertiary medical centers in Korea from January 2007 to December 2016. Late preterm period was defined as gestational age from 34^{+0} weeks to 36^{+6} weeks. All hospitals were referral institutions equipped with NICUs that were capable of providing comprehensive care for preterm infants. At least one obstetric specialist confirmed all medical records.

Inclusion criteria were a singleton pregnancy and clinically diagnosed ruptured membranes at 34^{+0} – 36^{+6} weeks of gestation. The exclusion criteria were multiple pregnancies, active labor at admission time, suspected clinical chorioamnionitis, placenta previa, placental abruption, preeclampsia, or any other contraindication to continue the pregnancy (Fig. 1).

Pregnancy management

Diagnosis of PPROM was based on maternal history (including the exact time of amniotic fluid leakage by history taking) and sterile speculum examination confirming amniotic fluid draining from the cervical os that changed the color of nitrazine paper, or biochemical tests when in doubt [3]. Eligible women in this study were divided into two groups according to management: immediate delivery and expectant management. Immediate delivery was defined as active management, such as decision of labor induction or caesarean delivery within 24 hours after rupture of membranes. Expectant management was defined as a decision of close observation with careful monitoring of maternal and fetal complications, and performing conservative management until 37 gestational weeks or any other indications for delivery during latent period, such as non-reassuring fetal heart rate (FHR) pattern, initiation of labor, or suspected intrauterine infections. Whether administration of antenatal corticosteroids and antibiotics during latent period was confirmed on medical records. All women were hospitalised and managed until delivery. Careful evaluation of labor and fetal well-being was assessed via continuous cardiotocography (CTG) and fetal ultrasonography. Indications for delivery during latent period included progress of labor, suspected clinical chorioamnionitis, or suspected fetal compromise.

Maternal, Obstetrics and Neonatal Outcomes

Clinical data including maternal demographics, obstetric outcomes, and neonatal outcomes were obtained from the electronic medical records. Maternal demographics included age, gestational age at the time of PPROM diagnosis, underlying medico-surgical illness, and cervical or vaginal culture. Data on obstetric outcomes including gestational age at delivery, latent period, mode of delivery, and incidences of complications such as maternal sepsis, endometritis, postpartum hemorrhage, and wound infection were collected. Neonatal outcomes included admission to the NICU, Apgar score, surfactant administration, and neonatal complications during the hospital stay. Progress of labor was defined as cervical change with regular labor. Clinical chorioamnionitis was defined as the presence of two or more of the following symptoms: maternal pyrexia, leukocytosis, uterine tenderness, maternal or fetal tachycardia, and malodorous vaginal discharge [12]. Suspected fetal compromise was defined as a non-reassuring FHR pattern or abnormal Doppler findings on ultrasonography. Non-reassuring FHR was defined as suspicious pattern of FHR in CTG such as loss of variability, recurrent late or variable deceleration, and persistent bradycardia.

The primary outcome was the rate of maternal sepsis as a maternal outcome, and the incidence of either clinical or culture-proven neonatal sepsis and neonatal death as neonatal outcomes. Maternal sepsis was defined as the presence of clinical infectious signs such as fever above 38°C, heart rate higher than 90 beats per minute (bpm), breathing rate higher than 20 bpm, oliguria, and probable or confirmed infection by culture in blood. Clinical neonatal sepsis was defined as the presence of clinical infectious signs such as abnormal C-reactive protein (CRP), temperature instability, diminished spontaneous activity, less vigorous sucking, apnea, bradycardia, respiratory distress, vomiting, diarrhea, abdominal distention, jitteriness, seizures, and jaundice [13]. Culture-proven neonatal sepsis was defined as a positive culture of a known pathogen from blood or cerebrospinal fluid, and the presence of one or more clinical signs of infection. Clinical signs of infection were respiratory distress, apnoea, lethargy, abnormal level of consciousness, circulatory compromise including hypotension, poor perfusion, need for inotropic support, volume expansion, temperature instability (temperature $< 36°C$ or $\geq 38°C$), or a combination thereof [14,15]. Antibiotic therapy was continued for 7–10 days in these neonates.

Secondary neonatal outcomes included other neonatal morbidities such as mechanical ventilation, RDS, BPD, surfactant administration, grade 3–4 IVH, periventricular leukomalacia (PVL), convulsion, NEC, retinopathy of prematurity (ROP), admission to the NICU, and duration of stay in the NICU. Mechanical ventilation included intermittent positive pressure ventilation, continuous positive airway pressure, or high-frequency ventilation. RDS was defined as respiratory distress, which was confirmed by chest radiography and the need for ventilator support in clinical examination. IVH and PVL were diagnosed via skull ultrasonographic examination. NEC was diagnosed by clinical symptoms including poor oral feeding, blood in the stool, frequent vomiting of bile-coloured fluid, abdominal distention, and radiographic findings [16]. ROP was diagnosed and graded according to the International Classification of Retinopathy of Prematurity revisited [17].

Secondary maternal outcomes were divided into antepartum and postpartum complications, respectively. Antepartum complications included antepartum fever, CRP elevation, antepartum hemorrhage, cord prolapse, and intrauterine fetal death. Postpartum complications included the primary cesarean section rate, postpartum fever, endometritis, postpartum hemorrhage, wound infection, deep vein thrombosis, and chorioamnionitis. A primary cesarean section was defined as the total percentage of caesarean deliveries for women without a history of previous caesarean delivery [18]. Chorioamnionitis was a trial entry of exclusion criteria, but the result of maternal outcomes was defined as a positive culture in amniotic fluid or inflammatory changes in visual/microscopic evaluation of the placenta in both groups after delivery.

Ethics

This study was conducted retrospectively. This study was carried out in accordance with the principles outlined in the Declaration of Helsinki, and the privacy of all subjects was protected. Only investigators had the permission to review personal medical records, and data anonymity was applied during data management. Because this is a retrospective study and authors planned to investigate the medical records, requirement for informed consent was approved exemption and the study protocol had been approved by the Institutional Review Board of each hospital (Institutional Review Board of Severance Hospital, 4-2017-0252; Institutional Review Board of CHA University Bundang medical center, CHAMC 2017-04-019-004; Institutional Review Board of Seoul St. Mary's Hospital, KC17RCDI0245; Institutional Review Board of Konkuk University Medical center, KUH1040063; Institutional Review Board of Seoul National University Bundang Hospital, B-1705/396 – 103; Institutional Review Board of Busan Paik Hospital, 17–0071; Institutional Review Board of Samsung Medical Center, SMC 2017-04-071; Institutional Review Board of Dongguk University Ilsan Hospital, 2017-54; Institutional Review Board of Asan Medical Center, 2017 – 0538; Institutional Review Board of Inha University Hospital, 2017-04-018-001; Institutional Review Board of Cheil General Hospital and Women's Healthcare Center, CGH-IRB-2017-20; Institutional Review Board of Ajou University School of Medicine, AJIRB-MED-MDB-17-113).

Statistical analysis

Continuous variables are expressed as means and standard deviations, while categorical variables are expressed as numbers and percentages. To evaluate the differences in outcomes according to management, we compared continuous variables using the two-sample t-test or Wilcoxon rank-sum test and categorical variables using the Chi-square test or Fisher's exact test between immediate delivery and expectant management. The association between delivery timing for women with PPROM and neonatal outcomes was evaluated through the calculation of adjusted odds ratio (OR) in a logistic regression analysis. The reference group was the immediate delivery and OR adjusted for maternal age, and gestational age at the diagnosed PPROM. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). P-values < 0.05 were considered statistically significant.

Results

Demographic and obstetric outcomes in the study population

A total of 2,429 eligible women were screened, and 1,072 women were enrolled. Of those, 782 women were assigned to the immediate delivery group, and 290 were assigned to the expectant management group (Fig. 1).

The mean maternal age was 33.4 ± 4.7 years and the mean gestational age at the time of PPROM was 35.5 ± 0.9 weeks of gestation. A total of 686 (64.0%) women were nulliparous and 164 (15.3%) had a previous cesarean section. The mean gestational age at delivery was 35.6 ± 0.8 weeks of gestation and 465 (43.4%) women underwent cesarean delivery. The mean neonatal birthweight was 2565.1 ± 342.8 g. Clinical or culture-proven neonatal sepsis occurred in 78 (7.3%) of the 1,072 neonates, and two neonatal deaths occurred in the immediate delivery group.

Demographic and obstetric outcomes of the study groups are presented in Table 1. There were significant differences in maternal age, gestational age at the time of PPROM, and parity between the two groups. The mean gestational age at the time of PPROM was 35 gestational weeks in both groups; however, the distribution of earlier gestational age was greater in the expectant management group than that in the immediate delivery group. In the expectant management group, 54.1% of women were diagnosed with PPROM at 34^{+0}–34^{+6} weeks of gestation, compared to 22.6% of those in the immediate delivery group ($p < 0.0001$). Women in the immediate delivery group were more likely to have a history of previous cesarean delivery than those in the expectant management group (19.3% vs 4.5%, $p < 0.0001$). Women in the expectant management group were more likely to receive antenatal corticosteroids (14.5% vs 3.3%, $p < 0.0001$), antibiotics (98.6% vs 85.8%, $p < 0.0001$), and tocolytic agents (24.1% vs 3.7%, $p < 0.0001$).

Women in the expectant management group were delivered at earlier gestational age (35.4 ± 0.7 weeks vs 35.7 ± 0.8 weeks, $p < 0.0001$) and had a longer latent period compared to those in the immediate delivery group (2.8 ± 2.9 days vs 0.5 ± 0.9 days, $p < 0.0001$). There was a significantly higher incidence of cesarean delivery in the immediate delivery group than in the expectant management group (50.8% vs 23.4%, $p < 0.0001$). More neonates born in the expectant management group showed smaller birthweights ($p < 0.0001$). All other maternal demographics and obstetric outcomes were similar between the two groups.

Primary maternal and neonatal outcomes

Results of maternal and neonatal outcomes are presented in Table 2. All neonatal sepsis and clinical neonatal sepsis were more frequently observed in the expectant management group (all, $p < 0.0001$); however, there was no significant difference in culture-proven neonatal sepsis in both groups ($p = 0.2108$). Two neonatal deaths occurred in the immediate delivery group. One neonate was complicated by culture-proven neonatal sepsis, and the other was due to unknown origin. However, there was no significant difference in neonatal death between the immediate delivery group and the expectant management group

(p = 0.3899). Maternal sepsis occurred in the immediate delivery group, but there was no significant difference between the two groups.

Secondary neonatal outcomes

Neonates born in the immediate delivery had a significant need for surfactant compared to those delivered after expectant management (6.1% vs 2.9%, p = 0.0102). The incidence of ROP, hyperbilirubinemia, admission to the NICU, and administration of antibiotics were significantly higher in neonates born in the expectant management group (all, p < 0.0001) than those born in the immediate delivery group. The period of NICU stay showed significantly longer in the expectant management group (p = 0.0052). Other neonatal outcomes including RDS, BPD, PVL, convulsion, NEC, and hypoglycemia were not significantly different between the two groups. Grade 3–4 IVH was not occurred in both groups (Table 2).

Secondary maternal outcomes

In secondary maternal outcomes, the proportion of primary cesarean section was significantly higher in the immediate delivery group than in the expectant management group (31.5% vs 19.0%, p < 0.0001). Women in the expectant management group had a higher frequency of CRP elevation during the latent period (21.4% vs 9.0%, p < 0.0001); however, other antenatal and postpartum complications did not differ between the two groups. Antepartum haemorrhage and IUFD was not occurred in both group (Table 2).

Associated risk of expectant management compared to immediate delivery

Compared with immediate delivery, expectant management was associated with a reduced risk of surfactant administration in premature infants (OR 0.28, 95% CI 0.13–0.62) and primary cesarean section (OR 0.47, 95% CI 0.33–0.68). However, neonates born from mothers managed expectantly were associated with a higher risk of clinical neonatal sepsis (OR 3.11, 95% CI 1.83–5.28), NICU admission (OR 1.80, 95% CI 1.29–2.51), hyperbilirubinemia (OR 2.10, 95% CI 1.54–2.86), and antibiotic administration (OR 6.37, 95% CI 4.47–9.08). Women in the expectant management group had a significantly increased risk of fever and CRP elevation during latent period (OR 1.96, 95% CI 1.02–3.77 and OR 2.41, 95% CI 1.60–3.62, respectively). However, there was no significantly increased risk of culture-proven neonatal sepsis in the expectant management group. (Table 3).

Subgroup Analysis

A subgroup analysis was performed in women who were diagnosed with PPROM at 34^{+0}–34^{+6} weeks of gestation. Of the 335 women, 52.8% (177/335) underwent immediate delivery after the diagnosis of PPROM and 47.2% (158/335) were managed expectantly. Women in the immediate delivery group showed older age (34.07 ± 4.23 vs 31.70 ± 4.88, p < 0.0001) and earlier gestational age at delivery (34.55 ± 0.34 vs 34.95 ± 0.46, p < 0.0001). Neonatal complications (e.g., BPD, grade 3 or 4 IVH, NEC and ROP) and maternal complications (e.g., maternal sepsis, cord prolapse, and wound infection) were not presented in both groups.

Similar to the entire cohort, women in the expectant management group showed more frequent neonatal complications (e.g., clinical neonatal sepsis, neonatal hyperbilirubinemia, antibiotic administration for neonates, and maternal CRP elevation in the latent period), and had a lower frequency of surfactant administration in neonates and primary cesarean section. However, unlike in the entire cohort, expectant management for women who were diagnosed with PPROM at 34^{+0}–34^{+6} weeks of gestation was significantly associated with decreased risk of mechanical ventilation for premature neonates (OR 0.49, 95% CI 0.26–0.96) and neonatal RDS (OR 0.33, 95% CI 0.15–0.73) (Table 4).

Discussion

In this retrospective study, we evaluated neonatal and maternal outcomes following different delivery timing for the management of PPROM during the late preterm period. Neonates in the expectant management group required less surfactant use; however, they were associated with an increased risk of clinical neonatal sepsis, admission to the NICU, hyperbilirubinemia, and antibiotic administration. Women managed expectantly were associated with a lower risk of primary cesarean section; however, they had a higher risk of antepartum fever and CRP elevation. There were no significant differences in maternal sepsis and neonatal death between the two groups.

Neonatal sepsis is one of the main causes of neonatal mortality and long-term complications of development, especially in preterm infants. Rupture of the membrane may result in loss of a barrier to ascending infection from the lower genital tract, and it is possible that the prolonged latent period in PPROM can increase the risk for neonatal sepsis. To reduce the risks of late-onset sepsis, NEC, and mortality, broad-spectrum antimicrobial agents should be administered. In our study, the incidence of clinical neonatal sepsis was higher in the expectant management group. This may lead to more NICU admissions and antibiotics use. However, infectious complications, including severe IVH, PVL, NEC, and neonatal death, were not significantly increase in the expectant management group.

Several studies have attempted to demonstrate the significant benefits or risks of neonatal sepsis in immediate delivery and expectant management for women with PPROM; however, optimal management remains controversial. Similar to our findings, Ocviyanti D [19] et al. and Gyamfi-Bannerman et al. [20] reported that the long interval between membrane rupture and delivery was associated with an increased risk for neonatal sepsis after adjusting for gestational age. In contrast, other studies demonstrated that the prolonged latent period was not associated with the risk of neonatal sepsis [21–23]. In randomised controlled trials, the PPROMT trial and PPROMEXIL studies suggest that expectant management for women with PPROM has benefits without a significant increase in the risk of neonatal sepsis [8,9,24]. This inconsistency may be explained by the difficulty in assessing clinical neonatal sepsis. The clinical diagnosis of infection in a neonate is unreliable [25] because clinical manifestations of neonatal sepsis are nonspecific and laboratory values are inaccurate [26]. A high index of suspicion for the diagnosis of clinical neonatal sepsis is required for early diagnosis, and diagnosis can only be varied and rely on physicians. Clinical neonatal sepsis is diagnosed more often in the expectant management group probably because

neonates in that group are more likely to be exposed to infection during the latent period. However, there was no significant difference in culture-proven neonatal sepsis.

Neonates in the expectant management group required less surfactant use after controlling for gestational age. This may be associated with gestational age at delivery and antenatal corticosteroid administration. In our study, although gestational age at delivery was higher in the immediate delivery group, 41.6% of women in the immediate delivery group were diagnosed with PPROM and delivered after 36 weeks of gestation; however, a high proportion of women (54.1%) with expectant management were diagnosed with PPROM at 34^{+0}–34^{+6} weeks and delivered at 35^{+0}–35^{+6} weeks of gestation (44.5%). In the subgroup analysis of women with PPROM at 34 weeks of gestation, expectant management was associated with a reduced risk of surfactant administration as well as the need for mechanical ventilation and neonatal RDS. Women managed expectantly could be prolonged gestational age and may be injected a complete course of antenatal corticosteroids therapy during the latent period. This finding was consistent with those of previous studies. Earlier gestational age is associated with more frequent neonatal respiratory complications than a longer latent period [22,27]. The results of our study and other studies are rational because gestational age and antenatal corticosteroid therapy at ≥ 34 weeks of gestation can improve fetal lung maturation and reduce neonatal respiratory complications [28,29].

Women delivered immediately after PPROM showed a significantly higher frequency of cesarean section. The number of women who previously underwent a cesarean section was higher in the immediate delivery group, and the primary cesarean section rate was also higher in the immediate delivery group than that in the expectant management group. This may be related to the unfavourable cervix and the concerning about fetal distress with oligohydramnios during labor. However, primary cesarean section is associated with higher morbidity and mortality, such as placenta accrete, cesarean section scar pregnancy, postpartum hemorrhage, hysterectomy, and subsequent uterine rupture [18,30]. To reduce maternal complications related to cesarean section, expectant management of PPROM during the late preterm period may be helpful.

Women managed expectantly show a higher incidence of non-reassuring FHR pattern, CRP elevation, and fever during the latent period. These findings could be applied to predict chorioamnionitis, which is necessary for prompt delivery [31,32]. However, low sensitivity limits clinical utility [33].

For the time of delivery on PPROM, several guidelines recommend that delivery should be considered at 32 weeks [6] or 34 weeks of gestation [3,34]. After 34 weeks of gestation, the risk for developing intrauterine infection-related adverse perinatal outcomes exceeds the advantages of continuing the pregnancy. As per these guidelines, in Korea, immediate delivery is usually performed for the management of PPROM at 34–37 weeks. However, the management of pregnancies complicated with PPROM during the late preterm period is challenging. In contrast to several national guidelines, some studies have demonstrated that expectant management does not increase the risk of adverse perinatal outcomes, compared to immediate delivery. In the Cochrane review, the rate of neonatal sepsis was not significantly different between the immediate delivery and expectant management for PPROM [11]. Expectant management was

associated with decreased neonatal RDS and need for ventilation; however, it was associated with an increased incidence of chorioamnionitis. For preferable maternal and neonatal outcomes, the authors suggest that expectant management with careful monitoring should be considered in women with PPROM before 37 weeks of gestation with no contraindications to continuing the pregnancy. However, this meta-analysis included a wide range of gestational ages between 25 and 37 weeks of gestation; thus, the results could not be applied in women with late PPROM. Several multi-centre randomised controlled trials, which only included women with a late preterm period, were similar to the Cochrane review [8–10, 35]. These studies demonstrated that the rate of neonatal sepsis did not increase in expectant management, and immediate delivery did not improve perinatal outcomes in women with PPROM in the late preterm period. Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians reported that expectant management is recommended for uncomplicated PROM before 37 weeks despite positive results for Streptococcus B and antibiotic prophylaxis administration at admission [36]. Based on these studies and our study, expectant management for PPROM in the late preterm period is a reasonable option.

For optimal expectant management of PPROM during the late preterm period, there are several recommendations. It is important to distinguish patients who have clear indications for delivery. Women with strongly suspected chorioamnionitis, significant placental abruption, and non-reassuring fetal status should be delivered immediately. To reduce the risk of intra-amniotic infection, antibiotics for group B streptococcus prophylaxis should be administered. Periodic assessment for infection, fetal well-being, umbilical cord prolapse, and regular uterine contraction should be performed. Evidence of tocolysis was insufficient.

Our study had several limitations. The retrospective data review was limited by the accuracy of previously recorded information, and not all data fields were available for each patient. In addition, most hospitals were referral centres; thus, this study was subject to preadmission selection bias. Data on composite neonatal morbidity may not appropriately represent future childhood developmental outcomes. However, to the best of our knowledge, this is the first study to evaluate immediate delivery and expectant management in women with PPROM during the late preterm period in multi-tertiary centers in Korea. Our results may be useful for patient counselling and for further research on the optimal timing of delivery in women with PPROM in the late preterm period. In addition, we evaluated various neonatal complications and short-term neonatal morbidities.

In conclusion, we evaluated the benefits and risks of immediate delivery and expectant management in women with late preterm PPROM. These findings may provide a foundation for future clinical research to investigate the optimal timing of delivery for PPROM during the late preterm period, considering both short- and long-term pregnancy outcomes.

Declarations

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Correspondence and requests for materials should be addressed to Kim YN or Yang JI.

Author contributions

Yang JI. and Kim YN. conceived and designed this project; Kwon H., Sul AR., Jung Y., Kim J, Park JJ, Lee J, Yang JI, and Kim YN. performed the analysis; Kwon H., Kim YN., and Yang JI. wrote the manuscript; Kwon H., Kang SH., Ko HS., Kwon JY., Kwon HS., Kim YN., Oh KJ., Oh M., Oh SY., Lee MY., Choi SR., Han YJ., and Yang JI. helped in data collection; Kim YN. and Yang JI. supervised this project; Kwon H. and Kim YN. helped in data analysis. All authors have contributed to read and agreed to the final content of the manuscript for submission.

Competing interests

The authors declare no competing interests.

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Tables

Table 1. Demographic characteristics and obstetric outcomes of the study groups

	Immediate delivery (n=782)	Expectant management (n=290)	p-value
Maternal age, years	33.8 ± 4.6	32.5 ± 4.7	0.0004
Gestational age at PPROM, weeks	35.6±0.8	35.0±0.7	<0.0001
34.0 - 34.6 weeks	177 (22.6)	158 (54.1)	
35.0 - 35.6 weeks	280 (35.8)	91 (31.7)	
36.0 - 36.6 weeks	325 (41.6)	41 (14.2)	
Nulliparous	473 (60.5)	213 (73.4)	<0.0001
Diabetes	46 (5.9)	21 (7.2)	0.4142
Chronic hypertension	5 (0.6)	1 (0.3)	1.0000
Prior preterm delivery history	47 (6.0)	10 (3.5)	0.0968
Previous CS	151 (19.3)	13 (4.5)	<0.0001
ART	64 (8,2)	20 (6.9)	0.6182
Cervical or Vaginal swab at diagnosis	106 (13.6)	90 (31.0)	
Any culture, positive	45/106 (42.5)	30/90 (33.3)	0.2381
Group B streptococcus, positive	5/106 (4.7)	1/90 (1.1)	0.1442
Antepartum Corticosteroid	26 (3.3)	42 (14.5)	<0.0001
Antibiotics treatment	671 (85.8)	286 (98.6)	<0.0001
Use of tocolytics	29 (3.7)	70 (24.1)	<0.0001
Obstetric outcomes			
Gestational age at delivery, weeks	35.7±0.8	35.4±0.7	<0.0001
34.0 - 34.6 weeks	159 (20.3)	84 (29.0)	
35.0 - 35.6 weeks	272 (34.8)	129 (44.5)	
36.0 - 36.6 weeks	345 (44.1)	75 (25.8)	
≥37.0 weeks	6 (0.8)	2 (0.7)	
Latent period, days	0.5±0.9	2.8±2.9	<0.0001
Mode of delivery			<0.0001
VD	385 (49.2)	222 (76.6)	
CS	397 (50.8)	68 (23.4)	
Birthweight,g	2592.6±347.5	2490.1±318.3	<0.0001

Data are represented as mean ± standard deviation or no. (%)

PPROM, preterm prelabr rupture of membranes; CS, cesarean section; ART, assisted reproductive technology; VD, vaginal delivery

The latent period was defined as the period from the diagnosis of rupture of membranes to delivery.

Positive results of cervical or vaginal swab included *Candida albicans*, *Ureaplasma urealyticum*, *Ureaplasma parvum*, *Mycoplasma hominis*, *Chlamydia tracomatis*, *Gardnerella vaginalis*, *Escherichia coli*, *Leclercia adecarboxylata*, and Group B streptococcus.

Table 2. Neonatal and maternal outcomes

	Immediate delivery (n=782)	Expectant management (n=290)	p-value
Primary outcomes			
Maternal sepsis	1 (0.13)	0 (0.0)	0.5424
Neonatal Sepsis	32/771 (4.2)	46/284 (16,2)	<0.0001
Clinical	29/771 (3.8)	45/284 (15.8)	<0.0001
Culture-proven	5/771 (0.6)	4/284 (1.4)	0.2108
Neonatal deaths	2/778 (0.3)	0/287 (0.0)	0.3899
Secondary outcomes			
Neonatal outcomes			
Mechanical ventilation§	77/773 (10.0)	29/286 (10.1)	0.9315
Respiratory distress syndrome	53/766 (6.9)	17/282 (6.0)	0.6090
Bronchopulmonary dysplasia	1/770 (0.1)	0/282 (0.0)	0.1644
Surfactant administration	47/767 (6.1)	8/278 (2.9)	0.0102
Periventricular leukomalacia	37/769 (4.8)	17/281 (6.0)	1.0000
Convulsion	9/769 (1.2)	2/282 (0.7)	0.3029
Necrotizing enterocolitis	0/769 (0.0)	1/282 ((0.4)	0.0872
Retinopathy of prematurity	1/760 (0.1)	1/263 (0.4)	<0.0001
Apgar score <7 at 1 min	107/781 (13.7)	34/288 (11.8)	0.4166
Apgar score <7 at 5 min	10/781 (1.3)	6/288 (2.1)	0.3375
Admission to NICU	303/775 (39.1)	191/287 (66.6)	<0.0001
Mean length of NICU stay	8.41±7.5	9.07±6.3	0.0052
Hypoglycaemia	43/768 (5.6)	15/279 (5.4)	0.1151
Hyperbilirubinemia	318/768 (41.4)	184/283 (65.0)	<0.0001
Antibiotics given	246/769 (32.0)	229/285 (80.4)	<0.0001
Duration, days	5.12±3.15	4.84±2.96	0.3307
Maternal outcomes			
<Antepartum complications>			
Antepartum fever	28 (3.6)	18 (6.2)	0.0594
Antepartum CRP elevation	70 (9.0)	62 (21.4)	<0.0001
Cord prolapse	1 (0.1)	0 (0.0)	0.5424
<Postpartum complications>			
Primary cesarean section*	246 (31.5)	55 (19.0)	<0.0001
Postpartum fever	33 (4.2)	19 (6.6)	0.1144
Postpartum endometritis	0 (0.0)	1 (0.3)	0.1004

Postpartum hemorrhage	5 (0.6)	1 (0.3)	0.5658
Wound infection	3 (0.4)	0 (0.0)	0.2909
DVT	0 (0.0)	1 (0.3)	0.1004
Chorioamnionitis†	27 (3.5)	12 (4.1)	0.5945

Data are represented as mean ± standard deviation or no. (%)

IVH, intra-ventricle hemorrhage; NICU, neonatal intensive care unit; CRP, C-reactive protein; DVT, deep vein thrombosis

* Primary cesarean section was defined as cesarean delivery in women who had not undergone a previous cesarean section.

§Mechanical ventilation included intermittent positive pressure ventilation, continuous positive airway pressure, or high frequency ventilation.

†Chorioamnionitis was diagnosed by positive culture in amniotic fluid or histologic inflammatory changes in the gross/microscopic evaluation of the placenta.

Table 3. Adjusted odds ratio of outcomes in expectant management compared to those in the immediate delivery group

	Odd ratio	95% CI	P-value
Neonatal outcomes			
Neonatal Sepsis	2.94	1.76-4.92	<0.0001
Clinical	3.11	1.83-5.28	<0.0001
Culture proven	1.51	0.36-6.44	0.5754
Mechanical ventilation§	0.76	0.46-1.24	0.2657
Respiratory distress syndrome	0.56	0.30-1.03	0.0636
Surfactant administration	0.28	0.13-0.62	0.0017
Periventricular leukomalacia	0.94	0.48-1.82	0.8488
Convulsion	0.37	0.08-1.85	0.2261
Retinopathy of prematurity	5.18	0.27-100.86	0.2777
Low Apgar score¥	1.08	0.37-3.14	0.8859
Admission to NICU	1.80	1.29-2.51	0.0005
Hypoglycemia	0.68	0.36-1.30	0.2437
Hyperbilirubinemia	2.10	1.54-2.86	<0.0001
Antibiotics administration	6.37	4.47-9.08	<0.0001
Maternal outcomes			
Primary cesarean section*	0.47	0.33-0.68	<0.0001
Antepartum fever	1.96	1.02-3.77	0.0427
Antepartum CRP elevation	2.41	1.60-3.62	<0.0001
Postpartum fever	1.50	0.81-2.77	0.2006
Postpartum hemorrhage	0.37	0.04-3.40	0.3793
Chorioamnionitis†	0.76	0.37-1.60	0.4731

* Primary cesarean section was defined as cesarean delivery in women who had not undergone a previous cesarean section.

§Mechanical ventilation included intermittent positive pressure ventilation, continuous positive airway pressure, or high frequency ventilation.

¥Low Apgar score defined as an Apgar score below 7 at 5 minutes.

†Chorioamnionitis was defined as a positive culture in amniotic fluid or inflammatory changes in the visual/microscopic evaluation of placenta postpartum.

Odds ratio adjusted for maternal age, pre-pregnancy body mass index, and gestational age at preterm premature rupture of membranes (PPROM)

Table 4. Outcomes and adjusted odds ratio of expectant management compared to the immediate delivery group in women diagnosed with PPROM between 34 weeks and 34 weeks and 6 days of gestation

	Immediate delivery (n=177)	Expectant management (n=158)	Odds ratio (95% confidence interval)	p-value
Neonatal outcomes				
Neonatal Sepsis	15/174 (8.6)	29/156 (18.6)	2.02 (1.01-4.06)	0.0078
Clinical	14/174 (8.0)	29/156 (18.6)	2.21 (1.07-4.50)	0.0045
Culture proven	3/174 (1.7)	1/156 (0.6)	0.29 (0.03-2.92)	0.3693
Neonatal death	1/177 (0.3)	0/157 (0.0)		0.3456
Mechanical ventilation*	39/175 (22.3)	16/156 (10.3)	0.49 (0.26-0.96)	0.0033
Respiratory distress syndrome	32/174 (18.4)	9/156 (5.8)	0.33 (0.15-0.73)	0.0005
Surfactant administration	28/174 (16.1)	4/152 (2.6)	0.16 (0.05-0.48)	<0.0001
Periventricular leukomalacia	20/173 (11.6)	14/155 (9.0)	0.99 (0.45-2.16)	0.4533
Convulsion	5/174 (2.9)	1/155 (0.6)	0.23 (0.03-2.08)	0.1316
Low Apgar score¥	5/177 (2.8)	4/158 (2.5)	1.10 (0.27-4.41)	0.8684
Admission to NICU	137/175 (78.3)	119/157 (75.8)	0.85 (0.49-1.47)	0.5899
Mean length of NICU stay, day	12.70±8.9	11.30±6.52		0.1584
Hypoglycemia	18/174 (10.3)	10/154 (6.5)	0.63 (0.28-1.45)	0.2128
Hyperbilirubinemia	96/174 (55.2)	109/156 (69.9)	2.05 (1.26-3.35)	0.0059
Antibiotics administration	99/175 (56.6)	137/156 (87.8)	5.52 (3.04-10.05)	<0.0001
Duration, day	5.66±3.29	4.86±2.68		0.0413
Maternal outcomes				
<Antepartum complications>				
Antepartum fever	5 (2.8)	8 (5.1)	1.74 (0.53-5.72)	0.2896
Antepartum CRP elevation	22 (12.4)	39 (24.7)	2.82 (1.50-5.27)	0.0037
<Postpartum complications>				
Maternal sepsis	0 (0.0)	0 (0.0)		1.0000
Primary cesarean section	58 (32.8)	21 (13.3)	0.25 (0.14-0.45)	<0.0001
Postpartum fever	11 (6.2)	7 (4.4)	0.83 (0.30-2.29)	0.4697
Postpartum endometritis	0 (0.0)	1 (0.6)		0.2891
Postpartum hemorrhage	1 (0.6)	1 (0.6)	1.45 (0.08-25.61)	0.9358
DVT	0 (0.0)	1 (0.6)		0.2891
Chorioamnionitis†	13 (7.3)	6 (3.8)	0.44 (0.16-1.24)	0.1612

NICU, neonatal intensive care unit; CRP, C-reactive protein; DVT, deep vein thrombosis

* Primary cesarean section was defined as cesarean delivery in women who had not undergone a previous cesarean section.

§Mechanical ventilation included intermittent positive pressure ventilation, continuous positive airway pressure, or high frequency ventilation.

¥Low Apgar score defined as an Apgar score below 7 at 5 minutes.

†Chorioamnionitis was defined as a positive culture in amniotic fluid or inflammatory changes in the visual/microscopic evaluation of placenta postpartum.

Odds ratio adjusted for maternal age and pre-pregnancy body mass index.

Figures

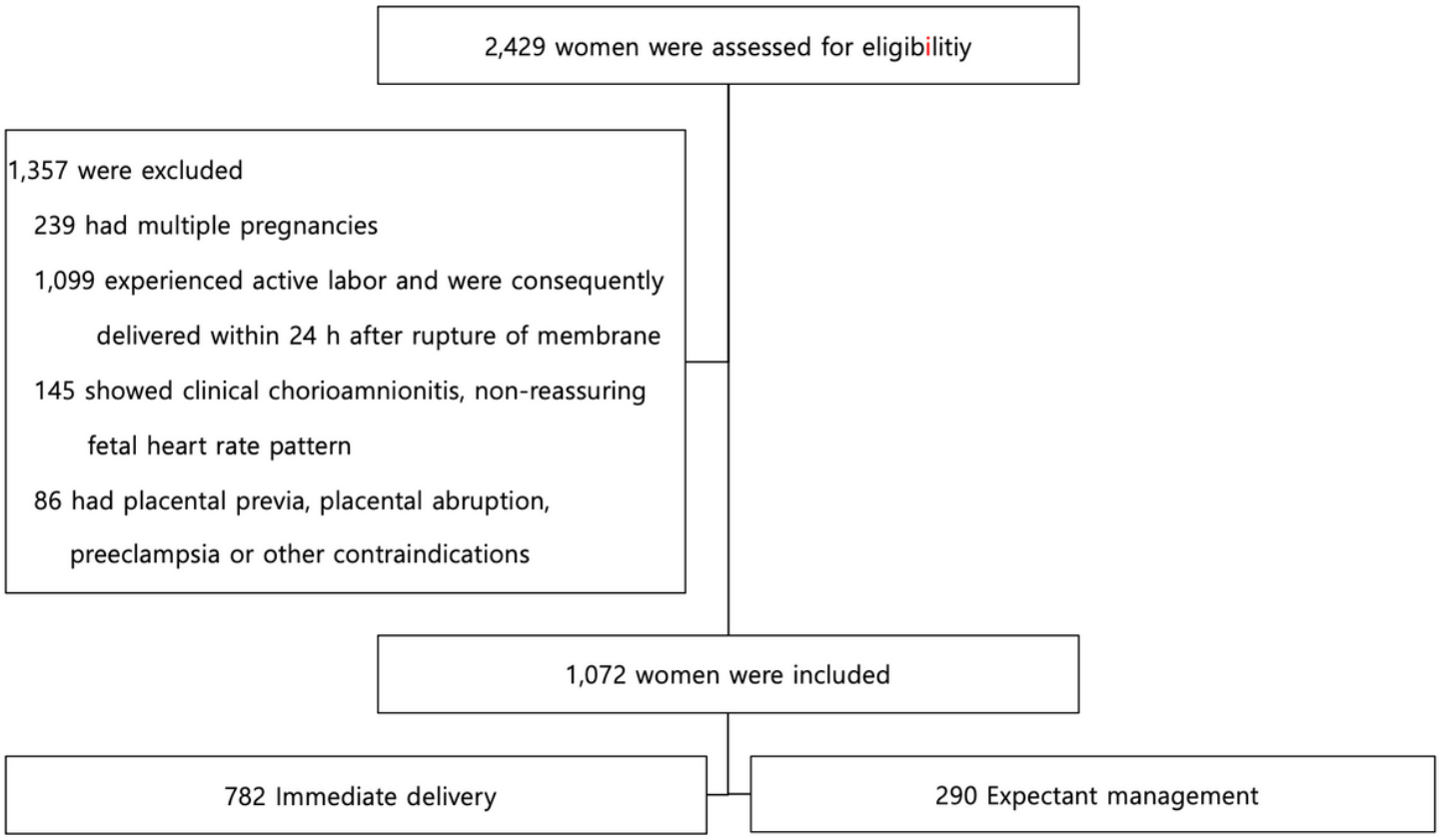

Figure 1

Study population