

## Executive Summary

### A Comparison Study of Perinatal Outcomes of Expectant Management and Immediate Delivery in Late-Preterm Premature Rupture of Membranes

Jeong In Yang<sup>1,2</sup>, Ah Ram Sul<sup>1</sup>, Youjin Jung<sup>1</sup>, Jimin Kim<sup>1</sup>, Ji Jeong Park<sup>1</sup>, Jayoun Lee<sup>1</sup>, Suk Ho Kang<sup>3</sup>, Hyun Sun Ko<sup>4</sup>, Ja Young Kwon<sup>5</sup>, Hayan Kwon<sup>6</sup>, Han-sung Kwon<sup>7</sup>, Young Nam Kim<sup>8</sup>, Kyung Joon Oh<sup>9</sup>, Minkyung Oh<sup>10</sup>, Soo-Young Oh<sup>11</sup>, Mi-Young Lee<sup>12</sup>, Soo Ran Choi<sup>13</sup>, You Jung Han<sup>14</sup>

<sup>1</sup> National Evidence-based Healthcare Collaborating Agency, Seoul, Republic of Korea

<sup>2</sup> Department of Obstetrics and Gynecology, Ajou University School of Medicine, Suwon, Republic of Korea

<sup>3</sup> Department of Obstetrics and Gynecology, Bundang CHA General Hospital, Bundang, Republic of Korea

<sup>4</sup> Department of Obstetrics and Gynecology, School of Medicine, Catholic University of Korea, Seoul, Republic of Korea

<sup>5</sup> Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Severance Hospital, Seoul, Republic of Korea

<sup>6</sup> Department of Obstetrics and Gynecology, Dongguk University Ilsan Medical Center, Ilsan, Republic of Korea

<sup>7</sup> Department of Obstetrics and Gynecology, Konkuk University Medical Center, Seoul, Republic of Korea

<sup>8</sup> Department of Obstetrics and Gynecology, Busan Paik Hospital, College of Medicine, Inje University, Busan, Republic of Korea

<sup>9</sup> Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

<sup>10</sup> Department of Pharmacology, Inje University College of Medicine, Busan, Republic of Korea

<sup>11</sup> Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

<sup>12</sup> Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea

<sup>13</sup> Department of Obstetrics and Gynecology, Inha University hospital, Inha University College of Medicine, Incheon, Republic of Korea

<sup>14</sup> Department of Obstetrics and Gynecology, Cheil General Hospital and Women's Healthcare Center, Dankook University College of Medicine, Seoul, Republic of Korea

## □ Background

Premature rupture of the membranes (PROM) refers to rupture of the fetal

membranes occurring prior to the onset of labor. It is estimated to complicate 20% of all births and 40% of all preterm births. Rigorous evidence suggests that, at term, immediate delivery results in a lower risk of maternal infection and higher maternal satisfaction than a ‘wait and see’ approach (expectant management), without increasing the risks of perinatal morbidity or mortality. Contrastingly, the best management for women with PROM before 37 weeks of gestation has not yet been established (Morris et al, 2016).

Globally, medical practice differs significantly, especially for women who present with PROM beyond 34 weeks gestation (near term). Planned immediate delivery is often practiced. In addition, per the American College of Obstetricians and Gynecologists and the Royal College of Obstetrics and Gynaecology “at 34 0/7 weeks or greater gestation, delivery is recommended for all women with ruptured membranes”, and “delivery should be considered at 34 weeks of gestation.” However, these recommendations are considered to be “based on limited and inconsistent scientific evidence” (Morris et al, 2016).

Thus, unlike PROM at term, preterm PROM is still an unresolved clinical dilemma. A delay can result in the risk of placental abruption, ascending infection, intrapartum fetal distress, and cord prolapse. Therefore, it is imperative that steps are taken to solve the problems resulting from delay with the associated risk of iatrogenic prematurity from immediate delivery. When the fetus has reached, or is close to, viability (23 to approximately 30 weeks of gestation), in so called extreme preterm gestations, there is unanimous consensus that expectant management is beneficial provided there is no established infection and maternal or fetal compromise. This is because preterm fetuses born before 30 weeks are more vulnerable to neonatal mortality, intraventricular hemorrhage, hyaline membrane disease, and necrotizing enterocolitis. However, as the gestational age lengthens towards term, these risks decrease. Both in the short and long term, even mild prematurity is related to a considerable health burden. Therefore,

recommendations for immediate delivery regarding preterm PROM close to term are required to be supported by good clinical evidence (Morris et al, 2016).

## □ Objective

Many controversies have arisen regarding the choice between expectant management and immediate delivery when PROM occurs during the late preterm (between 34 and 37 weeks of gestation). More importantly, no study has been conducted on this subject in Korea.

In this regard, this study aimed to provide evidence regarding the perinatal outcomes from expectant management and from immediate delivery in patients who presented with PROM during the late preterm. This study involved a systematic review of the literature regarding the perinatal outcomes of the two approaches, analysis of patient data, and a questionnaire survey for obstetricians to identify the status of medical treatment in Korea.

## □ Methods

### 1. Systematic review

To analyze and compare the perinatal outcomes of expectant management and immediate delivery of pregnant women who were at 34 to 37 weeks of gestation and presented with PROM, this study conducted a systematic review of related literatures. Three international databases (Ovid-MEDLINE, Ovid-EMBASE, and Cochrane Central Register of Controlled Trials) and 5 Korean domestic databases (KoreaMed, KMBASE, KISS, RISS, and NDSL) were searched along with manual searching of study reference lists; no limitation was applied on publication year or language. Of the peer-reviewed original articles published in English or Korean language, only randomized controlled trials were selected. The final articles from the databases were independently reviewed and agreed on by 2 or more researchers. For the risk of bias

assessment on the selected articles, the Cochrane risk of bias tool was used. When possible, this study involved performing a meta-analysis on the clinical outcome variables, or providing a qualitative description when a quantitative synthesis was not possible or appropriate.

## **2. Case series study**

Case series study was conducted on pregnant women who were clinically diagnosed with PROM from 34 weeks +0 days to 36 weeks +6 days of gestation. Medical records over the last decade (Jan. 1, 2007 to Dec. 31, 2016) were investigated from 12 hospitals in Korea and were analyzed retrospectively. The subjects chosen based on the selection criteria were categorized into two groups: the expectant management and the immediate delivery group, depending on whether an aggressive treatment (labor induction or caesarean delivery) was initiated within 24 hours after the rupture of membranes. Among the subjects, those pregnant women who were placed under aggressive treatment before 24 hours after the rupture were categorized into the immediate delivery group and the others into the expectant management group. Based on the survey, data on pregnant women's characteristics, antenatal complications, delivery outcomes, postpartum complication, and newborns' complications between the expectant management group and the immediate delivery group were compared and analyzed.

## **3. Questionnaire survey on obstetricians**

A survey study was conducted among obstetricians responsible for treating pregnant women with PROM before 37 weeks of pregnancy in hospitals or higher institutions in Korea. A structured questionnaire was used to survey specialists who were attending an academic conference (Korean Society of Maternal Fetal Medicine, July 1, 2017). The clinicians were asked questions related to treatment of PROM before 34 weeks and between 34 and 37 weeks of gestation.

Key questions included the respondent's choice of expectant management or immediate delivery (labor induction or caesarean delivery within 24 hours) for preterm PROM, the reasons for selecting immediate delivery, the timing of selective labor induction during expectant management, and contributing factors to immediate delivery decisions during expectant management. In addition, data was collected regarding the respondents' sex, age, institution, hospital location, type of antibiotics or corticosteroids prescribed to pregnant women, and the maximum week of pregnancy in which corticosteroids were prescribed. We asked clinicians to rate the importance of factors that contribute to the delivery decision during expectant management using a 4-point scale. The contributing factors suggested included reduction of residual amniotic fluid, chorioamnionitis symptoms, an increase in leukocytes or c-reactive proteins (CRP) values, problems with the amniotic fluid test, and the pregnant woman's preference.

## □ Results

- In the systematic review, 4 randomized clinical trials were included. In women whose pregnancy was complicated by late PROM, although the risk of clinical chorioamnionitis was higher after expectant management, no significant differences were observed for more critical outcomes (neonatal mortality and neonatal sepsis). Moreover, the incidence of neonatal respiratory distress syndrome (RDS) was decreased in the expectant management group.
- In the case series study, data from 1,072 pregnant women (290 for expectant management and 782 for immediate delivery), including the records from 12 hospitals in Korea for the last decade (2007 to 2016) were analyzed retrospectively. Among the pregnant women's characteristics, multipara, old age pregnancy, and a higher frequency of previous caesarean section were believed to have been key factors in making the decisions for immediate delivery after a PROM diagnosis. The cases in which at least one antenatal or postpartum complication occurred many times among various complications were analyzed. The expectant management group had significantly more antenatal and postpartum complications compared with immediate delivery. For delivery outcomes, caesarean delivery rates were higher in the immediate delivery group than in the expectant management group. With regard to neonatal outcomes, the two groups showed no difference in neonatal

mortality, but the frequency of neonatal sepsis was significantly higher in the expectant management group compared with that of the immediate delivery group.

- The respondents for the questionnaire survey were 112 obstetricians. Cephalosporins were the most frequently reported antibiotics prescribed before 37 weeks of gestation in women with PROM, followed by the single use of macrolides or the combined administration of macrolides and metronidazole. For the use of corticosteroids to promote maturation of the lungs, betamethasone was used 52% of the time, which was more frequent than dexamethasone (43%). Approximately 50% of the respondents reported that 34 weeks was the maximum week to administer antibiotics. In cases when pregnant women with PROM before 34 weeks reached her 34th week and in case in which they had PROM between 34 and 37 weeks, expectant management was frequently chosen compared with immediate delivery. In addition, the contributors to delivery decisions during expectant management were reported in the following order: chorioamnionitis symptoms, problems with the amniotic fluid, and problems in the blood test results.

## 1. Systematic review

Articles comparing the perinatal outcomes of expectant management and immediate delivery for pregnant women with PROM during the late preterm were critically appraised. The patients who were given aggressive treatment (labor induction or caesarean delivery) within 24 hours after the rupture of the membranes were categorized as the immediate delivery group and remainder were the expectant management group.

In total, 4 randomized controlled trials were analyzed. A total of 2,686 subjects were included: 1,339 in the expectant management group and 1,347 in the immediate delivery group. The review results are divided into three categories: fetal outcomes, neonatal outcomes, and maternal outcomes.

With regard to fetal outcomes, fetal death was the primary outcome and umbilical cord prolapse was the secondary outcome.

In 3 out of 4 studies which reported fetal death as an outcome, it did not occur in either the expectant management or immediate delivery group. However, the other study reported a fetal death due to acute suppurative chorioamnionitis in the immediate delivery group at the gestational age of 35 weeks, which accounted for 0.1% (1/923) of the pregnant women.

Umbilical cord prolapse was reported in 3 studies. A meta-analysis of 2

studies found no statistically significant difference between the expectant management group and the immediate delivery group (RR 0.57, 95% CI 0.12 ~ 2.71).

The primary neonatal outcomes included death, sepsis, and respiratory distress syndrome (RDS). Secondary outcomes included gestational age, weight at birth, Apgar score, ventilation, total hospitalization, and neonatal intensive care unit (NICU) admission.

Neonatal death did not occur in 2 out of 4 studies. A meta-analysis of the 2 studies showed no statistically significant difference in neonatal mortality between the expectant management group and the immediate delivery group (RR 0.63, 95% CI 0.08 ~ 5.13).

Neonatal sepsis was reported differently as there were varying definitions for total, proven, and suspected sepsis in the 4 studies. However, no statistically significant difference was observed between the expectant management group and the immediate delivery group (total neonatal sepsis: 4 studies, RR 1.39, 95% CI 0.90 ~ 2.16).

Neonatal RDS was also reported in the 4 studies. Meta-analysis showed that the expectant management group had a significantly lower risk of RDS compared with the immediate delivery group (RR 0.68, 95% CI 0.51 ~ 0.91).

The gestational age at birth (2 studies) was significantly higher in the expectant management group (MD 3.43, 95% CI 2.54 ~ 4.31). The weight at birth was also significantly larger in the expectant management group (MD 89.92, 95% CI 59.32 ~ 120.52). However, no statistically significant difference between the groups was observed in the Apgar score measured at 1 minute (1 study) and 5 minutes (3 studies) after birth.

The rate for ventilation of newborns was reported in 3 studies. Meta-analysis showed that the expectant management group had a significantly lower rate for ventilation of newborns than the immediate delivery group (RR 0.75, 95% CI 0.58 ~ 0.97).

In addition, newborns' total length of hospitalization, the rates of NICU admission, the rates of hypoglycemia, and rates of hyperbilirubinemia were

not statistically significantly different between the groups.

The primary maternal outcomes were sepsis, chorioamnionitis, endometritis, and frequency of caesarean delivery. Secondary outcomes were hemorrhage, fever, postpartum use of antibiotics, and length of hospitalization.

Maternal sepsis was reported as an outcome measurement in 2 studies. In one, maternal sepsis did not occur, and in the other, maternal sepsis occurred in 0.4% (1/266) of the expectant management group and 2.3% (6/266) of the immediate delivery group; this difference was not statistically significant.

Chorioamnionitis was reported in 3 studies. Meta-analysis found that the expectant management group had a significantly higher risk of clinical chorioamnionitis than the immediate delivery group (RR 3.41, 95% CI 1.51 ~ 7.69). Endometritis was reported in 3 studies, with no statistically significant difference in the incidence rate between the two groups.

The frequency of caesarean delivery was reported in 4 studies. Meta-analysis showed no statistically significant difference between the expectant management group and the immediate delivery group (RR 0.98, 95% CI 0.63 ~ 1.50).

Meta-analysis results of hemorrhage outcome (3 studies) confirmed that the expectant management group had a statistically significant higher risk of antepartum or intrapartum hemorrhage than the immediate delivery group (RR 1.75, 95% CI 1.12 ~ 2.72).

Meta-analysis of 3 out of 4 studies which reported the length of hospitalization showed that the expectant management group had a statistically significantly longer hospitalization than the immediate delivery group (MD 2.76, 95% CI 1.48 ~ 4.04).

## **2. Case series study**

Among 2,429 pregnant women, 1,072 met the selection criteria. A total of 290 pregnant women were included in the expectant management group and



782 in the immediate delivery group.

The immediate delivery group had a higher age compared with the expectant management group, who were more likely to have delivered at least 1 child in the past, and had a significantly higher frequency of previous caesarean delivery. The average number of weeks when diagnosed with PROM was statistically significantly higher in the immediate delivery group ( $35.5 \pm 0.6$ ) than in the expectant management group ( $35.0 \pm 0.5$ ). In addition, antibiotics and corticosteroids were used more often from diagnosis to delivery in the expectant management group. On the other hand, no difference was observed between the two groups for frequency of diabetes, chronic hypertension, or previous preterm birth.

The incidence of fever, CRP elevation, clinical chorioamnionitis, umbilical cord prolapse, and fetal heart rate deceleration were investigated as antenatal complications. The expectant management group was significantly more likely to have at least one antenatal complication compared with the immediate delivery group.

The mean number of weeks at birth was 35.5 in the immediate delivery group, which was higher than the expectant management group mean of 35.3 weeks, but this likely relates to the difference in the number of weeks of pregnancy at the time of diagnosis between the two groups. The expectant management group had an extension of 3 days on average for the pregnancy period. No difference was observed in the frequency of labor induction between the two groups. On the other hand, caesarean delivery was reported for 50.8% of the immediate delivery group, which was significantly higher than the 23.5% in the expectant management group. Even when excluding those in the immediate delivery group who had previous caesarean deliveries, the rate of primary caesarean sections in this study was significantly higher in the immediate delivery group.

Regarding postpartum complications, the incidence of fever, puerperal infection, leukocytosis, sepsis, CRP increase, endometritis, pneumonia, postpartum hemorrhage, wound infection, deep vein thrombosis, and

pulmonary embolism were investigated. The expectant management group was significantly more likely to have at least one complication compared with the immediate delivery group.

Neonatal sepsis and death rates were the primary neonatal complication outcomes. The frequency of neonatal sepsis was significantly higher in the expectant management group. No difference was found in neonatal mortality. Birth weight and use of surfactant were secondary outcomes and were significantly higher in the immediate delivery group. Other secondary outcomes such as NICU admission rates, length of hospitalization, rates of hyperbilirubinemia, and antibiotic use were increased in the expectant management group compared with the immediate delivery group. Other neonatal complications such as rates of mechanical ventilation, periventricular leukomalacia, conversion, and hypoglycemia were not significantly different between the two groups.

### **3. Questionnaire survey of obstetricians**

A total of 112 obstetricians provided responses to the survey. Cephalosporin alone was the most frequently used antibiotic in pregnant women with PROM before week 37, followed by macrolides alone or a combination of macrolides and metronidazole. Betamethasone was used more frequently than dexamethasone. Antibiotics were most frequently prescribed until 34 weeks, followed by 35 to 36 weeks.

Both pregnant women diagnosed with PROM before 34 weeks who reached their 34<sup>th</sup> week, and those who had PROM diagnosed between 34 and 37 weeks were more likely to choose expectant management than immediate delivery. Delivery decisions were based on the following contributing factors in order of importance: chorioamnionitis symptoms, problems in the amniotic fluid, and problems in the blood test values.

The questionnaire survey provided information regarding the current trends in PROM treatment in hospitals in Korea. Provision of expectant management to pregnant women with PROM after 34 weeks was confirmed

to be common in Korea. In addition, the existing guidelines recommend using steroids to induce lung maturation before 34 weeks, but a growing controversy exists as to the use of steroids after 34 weeks, as many studies have reported late preterm birth complications. The percentage of obstetricians in Korea who prescribe steroids after 34 weeks is approximately 39%. Nevertheless, limitations are found in endorsing the findings of this study definitively; not all obstetricians were included in the survey's respondents, and most of the respondents were in Seoul and the Seoul metropolitan area.

## □ Conclusions

This study comparing the perinatal outcomes of expectant management and immediate delivery for late preterm PROM was meaningful as this is the first evaluation of treatment status in Korea. The literature review indicates that clinical chorioamnionitis is the only important measure significantly more frequent in the expectant management group, the case series indicates no difference in infant mortality, and the survey results indicate that expectant management is the more frequently used approach in Korea.

Nonetheless, an additional study is required in the future to clearly conclude whether expectant management or immediate delivery is better in terms of perinatal outcomes. A well-designed, large-scale, randomized clinical trial in a Korean population is needed, as well as long-term cohort studies with follow-up periods of 2 to 3 years, in order to validate the prognosis.

If these are in combined and recommendations accommodating circumstances specific to Korea are developed and used to help a pregnant woman to decide between expectant management and immediate delivery, it would ultimately contribute to the healthy delivery of premature infants and the management of high-risk pregnant women.

## □ Plain Language Summary

When breaking of the mother's water(s) (i.e., premature rupture of membranes or PROM) takes place between 34 and 37 weeks of pregnancy, choosing between observing without taking any action (i.e., expectant management) and delivering a baby immediately within 24 hours (i.e., immediate delivery) has caused a great deal of controversy. We need to consider the risks and benefits of each management method in terms of the baby and mother. In particular, there has not been a study performed in Korea on this subject.

In this study, the literature evidence was systematically reviewed, patient case data was analyzed, and obstetricians were surveyed to identify the current status of treatment in Korea.

We reviewed available published articles, and found that the risk of clinically diagnosed chorioamnionitis (infection of the fetal membranes) was the only outcome that had a higher risk following expectant management. Moreover, one of the biggest concerns, respiratory distress syndrome (condition that may occur if a baby's lungs aren't fully developed when they are born), occurred less frequently among the newborns of women who had expectant management.

We also analyzed data from 12 hospitals in Korea for the last decade (2007 to 2016) and found that women who had immediate delivery had fewer complications just before and after giving birth, and the newborns were less likely to get infections. The need for a caesarean delivery was lower in the women who had expectant management.

We surveyed over 100 obstetricians in Korea and found that more of them choose expectant management than immediate delivery for their patients with PROM between 34 and 37 weeks of pregnancy.

This comparison study provided useful information for healthy delivery of premature infants and the management of high-risk pregnant women.

**□ Acknowledgement**

This study was supported by the National Evidence-based Healthcare Collaborating Agency (NECA) funded by the Korean Ministry of Health and Welfare (No. NC17-004).

**Key words**

Late preterm delivery, Premature rupture of membranes, Expectant management, Immediate delivery