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Management and outcomes of preterm premature rupture of the membranes

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Summary

Purpose of investigation: To compare the maternal and neonatal outcomes of preterm premature rupture of the membranes (PPROM) between two management strategies. *Materials and Methods:* This retrospective cohort study involved 153 pregnant women who presented with PPROM at a gestational age of 28+0 to 36+6 weeks to evaluate the effects of expectant management (EM; labor > 36 hours) and active management (AM; labor < 36 hours) on maternal and neonatal outcomes. The EM and AM groups were also compared independently of gestational age and after being divided into two subgroups: early PPROM (gestational age 28+0 to 33+6 weeks) and late PPROM (34+0 to 36+6 weeks). *Results:* There were no differences between the AM and EM groups in the rates of maternal infection or placental abruption, or in neonatal outcomes, including low Apgar scores, respiratory distress syndrome, or the need for continuous positive airway pressure (CPAP). In the early PPROM subgroup, arterial umbilical blood base excess levels were more negative in the AM group ($p = 0.007$). In the late PPROM subgroup, the change in systolic blood pressure between admission to the maternity care center and membrane rupture was greater in the AM group ($p = 0.049$). *Conclusions:* There were no clinically significant differences in the maternal and neonatal outcomes of PPROM between AM and EM.

Key words: Preterm; Premature; Rupture of membrane; Delivery; Expectant management; Active management; Neonatal and maternal outcomes.

Introduction

Preterm premature rupture of membranes (PPROM) is defined as membrane rupture before 37+0 weeks of gestation and before the onset of labor [1]. PPROM occurs in one-third of all preterm births [2]. It is often associated with intra-amniotic infection, especially when PPROM occurs in early gestation [3]. The risk of severe intrauterine infection increases as the latency between PPROM and delivery increases. Clinically evident intra-amniotic infection occurs in 13–60% of women with PPROM and postpartum infection occurs in 2–13% [4-8]. Chorioamnionitis, sepsis, and placental abruption are serious maternal complications of PPROM. Placental abruption occurs in 4–12% of pregnancies with PPROM [3, 9, 10]. The risk of fetal malpresentation is also increased in women with PPROM. Oligohydramnios can also occur after PPROM, and can lead to umbilical cord compression, pulmonary hypoplasia, and fetal deformation syndrome [11]. These problems are potentially life-threatening to the mother and fetus. An early gestational age at the time of membrane rupture also increases the risk of neonatal morbidity and mortality [12]. The most significant risks to the fetus after PPROM are associated with complications of prematurity, particularly respiratory distress syndrome (RDS), which is the most common complication of preterm birth [1, 2, 13]. Continuous positive airway pressure (CPAP) is often used to treat infant RDS that prevents atelectasis and airway closure, and improves oxygenation.

The optimal approach to managing PPROM remains controversial and the management strategy is selected after balancing the risks of preterm delivery and the risks of expectation [1]. The management of PROM is dependent on several factors, especially the gestational age at occurrence and the maternal and fetal clinical conditions.

Previous studies were inconclusive regarding the short- and long-term effects of various management strategies on maternal and fetal outcomes of PPROM [12, 14-17]. This study was performed to aid the assessment and quality assurance of healthcare services in obstetric departments by comparing the outcomes of different management strategies of PPROM. This is an important area of research because PPROM affects many women physically and psychologically, and has socioeconomic consequences.

Materials and Methods

The authors conducted a retrospective cohort study of women with singleton pregnancies who presented with PPROM in county hospital, Sundsvall, Sweden over fiver years from January 2010

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Table 1. — *Demographic and baseline characteristics of the patients.*

	EM group (n = 53)	AM group (n = 100)	*p*-value
Maternal age (year)	29 (24-32.5)	29 (24-33)	NS
BMI at admission (kg/m^2)	24.8 (22.5-31.5)	25.1 (22.3-29.8)	NS
Weight at admission (kg)	70.5 (61.3-88.0)	69.5 (61-80.3)	NS
Weight change (kg)	10 (6-13)	11.5 (6.8-16)	NS
Systolic blood pressure at admission (mmHg)	113 (108.5-122.8)	120 (111.5-129.3)	NS
Gestational age at PPROM (weeks)	32 (28-34.5)	35 (34-36)	<0.001
Pregnancy complications			NS
Gestational diabetes	0 (0%)	4 (4%)	NS
Preeclampsia or hypertension	1 (1.9%)	4 (4%)	NS
Nulliparous	22 (41.5%)	63 (63%)	0.016

Values are presented as the median (interquartile range) or n (%). Data were compared using the Mann–Whitney U test, the χ^2 test, or Fisher's exact test, as appopriate. Significance was set at p < 0.05. EM = expectant management; AM = active management; NS = non-significant; BMI = body mass index; PPROM = preterm premature rupture of the membranes.

until December 2014. This study was approved by the Regional Ethical Review Board in Umeå, Sweden.

PPROM was defined as membrane rupture > one hour before the onset of labor and before week 37+0 of the pregnancy [18]. Women aged < 18 or > 40 years, and women with a stillborn fetus, duplex pregnancies, systemic diseases, or prolonged infectious/contagious diseases were excluded. However, women with minor conditions such as hypothyreosis or asthma were included. According to the institutional guidelines, pregnant women with PPROM at a gestational age of < 28+0 weeks with a likely delivery were referred to a tertiary center. Therefore, the authors could not obtain complete data for these patients and they were excluded from the present study. Accordingly, only patients with PPROM at a gestational age of 28+0 to 36+6 weeks were included. Eligible patients were divided into two groups according to the management strategy: expectant management (EM) or active management (AM) with induction/spontaneous onset of labor. EM was defined as no active decision to induce labor < 36 hours of PPROM and labor was not prevented if it began spontaneously. AM was defined as the induction of labor < 36 hours of PPROM or spontaneous onset of labor < 36 hours of PPROM in patients with planned induction of labor.

The Swedish Electronic Medical Record Database for prenatal care and childbirth (Obstetrix; Siemens Corporation, Upplands Väsby, Sweden) was searched to identify patients who met the inclusion criteria. A total of 176 patients were identified and their eligibility was assessed. Eligible patients were divided into the EM (n = 53) and AM (n = 100) groups according to their management strategy.

Although the management of patients with PPROM was individualized, patients with PPROM at a gestational age of 28+0 to 34+0 weeks were managed according to the following protocols.

If birth was expected before the gestational age 34+0 weeks, a single dose of terbutaline 0.25 mg was subcutaneously injected for tocolysis to prevent preterm delivery. Tocolytic treatment was performed to ensure there was time to administer steroids, as described below, but it was not indicated in patients with signs of infection or complicated pregnancy (e.g pre-eclampsia). The basic principle was to administer a single dose of terbutaline and limit tocolysis to 48 hours, but multiple doses were possible if it was necessary to increase the duration of tocolysis and if there were no contraindications. Patients without complications (e.g. fetal distress, oligohydramnios, or infection) were given an intramuscular injection of betamethasone 12 mg + 12 mg at 24-hour intervals to prevent complications associated with fetal lung immaturity. Patients also received erythromycin treatment 50 mg, four tablets per day for ten days, commencing as soon as possible after admission.

After gestational week 34+0, the obstetrician generally waited for contractions to start spontaneously. If labor did not start within 36 hours of PPROM, the obstetrician generally induced delivery to minimize the risk of infection in the fetus and mother.

The baseline characteristics of the women were collected from medical records at their first visit to the maternity clinic in the first trimester. The main maternal outcomes were pregnancy complications, including maternal infection (e.g. chorioamnionitis and endometritis) and placental abruption. Neonatal outcomes included Apgar score, arterial umbilical blood gases (pO_2, pCO_2, pH, and base excess [BE]), the presence of fetal growth restriction, and/or fetal anomalies, need for CPAP, and the presence of respiratory distress syndrome.

The maternal and neonatal were compared between the two management methods (EM and AM). In addition, the outcomes were compared after dividing the two groups into two subgroups according to the gestational age at the time of PPROM: early PPROM (gestational age < 34+0 weeks) and late PPROM (gestational age ≥ 34+0 weeks).

SPSS software version 23 was used for statistical analyses. Descriptive statistics were used to present the data depending on the variable type (categorical or continuous). The Shapiro–Wilks test was used to assess the normality of distribution of continuous variables and the results are presented as the mean ± standard deviation or median and interquartile range. The Mann–Whitney U test was used to compare continuous variables. Categorical variables are presented as the percentage of observations in a group (%) and were compared using the χ^2 test or Fisher's exact test, as appropriate. Pearson's and Spearman's correlation tests were used for correlation analysis. Multiple regression was also performed to compare outcomes between each group with adjustment for potential confounding variables described in the Results.

Results

After excluding 23 patients due to stillbirth (n = 2) or twin pregnancy (n = 21), a total of 153 women were included in the study. The AM and EM groups comprised 100 and 53 patients, respectively. The demographic and baseline characteristics of both groups are summarized in Table 1. Both groups were similar in terms of their maternal age, body mass, weight, and systolic blood pressure at admission. The gestational age was significantly different between the two groups, therefore all study results controlled

Table 2. — *Maternal outcomes.*

	EM group (n = 53)	AM group (n = 100)	*p*-value
Ablatio placentae	5 (11.3%)	3 (3%)	NS
Chorioamnionitis	5 (9.4%)	0 (0%)	0.004
Systolic blood pressure after PPROM (mmHg)	124 (113-132)	131 (122-140)	0.035
Change in systolic blood pressure (mmHg)	9.5 (-3.5-20.25)	12 (2.5-18.5)	NS
Postpartum infection (endometritis)	3 (5.7%)	0 (0%)	0.042
CRP (mg/L)	6 (2-16)	5 (3-7.5)	NS
WBC ($\times 10^9$/L)	12.2 (10-15.5)	10.5 (7.8-12.8)	NS
Temperature >38 (°C)	4 (7.5%)	1 (1%)	NS

Values are presented as the median (interquartile range) or n (%). Data were compared using the Mann–Whitney U test, the χ^2 test, or Fisher's exact test, as appopriate. Significance was set at $p < 0.05$. EM = expectant management; AM = active management; NS = non-significant; PPROM = preterm premature rupture of the membranes; CRP, c-reactive protein; WBC, white blood cell count.

Table 3. — *Neonatal outcomes.*

	EM group (n = 53)	AM group (n = 100)	*p*-value
Birth weight (g)	2290 (1773-2703)	2835 (2490-3089)	0.0001
Apgar scores < 7 at 5 minutes	1 (1.9%)	2 (2.0%)	NS
pO_2 (kPa)	3.1 (2.2-3.7)	2.9 (2.3-3.6)	NS
pCO_2 (kPa)	6.6 (5.8-7.7)	7 (6.1-8.1)	NS
pH (7.05–7.38)	7.28 (7.23-7.34)	7.24 (7.2-7.29)	0.015
BE (mmol/L; -2.5 to -10,0)	-3.1 (-6.2 to +0.7)	-3.9 (-6.6 to +2.1)	NS
Fetal growth retardation	1 (1.9%)	2 (2%)	NS
Fetal anomaly	5 (9.4%)	7 (7%)	NS
CPAP	24 (45.3%)	27 (27%)	0.007
Respiratory distress syndrome	6 (11.3%)	5 (5%)	NS

Values are presented as the median (interquartile range) or n (%). Data were compared using the Mann–Whitney U test, the χ^2 test, or Fisher's exact test, as appopriate. Significance was set at $p < 0.05$. EM = expectant management; AM = active management; NS = non-significant; BE = base excess; CPAP = continuous positive airway pressure.

by adjusting for gestational age.

The median time from PPROM to delivery differed significantly between the EM and AM groups, being 81 (61.5–196) hours and 13 (9–24) hours, respectively ($p < 0.05$). The median gestational age at delivery was 34 (32–35) weeks and 35 (34.3–36) weeks, respectively. The maternal complications chorioamnionitis ($p = 0.004$) and postpartum infection ($p = 0.042$) were significantly more frequent in the EM group than in the AM group (Table 2). However, the differences in these complications were not significant in logistic regression with adjustment for gestational age at PPROM as a potential confounding.

Regarding neonatal outcomes (Table 3), the birth weight was significantly different between the EM and AM groups, as expected. A greater number of infants required CPAP after delivery in the EM group than in the AM group (Table 3). However, this difference disappeared after adjusting for gestational age. Neonatal umbilical arterial pH was significantly lower in the AM group than in the EM group ($p = 0.015$), but this difference disappeared after adjusting for gestational age.

Because the differences between the two AM and EM groups disappeared after adjusting for gestational age, the authors divided both groups into subgroups based on the gestational age at PPROM to further compare the outcomes of the management techniques. Early PPROM was defined as rupture of the membranes before gestational age 34+0. This subgroup comprised 44 women, of which 34 received EM (eEM subgroup) and ten received AM (eAM subgroup). There were no significant differences in baseline characteristics between the two subgroups. The median gestational age at PPROM was 31 and 32 weeks in the eEM and eAM subgroups, respectively.

The median interval from PPROM to delivery was 151.5 and 21 hours in the eEM and eAM subgroups, respectively. There were no differences in total bleeding volume, treatment with antibiotics, and/or steroids, spontaneous onset of labor, or delivery method between these subgroups. In addition, there were no significant differences in maternal outcomes. Ablatio placentae occurred in six patients (17.6%) and three patients (30%) in the eEM and eAM subgroup, respectively, while clinical chorioamnionitis occurred in five patients (14.7%) and 0 patients, respectively. There were no differences in neonatal outcomes between the eEM and eAM subgroups, except for umbilical arterial blood gas pH ($p = 0.03$) and base excess (BE) ($p = 0.007$) (Table 4). In order to examine whether the differences in pH and BE were associated with the management method, multivariable regression analyses were performed with the following potential confounders: maternal age, maternal

Table 4. — *Neonatal outcomes in the early PPROM subgroup.*

	eEM subgroup (n = 34)	eAM subgroup (n = 10)	*p*-value
Birth weight (g)	1966 (1571-2303)	2153 (1534-2352)	NS
Apgar score <7 at 5 min	1 (3%)	0 (0%)	NS
pO_2 (kPa)	2.6 (2.1-3.5)	2.4 (2-3)	NS
pCO_2 (kPa)	6.5 (5.7-6.9)	6.1 (5.6-7)	NS
pH (7.05–7.38)	7.3 (7.3-7.4)	7.2 (7.2-7.3)	0.03
BE (mmol/L; -2.5 to -10.0)	-1.9 (-4.2 to +0.4)	-6.2 (-8.3 to +3.4)	0.007
Fetal growth retardation	1 (2.9%)	0 (0%)	NS
Fetal anomaly	4 (13.3%)	0 (0%)	NS
CPAP	21 (77.8%)	8 (88.9%)	NS
Respiratory distress syndrome	5 (21.7%)	2 (25%)	NS

Values are presented as the median (interquartile range) or n (%). Data were compared using the Mann–Whitney U test, the χ^2 test, or Fisher's exact test, as appopriate. Significance was set at p < 0.05. PPROM = preterm premature rupture of the membranes; eEM = expectant management in the early PPROM subgroup; eAM = active management in the early PPROM subgroup; NS = non-significant; BE = base excess; CPAP = continuous positive airway pressure.

Table 5. — *Maternal outcomes in the late PPROM subgroup.*

	lEM subgroup (n = 19)	lAM subgroup (n = 90)	*p*-value
Ablatio placentae	0 (0%)	0 (0%)	NS
Chorioamnionitis	0 (0%)	0 (0%)	NS
Systolic blood pressure after PPROM (mmHg)	131 (128-142)	131 (122-140)	NS
Change in systolic blood pressure (mmHg)	17.5 (10-24)	12 (2.5-18.5)	0,049
Postpartum infection	0 (0%)	0 (0%)	NS
Body Temperature >38 °C	0 (0%)	1 (1.3%)	NS

Values are presented as the median (interquartile range) or n (%). Data were compared using the Mann–Whitney U test, the χ^2 test, or Fisher's exact test, as appopriate. Significance was set at p < 0.05. PPROM = preterm premature rupture of the membranes; lEM = expectant management in the late PPROM subgroup; lAM = active management in the late PPROM subgroup; NS = non-significant.

body mass index (BMI) at admission, and systolic blood pressure at admission. BE was more negative (i.e. more acidic) in the eAM subgroup than in the eEM subgroup even after adjusting for the confounding variables (p = 0.008; 95% CI: −7.5 to 1.3). By contrast, the difference in pH observed in the univariate analysis was not statistically significant in multivariable regression.

Patients in the late PPROM subgroup (n = 109) experienced PPROM at a gestational age between 34+0 and 36+6 weeks. In this subgroup, 19 patients received EM (lEM subgroup) and 90 received AM (lAM subgroup).

The median gestational age at delivery was 35 and 36 weeks in the lEM and lAM subgroups, respectively (p = 0.039). None of the women in the late PPROM group experienced any infection. The change in systolic blood pressure from admission to after PPROM was greater in the lEM subgroup than in the lAM subgroup (p = 0.049; Table 5). This difference remained significant after adjusting for maternal age, maternal BMI, and gestational age at PPROM. There were no significant differences in neonatal outcomes between the lEM and lAM subgroups.

Discussion

The present study revealed no significant differences in the maternal and neonatal outcomes of PPROM between EM and AM.

In order to minimize maternal and neonatal risk, the timing of delivery in patients with PPROM has been evaluated in several studies. However, the optimal timing of delivery remains somewhat controversial because the British and American guidelines recommend AM by induction [1, 19], whereas a meta-analysis published in 2010 that included seven randomized controlled trials concluded that there is insufficient evidence to guide clinical practice [12]. In the present study, women with PPROM at ≥ 35+0 weeks of gestation are induced 36 hours after PPROM to minimize the risk of infection if labor has not started spontaneously.

The present findings in the PPROM subgroups differ from those of earlier studies, which found a higher rate of infection in patients managed with an expectant policy [14, 15]. However, those studies were performed before administration of maternal antibiotics was introduced as a standard approach in order to reduce morbidity and to prolong latency. The present findings in the late PPROM group are consistent with those of a randomized controlled trial of 776 women with PPROM at between 34+0 and 37+0 weeks of gestation [16]. That study found no evidence that induction of labor substantially improved pregnancy outcomes relative to EM [16]. The more recent PPROM study of pregnant women with PPROMT at the gestational ages of

34+0 to 36+6 weeks was the most adequately powered study to date. This study showed that the immediate delivery did not reduce the rate of neonatal sepsis compared with EM, but the likelihood of early neonatal morbidity actually increased in terms of the rate of RDS and the need for mechanical ventilation [17]. In contrast to the American and British guidelines [1, 19], the authors of the PPROMT study argued that an EM policy should be applied to women with late PPROM if there are no contradictions to EM. However, the results of the PPROMT study differ from those of the present study because the risk of neonatal morbidity was not increased in the AM group in this study. Further studies with a larger population and greater statistical power are needed to confirm the present findings.

In earlier studies, chorioamnionitis occurred in 15–25% of women with PPROM [20]. In the present study, 3.5% (n = 5) of women experienced clinical chorioamnionitis. All of these women were in the early PPROM subgroup and were managed expectantly. Although the rate of chorioamnionitis was low and was not significantly different between the AM and EM groups, it seems that an earlier gestational age at PPROM with a longer latency to delivery were independent risk factors for maternal infection, consistent with the results of earlier studies [3].

In the late PPROM subgroup (gestational age of 34+0 to 37+0), the change in systolic blood pressure between admission to a maternity center and the time of membrane rupture was significantly different between the AM and EM groups. Earlier studies have reported that women held more positive opinions of inducing labor than they did of EM [14]. This negative perception of EM may contribute to increased stress levels and hence greater blood pressure. The longer hospitalization time associated with EM may have psychological and physical effects on women, and also contribute to the greater change in blood pressure. However, a slight rise in blood pressure during the third trimester is an expected physiological change [21], and the difference between the groups is of limited clinical importance.

In the early PPROM subgroup, the umbilical arterial blood BE levels were more negative (i.e. more acidic) in the AM group than in the EM group, and this difference remained after adjusting for confounding variables. These results imply that the management strategies had differing effects on BE in the neonates in this study group. The more acidic BE in the AM neonates could indicate that this strategy causes greater hypoxic stress and acidosis during labor. Interestingly, the umbilical artery blood pH was not significantly different between the two groups after adjusting for potential confounders. This could suggest that more bases are consumed to keep the pH stable and prevent hypoxia. However, the reference range for BE in normal neonates is from −2.5 to −10. Therefore, the BE values in both groups were within the normal range and the difference may be of limited clinical importance. However, a clinically significant difference may emerge in a larger study population.

The small population size in the early PPROM subgroup is a limitation of the present study, and larger studies are needed in order to detect potential differences in the rates of chorioamnionitis between AM and EM in patients with early PPROM. The retrospective design of this study is another limitation because it may introduce recruitment bias. However, there are some strengths to this study. In particular, all of the patients were treated at the same institution and using the same management guidelines. The AM and EM groups were also similar in terms of their baseline characteristics, and the overall sample size was larger than that of similar studies. The division of patients into the early and late PPROM subgroup allowed us to compare the effects of management strategy independently of the gestational age as a confounding factor. However, this decreased the sample size and resulted in unevenly sized subgroups, and reducing the statistical power of the analyses.

Conclusion

The present study showed that there were no differences in maternal and neonatal outcomes or complications between EM and AM of women with PPROM. The present results suggested that the decision to use EM or AM in women with PPROM should take into account the individual patient's clinical status, including gestational age, and to carefully monitor signs of infection and fetal distress. Because there were no differences in the rates of infection or neonatal complications between AM and EM in women with late PPROM, an expectant policy may be appropriate in patients with membrane rupture close to term, providing there is careful monitoring of signs of infection and fetal distress. However, further studies with larger groups of patients are needed to confirm the present findings before proposing any changes to clinical practice.

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