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Original Article

J Clin Gynecol Obstet. 2018;7(1):13-19

Maternal and Perinatal Outcomes Following Expectant Management of Preterm Premature Rupture of Membranes Before 25 Weeks of Gestation: A Retrospective Observational Study

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Abstract

Background: The aim of the study was to determine maternal and perinatal outcomes of expectantly managed pregnancies complicated by preterm premature rupture of membranes (PPROM) prior to 25 weeks gestation.

Methods: A retrospective observational study was conducted of women with singleton pregnancies, complicated by PPROM occurring between 14+0 and 24+6 weeks at Ibri Regional Hospital, for a period of 5 years (January 2011 to December 2015). Risk factors and maternal and neonatal outcomes following expectant management were assessed and comparisons were made between early (14 - 19+6) and late (20 - 24+6) previable PPROM.

Results: The prevalence of PPROM was 0.24% (46 cases/birth). There were 20 cases (48%) in the early PPROM group and 21 cases (51%) in the late group. A total of 21 babies (51.2%) were born alive, 15 from the late group and six from the early group. Sixteen women (39%) had miscarriage. One baby (2.43%) died *in utero*, two babies (4.7%) died intrapartum, and 10 babies (24.4%) died in the neonatal period. Nine babies (21.9%) survived to discharge without major morbidities. There were no cases of maternal sepsis or mortality.

Conclusion: Previable PPROM represents a rare but significant challenge to obstetricians in terms of management. Most cases are managed expectantly. Despite advances in obstetric and neonatal care, perinatal prognosis remains poor. However, the risk of severe maternal morbidity and mortality is low. A quarter of these women can take home a live baby.

Manuscript submitted October 17, 2017, accepted November 9, 2017

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doi: https://doi.org/10.14740/jcgo466w

Keywords: Preterm; Premature rupture of membrane; Expectant management

Introduction

Previable preterm premature rupture of membranes (PPROM) between 14 and 24 weeks of gestation complicates < 1% of pregnancies. PPROM occurs in approximately 5-7% of pregnant women. The incidence of previable (< 24 weeks) PPROM is lower but associated with significant neonatal morbidity and mortality [1-3].

The etiology of previable PPROM is multifactorial. It is hypothesized that a weakness in the chorioamniotic membrane occurs as a result of either membrane stretch or degradation of the extracellular matrix [1].

Although there are many studies in PPROM occurring after 24 weeks of gestation, there are few regarding outcomes following previable PPROM at < 24 weeks. Because of uncertain perinatal prognosis and lack of clearly defined protocols, previable PPROM presents a unique management and counselling dilemma for clinicians. Previous studies suggest that pregnancy outcome relates to gestational age at PPROM, latency, and severity of oligohydramnios [4, 5].

PPROM near viability is associated with high perinatal mortality and morbidity. Complications resulting from this condition are significant and include chorioamnionitis, fetal loss, endometritis, pulmonary hypoplasia, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), limb and joint deformities, and complications of extreme prematurity with major and minor impairments among surviving infants [1]. Recent advances in obstetric and neonatal care with the use of antibiotics, antenatal steroids and surfactant have improved outcomes, but remain very uncertain [2, 6]. In Middle Eastern countries with predominantly Muslim populations, women invariably choose expectant management following previable PPROM due to religious beliefs [7]. Perinatal prognosis primarily depends on the gestational age at PPROM occurring before viability. To the best of our knowledge, four prior studies compared obstetric outcome and neona-

tal survival between early and late previable PPROM [5, 6, 8, 9].

In this study, we observed the risk factors and maternal and neonatal outcomes following expectant management of spontaneous PPROM occurring between 14 and 24+6 weeks. We also evaluated how obstetric and neonatal outcomes vary according to gestational age at membrane rupture. Data from our study could be a valuable addition to the literature to counsel women regarding perinatal outcomes and maternal risks following expectant outpatient management according to the gestational age at membrane rupture.

Materials and Methods

This was a retrospective observational study performed on consecutive cases of previable PPROM at the Department of Obstetrics and Gynecology, Ibri Regional Hospital, Al Dhahirah region in the Sultanate of Oman. Women with singleton pregnancy and PPROM occurring between 14+0 and 24+6 weeks, from January 2011 to December 2015, were included in the study. Women who delivered within 24 h of membrane rupture were excluded from the study to avoid inclusion of patients with PPROM secondary to advanced cervical dilatation. Women with multiple gestations, a fetus with anomalies, and intrauterine demise at the time of presentation were excluded from the study. Cases of PPROM were identified through electronic databases following maternal and neonatal medical records, which were reviewed to obtain demographic information, risk factors, obstetric and neonatal management, and clinical course. The study was approved by the Regional Ethical Committee of Al Dhahirah region.

Management of previable PPROM was consistent over 4 years. Each patient had a sterile speculum examination to observe fluid leakage and a litmus test that turned blue. Digital examination was avoided as much as possible. Initial management included admission to hospital for surveillance, leucocyte count, C-reactive protein (CRP), high vaginal swab for microscopy and culture, urine for microscopy and culture, ultrasound to assess fetal wellbeing, amniotic fluid index (AFI) and a 10-day course of oral erythromycin. Parents were counselled about the care plan and guarded prognosis. All patients underwent expectant management. Most patients were discharged after 3 - 5 days of hospitalization and were regularly monitored on an outpatient basis. Ultrasound was done to reassess AFI and biophysical profile weekly and fetal growth every 2 weeks. Vaginal culture including group B streptococci was performed weekly, and CRP and leucocyte count twice weekly. Women were advised to report if they experienced fever, vaginal bleeding, labor pains, foul-smelling vaginal discharge, or decreased fetal movements. Pregnancy was terminated if there was evidence of chorioamnionitis, significant abruption, persistent anhydramnios, severe oligohydramnios, or abnormal fetal testing.

The diagnosis of chorioamnionitis was based on the presence of maternal fever (≥ 38 °C), uterine tenderness, maternal or fetal tachycardia, elevated leucocyte count and CRP levels. CRP more than 30 mg/L or serial CRP levels of > 20 mg/L was used for diagnosis of chorioamnionitis [10]. Patients with evidence of frank or developing chorioamnionitis received parental antibiotics such as ampicillin/cefuroxime and metronidazole. Patients received antenatal steroids using two doses of dexamethasone (12 mg at 12 h apart) after 33 weeks gestation and were routinely delivered on completing 34 weeks. Patients presenting in preterm labor or those with indications for delivery before 34 weeks received corticosteroids earlier. Tocolysis was not used in labor.

The following maternal characteristics were searched for and recorded: age, parity, risk factors, maternal leucocyte count, CRP, high vaginal swab culture, urine culture on admission and at the time of delivery, AFI on admission and later, indication and mode of delivery, evidence of chorioamnionitis, whether received steroids, and maternal outcomes. Gestational age at the time of PPROM and delivery were noted, and latency was calculated.

The following neonatal characteristics were searched for and recorded: birth weight, gender, Apgar score, pH of umbilical artery, need for oxygen inhalation, endotracheal intubation, active resuscitation, surfactant and inotrope support, details of neonatal course and morbidities like presence of sepsis, IVH (all grades), NEC (all grades), pulmonary hypoplasia, pneumonia, pneumothorax, RDS, bronchopulmonary dysplasia and periventricular leukomalacia. Diagnosis and therapy of these conditions were in accordance with national and international standards. Neonatal survival without major morbidities was the primary outcome measured.

Neonates who were discharged alive were followed up for 2 years, and the presence of long-term sequalae like cerebral palsy and hearing and speech impairment was analyzed. Mothers were followed up, and subsequent pregnancy outcome was noted. Prevention strategies were discussed, and a management plan was formulated for subsequent pregnancies. Most women received either vaginal or injectable progesterone starting from early pregnancy through 36 weeks. Prophylactic cervical encerclage was offered as per NICE guidelines [11].

Data analysis

The study cohort was divided into two groups based on gestational age at the time of membrane rupture: early PPROM (14+1 - 20+0 weeks) and late PPROM (20+1 - 24+6 weeks). Maternal and neonatal outcomes were analyzed and compared between the two groups. Co-variates assessed included demographic and pregnancy characteristics, obstetric management, and maternal and neonatal outcomes. The results were compared between the two groups. Neonatal outcomes among liveborns were analyzed separately. All data were collected using SPSS® Mac version 23. Quantitative data with normal distribution were presented as mean ± SD, otherwise median and range were used. Qualitative data were expressed as frequency and percentage. Chi-square (cross-tabulation) test was used for the analysis. P value < 0.05 (two-sided) was considered as statistically significant.

Results

The birth register identified 19,169 births during the 6-year

Table 1. Maternal Demographics and Pregnancy Characteristics

	Early PPROM: 14+1 - 20 weeks (n = 20) (%)	Late PPROM: 20+1 - 24+6 weeks (n = 21) (%)	P value
Maternal age, years (mean ± SD)	30.3 ± 5.263	31.7 ± 5.963	0.52
Parity (mean ± SD)	1.15 ± 1.725	1.43 ± 1.74	0.61
Gestational age at PPROM, weeks (median, IQR)	17+5 (16+2 - 18+6)	23 (21+3 - 24+1)	< 0.001
Prior PPROM	3 (15)	2 (9.5)	0.59
Prior preterm birth	3 (15)	2 (9.5)	0.59
Cervical insufficiency/short cervix	3 (15)	5 (23.8)	0.24
Cervical encerclage	1 (5)	2 (9.5)	0.57
Current urinary tract infection	4 (20)	4 (19)	0.93
Current vaginal infection	2 (10)	5 (23.8)	0.24
H/O threatened miscarriage	6 (30)	3 (14.3)	0.22
Recent urinary tract infection	5 (25)	2 (9.5)	0.18
Prior first trimester miscarriage	7 (35)	2 (9.5)	0.04
Prior second trimester miscarriage	5 (25)	1 (4.8)	0.06
AFI on admission < 5 cm	6 (30)	10 (47.6)	0.02
AFI on admission < 2 cm	11 (55)	3 (14.3)	0.02
Persistent leaking	11 (55)	13 (61.9)	0.65
OPD follow-up	10 (50)	9 (42.9)	0.64
Antenatal corticosteroids	5 (83.3)	11 (73.3)	0.62

All data are expressed as n (%) unless as specified.

study period from January 2011 through December 2015. We identified 46 cases of singleton pregnancies complicated by previable PPROM occurring between 14 and 25 weeks. This gave a prevalence of 0.24%. Five cases were excluded due to the loss of follow-up because they delivered elsewhere.

Maternal outcome

Out of 41 cases included in this study, 20 cases (48.78%) had early previable PPROM (14+1 - 20+0 weeks), and 21 cases (51.22%) had late previable PPROM (20+1 - 24+6 weeks). Demographic and clinical characteristics of these patients are shown in Table 1. All patients in this group were Omani women. Approximately 44% were multiparous. Twenty-four percent had a history of preterm birth or PPROM in a prior pregnancy. Cervical insufficiency was documented in 11 cases, and three cases of PPROM were following cerclage. History of prior first and second trimester miscarriages was seen significantly more in the early PPROM group (P = 0.04). Thirty-nine percent of all pregnancies had oligohydramnios on admission, and 34% had anhydramnios. Outpatient management was possible in 19 cases (46.3%). Sixteen cases (39%) received corticosteroids. Co-existing medical conditions included gestational diabetes (six cases), hypertension (five cases), hypothyroidism (three cases), anemia (Hb < 11 g) three cases, Grave's disease (two cases), fibroid (two cases), sickle cell trait (two cases), bronchial asthma (one case), and protein C deficiency (one case). One patient had PPROM following trauma. Five cases (12%) were following infertility treatment. One pregnancy was following *in vitro* fertilization. The prevalence of medical illness was similar in both groups (P = 0.64).

Table 2 shows maternal and neonatal outcomes of 41 cases of PPROM. Thirteen women (32%) had evidence of chorioamnionitis. Among them, five patients had fever. Eleven cases had elevated CRP, and 10 had leukocytosis. Median value of CRP was 65 (range 7 - 244). Median white cell count was 14,000 (range 7,600 - 25,000). Placenta showed histopathological evidence of chorioamnionitis in eight cases. Sixteen women (39%) had previable birth. Among them, 13 cases belonged to the early PPROM group. Among 41 women with PPROM, 24 patients (59%) had spontaneous labor and vaginal birth. Mean latency to delivery was not significantly different between the two groups.

Two women were delivered by lower segment cesarean section (LSCS); both were done electively at 34 weeks. One case was done on maternal request and the other for three previous LSCS procedures. Fifteen women needed induction of labor. Vaginal misoprostol was used for induction before 24 weeks, and vaginal PGE2 gel 1 mg/2 mg was used after 24 weeks. The most common indication for induction was clinical or suspected chorioamnionitis (seven women, 46% of those with chorioamnionitis). Two women were induced after 34 weeks as per protocol and had vaginal delivery. One of the babies was growth restricted. Two (13.3%) women were delivered at 26 weeks and 36 weeks due to antepartum hemorrhage and suspected abruption. Two pregnancies were induced, for breech presentation with persistent anhydramnios, one at 20

Table 2. Maternal and Neonatal Outcomes

	Early PPROM: 14+1 - 20 weeks (n = 20), %	Late PPROM: 20+1 - 24+6 (n = 21), %	P value
Gestational age at delivery, weeks (median, IQR)	19 (17+2 - 25+1)	25 (23 - 27)	0.45
Latency, days (median, IQR)	8 (2 - 56)	12 (3 - 45)	0.76
Cord prolapse	2 (10)	0	0.13
Chorioamnionitis	9 (45)	4 (19)	0.07
Febrile morbidity	3 (15)	1 (4.8)	0.26
Antepartum haemorrhage	2 (10)	3 (14.3)	0.67
Retained placenta	0	3 (14.3)	0.07
Retained products of conception	13 (65)	11 (52.4)	0.41
Surgical evacuation	10 (50)	7 (33.3)	027
Induced delivery	11 (68.1)	7 (38.9)	0.16
LSCS	2 (10)	0	< 0.001
Previable birth	13 (65)	3 (14.3)	0.001
Intrauterine death	0	1 (4.8)	0.32
Intrapartum still birth	0	2 (9.5)	015
Live born	6 (30)	15 (71.4)	0.001
Early neonatal death	2 (10)	8 (38.1)	0.03
Survival to discharge	4 (20)	5 (23.8)	0.76

All data are expressed as n (%) unless as specified.

and the other at 28 weeks. Other indications for induction were one case of intrauterine death at 22 weeks and another case of breech with cord prolapse at 19 weeks. Only four out of 41 cases (9.76%) remained undelivered at 34 weeks. Three of them belonged to the early PPROM group. All of them were followed as outpatients and had a normal AFI throughout. The remaining 37 pregnancies had preterm birth prior to 34 weeks, either spontaneously or induced for the indications mentioned earlier. Among the 41 patients, more than 24 women (59%) had retained products and 17 (42%) required surgical uterine evacuation. There were no major maternal morbidity or deaths in our study.

Women were followed up and outcome was noted in subsequent pregnancy. Twenty women had a subsequent pregnancy. Eight women underwent prophylactic cervical cerclage. The rest of the women had serial cervical length monitoring and progesterone supplementation in their pregnancies. Fourteen women (34%) had a term delivery. Six women (15%) had a preterm birth or PPROM. Among two patients with PPROM, membrane rupture occurred at 26 and 31 weeks of gestation. Three women (7%) had first trimester miscarriage. One patient with short cervix who refused cervical cerclage had second trimester miscarriage at 20 weeks.

Neonatal outcome

Twenty-one babies (51.2%) were born alive. Overall survival to discharge was 22%. Thirteen babies (62%) had an umbilical artery pH < 7.2 at birth. Neonatal morbidity and mortality among liveborn neonates were evaluated and compared between the two groups separately (Table 3). Fifty-three percent of liveborn babies were male. Among the 21 liveborn infants, four babies born between 22 and 23 weeks gestational age with low Apgar scores on delivery were treated palliatively without active resuscitation in the delivery suite and died within a few hours of delivery.

Seventeen babies were admitted to the neonatal intensive care unit. Among them, 53% survived to discharge. Major morbidities among liveborns in our study were severe RDS (43%) and sepsis (24%). Complications like IVH and NEC were of grade 2 and did not require any surgical treatment. There were no survivors with major morbidity since they died in the neonatal period itself. One baby in the early PPROM group, who was born after a latency of 10 weeks, had pulmonary hypoplasia and died 4 days later. Another baby in the late PPROM group was born at 26 weeks of gestation and had bronchopulmonary dysplasia. The baby died after 32 days. Regarding the survival outcomes, 30% of babies in the early periviable PPROM group were born alive. However, 33% of these liveborns died in the delivery suite or in neonatal intensive care unit in the neonatal period. Among the total early PPROM group, 20% survived to discharge. With the late previable PPROM group, 71.4% were born alive; however, 66.6% of these liveborn babies died subsequently. Among the late previable PPROM group, 53.3% of liveborns died in the neonatal period. Out of the two babies (13%) with later death, one baby died 32 days later and another after 120 days. Among the late previable PPROM group, 23.8% (33.3% of liveborns) survived to discharge. Among the total liveborn babies, there was no significant difference in sur-

Table 3. Neonatal Outcomes Among Liveborns

	Early PPROM: 14+1 - 20 weeks (n = 6), %	Late PPROM: 20+1 - 24+6 (n = 15), %	P value
Gestational age at PPROM, weeks (mean ± SD)	17.8 ± 1.58	22.8 ± 1.73	< 0.001
Gestational age at delivery, weeks (median, IQR)	33.2 (32 - 34.3)	29.3 (24.5 - 30.1)	0.02
Latency, days (median, IQR)	106 (102 - 112)	74 (5 - 87)	0.36
Birth weight, g (median, IQR)	1,960 (670 - 2,200)	870 (680 - 1,400)	0.02
Received antenatal steroids	5 (83.3)	11 (73.3)	0.62
Male gender	5 (83.3)	6 (40)	0.19
Apgar score < 5 at 5 min	3 (50)	5 (33.3)	0.47
Active rescuscitation needed	1 (16.7)	11 (73.3)	0.01
Human care	2 (33.3)	2 (13.3)	0.29
Length of NICU stay, days (mean ± SD)	4 (5.34)	28 (40.6)	0.01
RDS all grades	5 (83.3)	13 (86.7)	0.84
Severe RDS	3 (50)	6 (40)	0.67
O_2 inhalation, days (mean ± SD)	1.67 ± 1.86	17.93 ± 31.3	0.02
Endotracheal ventilation	1 (16.7)	10 (66.7)	0.03
Received surfactant	1 (16.7)	10 (66.7)	0.03
Inotrope support	0	9 (60)	0.01
Sepsis	0	5 (33.3)	0.10
Intraventricular hemorrhage	0	1 (6.7)	0.51
Necrotising enterocolitis	0	2 (13.3)	0.34
Pulmonary hypoplasia	0	1 (6.7)	0.51
Bronchopulmonary dysplasia	0	1 (6.7)	0.51
Periventricular leucomalacia	0	1 (6.7)	0.51
Early neonatal death	2 (33.3)	8 (53.3)	0.40
Survival to discharge	4 (66.7)	5 (33.3)	0.16

All data are expressed as n (%) unless as specified.

vival between the two groups. Further, there was no significant difference between the survival of male and female babies in our study. Among nine babies who survived to discharge, six were followed up to 2 years. Three were lost for follow-up. One baby in the late PPROM group, born at 26 weeks of gestation, was found to have microcephaly and hearing and speech impairment on follow-up. None of the babies followed up had documented cerebral palsy, retinopathy, or skeletal abnormalities.

Discussion

PPROM near viability complicates < 1% of pregnancies. Despite recent advances in obstetric and neonatal care, perinatal risks after previable PPROM remain very high and present a great challenge to clinicians. Previous studies have shown a wide range of neonatal survival from 8% to 55% [1, 8, 9, 12-17]. Many of the studies have included multiple pregnancy and women who delivered within 12 h of membrane rupture [4, 5, 16]. This may lead to selection bias and may affect survival outcomes. We excluded these cases from our study and analyzed patients with early and late previable PPROM separately. This gives a clearer picture of neonatal survival outcomes in singleton pregnancies. We analyzed the risk factors in detail, especially those contributing to the infectious etiology of PPROM. These include current vaginal and urinary infections. In addition to the above, we analyzed the history of recent vaginitis and urinary infection, which, if not properly treated, increases the risk for PPROM. In a similar study done in Oman in 2012, Nihal et al found that the most common risk factor was infection (55%) [7]. However, the site of infection was not mentioned separately. We have seen that almost half of the women had current urinary tract infection or vaginitis on admission. About a quarter of women also had recent urinary or vaginal infection. Hence, early detection and prompt treatment of these infections may prevent previable PPROM occurring due to infectious etiology. However, this needs to be evaluated by larger studies in future. In a study of 143 patients, Hunter et al reported that in 77% of cases, PPROM occurred between 20 and 24 weeks [12].

We had a nearly equal number of cases in both groups. We

also managed half of the patients as outpatients until delivery, whereas in many of the other studies, patients were routinely admitted after 24 weeks [1, 6, 12, 13]. Our study was different from previous studies in the timing of steroid administration. We avoided routine use of steroids at 24 weeks, when the lungs are not fully developed, necessitating repeat dose of steroids later [18].

However, repeat dose of steroid did not affect neonatal survival. Our study shows an overall neonatal survival of 22%, which is similar to survival rates observed in contemporaneous studies [5, 15]. Among studies that compared neonatal survival between early and late previable PPROM, Aaron et al reported significantly higher survival rates with PPROM between 22 and 24 weeks, compared to less than 22 weeks [9].

In a study of 143 singleton pregnancies, Huntel et al reported survival of 17% in the early previable PPROM group and 39% for the late group [5]. In our study, there was no significant difference between neonatal survivals between the two groups (22% and 24%). Survival was slightly better for late group. Our study shows that early previable PPROM is associated with significantly more risk of developing miscarriage ($P < 0.001$) and anhydramnios ($P = 0.02$). Early previable PPROM is also associated with probably more significant risk of chorioamnionitis ($P = 0.07$). A 2016 review by Wagner et al found that absence of anhydramnios or oligohydramnios was associated with a prolongation of pregnancy beyond 24 weeks [12] and also decreased risk of fetal and neonatal death and increased survival [1, 5]. In our study, women with early previable PPROM had one-third chance of having a liveborn baby; half of them were born at 34 weeks. This may be due to normal liquor volume and absence of persistent leaking in these patients due to the spontaneous sealing of membranes following early previable PPROM. Our study also shows that late previable PPROM is associated with significantly higher chance of having a live born ($P = 0.001$). However, almost half of them had a birth weight less than 1 kg and died in the neonatal period. A higher proportion of mothers needed evacuation for retained products of conception than in the other studies [7, 15].

This may be due to more stringent criteria for the diagnosis of retained products. However, we had a lower cesarean section rate than did many of the other studies [6, 14, 17]. In spite of advances in neonatal care, various studies, including recent ones, suggest that early-childhood outcomes of these babies remain poor [19-21]. Pristauz et al reported on long-term outcomes of 72 babies from 63 singleton and 11 multiple pregnancies with PPROM < 25 weeks [20]. Only 12 (17%) neonates survived to discharge, and after 2 years, half of these had mental and physical disability. In a study of 22 babies, Juliana et al reported similar outcomes [21]. Three-fourths of the babies in our study did not show any significant sequalae on follow-up. This may be due to the small number of cases and continuation of more pregnancies to a later gestation in our study. More studies with a large number of cases are needed to evaluate long-term outcomes. Vander et al reported reccurence risk of 10% for PPROM in subsequent pregnancies [22]. Our study also shows similar risk. Overall, one-third of these patients are at risk for preterm birth in a subsequent pregnancy. This helps in counselling women and in planning prophylactic measures in the next pregnancy. The main limitation of our study is its retrospective nature, its single institutional experience, and small number of cases available. Most studies in this field include a limited number of cases, as the clinical situation is rare and because a high proportion of women give birth within 24 h after membrane rupture.

Based on our results, we are now able to offer better counselling, in terms of what to expect, to families affected by this condition. Despite advances in obstetric and neonatal care, perinatal prognosis remains poor. However, the risk of severe maternal morbidity and mortality is low. A quarter of these women can take home a live baby.

Conflict of Interest

The authors declare that they have no conflict of interest.

Source(s) of Support

None.

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