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CLINICAL & BASIC RESEARCH

Perinatal Outcome in Pregnancies with Extreme Preterm Premature Rupture of Membranes (Mid-Trimester PROM)

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الولادة المبتسرة الناتجة عن تمزق أغشية الجنيين المدقع قبل اكتمال 26 أسبوعا من الحمل

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الملخص: الهدف: تمزق الأغشية قبل الأوان (PROM) يعرف بأنه تمزق الأغشية الجنينية قبل اكتمال 37 أسبوعا من الحمل، أما تمزق الأغشية الجنينية المدقع فإنه يعرف بأنه يحدث قبل اكتمال 26 أسبوعا من الحمل، ويمكن أن يؤدي إلى الاعتلال والوفيات في الفترة المحيطة بالولادة. كان الهدف من هذه الدراسة هو تقييم نتائج الولادة للأمهات اللآتي تمزقت الأغشية الجنينة لديهن قبل اكتمال 26 أسبوعاً من الحمل. **طرق الدراسة:** أجريت دراسة استعادية على 44 امرأة حاملا على التوالي ولدن مبتسرين نتيجة تمزق الأغشية المدقع قبل اكتمال 26 أسبوعاً من الحمل، من يناير 2006 إلى ديسمبر 2011 في مستشفى جامعة السلطان قابوس، سلطنة عمان. وقد تم جمع المعلومات عن الأم والوليد من السجلات الطبية، وسجلات وحدة حديثي الولادة. تم استبعاد كل الحالات التي بها تعدد للحمل أو ولدت بعد إكمال 26 أسبوعا من الحمل او أي أنواع أخرى من الولادات قبل الأوان من الدراسة. **النتائج:** من بين منتسبي الدراسة 24(55%) على قيد الحياة، 7(16%) توفي في غضون 24 ساعة من الولادة، سقط 9(20%) و 4(9%) موت الجنين داخل الرحم. كانت الإنتان الوليدي ونقص اكتمال الرئة هي الأسباب الرئيسية التي أدت للوفاة. وشملت المضاعفات التي تصيب الولدان الرضع على قيد الحياة من بين الخدج 11(46%)، متلازمة الضائقة التنفسية، 19(79%) والإنتان 12(50%)، وانخفاض الوزن عند الولادة في 11(46%) ارتبط معدل البقاء على قيد الحياة مع عمر الحمل عند الولادة ولكن ليس مع عمر الحمل عند تمزق الأغشية. **الخلاصة:** نتائج هذه الدراسة قد تساعد أطباء التوليد و حديثي الولادة على اسداء النصح للأزواج الذين عانوا من تمزق الأغشية الجنينية قبل اكتمال 26 أسبوعاً من الحمل. نحتاج الى العديد من الدراسات المستقبلية على المدى الطويل ذات عينات أكبر وتشمل عدد أكبر من المستشفيات.

مفتاح الكلمات: المدقع؛ الولدان؛ الأمهات؛ النتيجة؛ عمان.

abstract: ***Objectives:*** Preterm premature rupture of membranes (PPROM) is defined as the rupture of fetal membranes before 37 weeks. Extreme PPROM occurs before 26 weeks' gestation and can result in perinatal morbidity and mortality. The aim of this study was to study the perinatal outcomes of mothers with extreme PPROM. ***Methods:*** A retrospective cohort study of 44 consecutive pregnant women, presenting with PPROM before 26 weeks' gestation, was conducted from January 2006 to December 2011 at Sultan Qaboos University Hospital, Oman. Maternal and neonatal information was collected from medical records, and delivery and neonatal unit registries. Women with PPROM presenting after 26 weeks' gestation, those with multiple gestations, or other types of preterm deliveries were excluded from the study. ***Results:*** Of the 44 preterm infants admitted to the Neonatal Intensive Care Unit, 24 (55%) survived, 7 (16%) died within 24 hours of birth, 9 (20%) were miscarried, and 4 (9%) were stillbirths. Neonatal sepsis and pulmonary hypoplasia were the major causes of death. Neonatal complications among the surviving infants included prematurity in 11 (46%), respiratory distress syndrome in 19 (79%), sepsis in 12 (50%), and low birth weight in 11 (46%). The neonatal survival rate was significantly associated with the gestational age at delivery but not with the gestational age upon rupture of membranes. ***Conclusion:*** Extreme PPROM was associated with adverse perinatal outcomes. The results of this study will help obstetricians and neonatologists in counselling couples experiencing PPROM. Future studies of long-term neonatal morbidity should have larger sample sizes and include more hospitals.

Keywords: Extreme PPROM; Neonatal; Maternal; Outcome; Oman.

Advances in Knowledge

- *Few studies have looked at extreme preterm premature rupture of membranes (PPROM) or possible outcomes for mothers and fetuses. This complication carries a significant morbidity and mortality rate and affects the perinatal outcome.*

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Application to Patient Care

- *The results of this study will help in increasing awareness of PPROM for both the obstetricians and neonatologists and encourage close follow-up, proper management and counselling for this high risk group.*

The major cause of neonatal morbidity and mortality is preterm birth. It is divided into three categories: preterm premature rupture of membrane (PPROM), preterm labour, and early delivery resulting from medical intervention. PPROM is defined as a rupture of the amniotic membranes before 37 weeks' gestation and before the onset of labour, while extreme PPROM occurs before 26 weeks' gestation. PPROM is a serious condition leading to approximately one-third of preterm births and it complicates about 3% of pregnancies.[1] It is associated with many perinatal complications including neonatal sepsis, respiratory distress syndrome (RDS), placental abruption, and eventually fetal death, and carries a 1 to 2% risk of fetal death.[2] In addition, PPROM puts the mother at risk for infection (chorioamnionitis) and premature delivery, and increases the risk of Caesarean section delivery.

Risk factors for PPROM are trauma, smoking, bacterial infection, or inflammation. Women with darker skin tone are at higher risk compared to women with lighter skin.[3] Other higher risk groups are those with a previous history of preterm delivery, those who are experiencing vaginal bleeding, or those with uterine distension. In addition, low socioeconomic status, a history of sexually transmitted infections, genetic and/or enzymatic abnormalities, nutritional deficiencies, an incompetent cervix, and placental abruption are known predisposing factors.[4,5] Procedures like amniocentesis and cerclage may result in PPROM. PPROM has been suggested to be due less to the collagen content of the amniotic membranes and is more likely a multifactorial phenomenon.[6] Proper evaluation and management are necessary in order to improve neonatal outcomes. Corticosteroids are effective in reducing many neonatal complications, especially RDS and intraventricular haemorrhage. Antibiotics can be used effectively to increase the latency period. However, management of PPROM varies according to the gestational age of the fetus. In the United States, approximately 1% of pregnancies are complicated by PPROM between 16 and 26 weeks' gestation, resulting in a potential risk of neonatal complications and death.[7,8]

Extreme PPROM has not been studied and little has been published in the literature. PPROM, as far as we know, has not been studied in Oman. Studying our experience at SQUH will help in counselling parents, and allow us to compare our maternal and fetal outcomes with other institutions in the world. Therefore, the purpose of this study was to look at maternal and fetal outcomes, including the survival rate of the neonates at the Sultan Qaboos University Hospital (SQUH) neonatal intensive care unit (NICU) who were born to mothers with PPROM before 26 weeks' gestation. The results of the study will help obstetricians and neonatologists in counselling couples.

Methods

After obtaining ethical approval from the Sultan Qaboos University Hospital Ethics Committee, we started collecting the data and information needed. A retrospective cohort study with a sample size of 44 consecutive pregnant women was conducted from January 2006 to December 2011. All the participants were Omani women who presented with PPROM between 16 and 26 weeks' gestation. They delivered and received medical care at SQUH and their data was available. The hospital database, including medical records, and labour ward and NICU registries were used to obtain the following information: 1) maternal demographics; 2) gestational age at PPROM and at admission; 3) use of antibiotics and corticosteroids for fetal lung maturity; 4) gestational age at birth and mode of delivery (spontaneous vaginal or Caesarean section delivery); 5) presence of chorioamnionitis; 6) 1- and 5-min Apgar scores; 7) maternal and neonatal outcomes (morbidity and mortality rates), and 8) birth weight and sex of the baby.

Women who had PPROM after 26 weeks' gestation, who were pregnant with multiple gestation, or had a delivery due to medical intervention were excluded from the study. Gestational age was determined by asking the

Table 1: Maternal demographics (N = 44)

Maternal Age	
Mean	30
SD	5.4
Range	18-42
Gravidity	
Mean	3.5
SD	1.8
Range	1-15
Parity	
Mean	2
SD	2.5
Range	0-10
Maternal BMI	
Mean	30
SD	6.4
Range	18-44
GA at PPROM	
Mean	20.7
SD	3.2
Range	16-26
GA at delivery	
Mean	29.5
SD	7.6
Range	17-40

GA = gestational age; BMI = body mass index; PPROM = preterm premature rupture of membranes.

mother the date of her last menstrual period, if reliable, or by doing an ultrasound before 20 weeks gestation. Diagnosis of PPROM was based on history and vaginal examination. A history of sudden discharge of amniotic fluid from the vagina or feeling wet with a pooling of amniotic fluid in the posterior fornix on sterile speculum examination or ferning test confirmed the diagnosis. Finally, ultrasonography was done to assess the amniotic fluid index level. The patients were managed conservatively in the obstetrical ward and monitored for signs of chorioamniotis or fetal compromise. All patients received oral erythromycin for 10 days and steroids for fetal lung maturity at gestational ages of 24 weeks and above. The diagnosis of clinical chorioamnionitis was based on the presence of two or more of the following symptoms: purulent vaginal discharge, maternal pyrexia with uterine tenderness, fetal tachycardia, or non-reassuring fetal heart tracing on the cardiotocogram. Indications for delivery included clinical chorioamnionitis, fetal death, or advanced labour. Viability was defined as a gestational age of 24 weeks and above, or an estimated fetal weight of 500 gr or above. Patients who stopped leaking and had a normal amniotic fluid index were managed as outpatients with

Table 2: Causes of neonatal deaths in newborns delivered after 24 weeks (N = 7)

Case no.	GA at PPROM	GA at delivery	Cause of death
1	23	31	Pulmonary hypoplasia
2	21	36	Pulmonary hypoplasia/ neonatal sepsis
3	24	24	Pulmonary hypoplasia
4	22	26	Pulmonary hypoplasia
5	18	28	Neonatal sepsis
6	23	25	Neonatal sepsis
7	22	26	Neonatal sepsis

GA = gestational age; PPROM = preterm premature rupture of membranes.

weekly complete blood count (CBC) and fetal ultrasound. They were asked to report to hospital for concerns such as fever, abdominal pains, foul smelling discharge, or reduced fetal movements. These patients were allowed to go to term. Patients who continued to leak were managed as inpatients and delivered at 34 weeks' gestation.

A multivariate analysis was used to find the association between PPROM and neonatal morbidities. Microsoft Excel (Microsoft, Redmond, Washington, USA) and the Statistical Package for the Social Sciences (SPSS), Version 19 (IBM, Inc, Chicago, Illinois, USA) was used to do the data analysis. A P value of <0.05 was determined to be statistically significant. Appropriate charts (e.g. pie and bar charts), depending on the type of variables, were drawn to illustrate the results.

Results

Forty-four consecutive pregnant women with PPROM were included in this retrospective study. The median maternal age was 30 ± 5.4 years, while the median gravidity and parity were 3 and, 1 respectively. The mean gestational age at onset of PPROM and at delivery/miscarriage was 20.7 weeks, (ranging from 16 to 26 weeks) and 29.7 weeks (ranging from 17 to 40 weeks), respectively. Other maternal demographics are listed in Table 1. Among the 44 neonates delivered, 9 (20%) were miscarried, 4 (9%) were stillbirth, 24 (55%) survived, and 7 (16%) died within 24 hours of delivery. The cause of death was pulmonary hypoplasia in 4 of the neonates, with 3 complicated by neonatal sepsis.

Table 3: Other neonatal complications among surviving infants (n = 24)

Conditions	No.
Bronchiolitis	4
Inguinal hernia	3
Umbilical hernia	1
Intestinal obstruction	1
Pulmonary hypoplasia	1
Umbilical cord compression	1
Bronchopneumonia	2
Omphalitis	2
Conjunctivitis	1
Congenital malformation	1
Esophageal atresia	1
Tracheoesophageal fistula	1
Laryngomalacia	1
Hyperbilirubinemia	1
Osteopenia	1
Clitromegaly	1

Based on gestational age at the onset of PPROM, the survival rate was 41.7% when the rupture occurred before 21 weeks of gestation and 8.3% at 21 weeks. A survival rate of 50% was found in the 22 to 26 weeks' gestational age group [Figure 1].

Among the miscarried fetuses, the range of occurrence of PPROM was between 17 and 21 weeks (miscarriage is defined as loss of pregnancy before 22 weeks). The fetal membranes for the majority of stillbirth fetus were ruptured at or before 21 weeks of gestation and all were born before 26 weeks. Out of the neonatal deaths, 3 out of 7 were

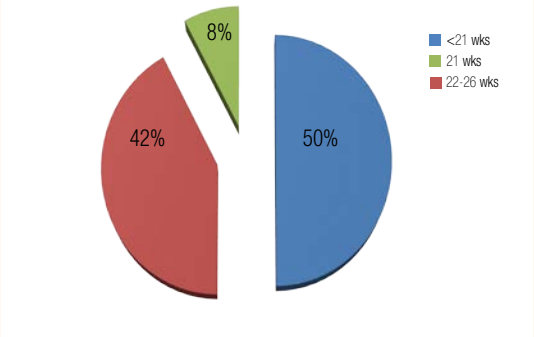

Figure 1: Survival rate based on GA at PROM
GA = gestational age; PPROM = preterm premature rupture of membranes.

Table 4: Maternal complications

Outcome	Frequency (out of 44 mothers)	95% CI
Maternal infection	20	30–61
Cesarean section	12	15–43
Antepartum hemorrhage	11	13–40

due to pulmonary hypoplasia, 3 were the result of neonatal sepsis, and one was complicated by both as shown in Table 2.

This study showed a significant association between death and gestational age at delivery (P = 0.001), but not with the gestational age at rupture of membranes (P = 0.541) This means that the earlier the gestational age at delivery, the higher the risk of perinatal death.

A total of 24 (55%) live born infants survived. Of these, 12 (50%) were boys and 12 (50%) were girls. Eight (33%) neonates were delivered by Caesarean section and 16 (67%) were delivered vaginally. The mean Apgar scores at 1 and 5 minutes were 8.7 and 10, respectively. The birth weight showed a mean of 2.22 kg. Eleven (46%) surviving neonates were preterm and were born with extreme low birth weight. Diagnosis of RDS was established in 19 (79%) babies; 12 (50%) newborns had neonatal sepsis; inguinal hernia occurred in 3 (13%). Other significant neonatal complications are illustrated in Table 3.

The most common maternal complication noted was infection. Out of 44 women with PPROM, 20 mothers (45%) developed infection, 11 mothers (25%) had antepartum haemorrhage, and 12 mothers (27%) required Caesarean section. One mother (3%) had no complications [Table 4].

Discussion

About 1% of PPROM pregnancies occur in the second trimester, leading to a significant level of morbidity among infants who survive. Among the 44 patients, there were 4 stillbirths, 9 miscarriages, and 7 neonatal deaths. The major causes for the neonatal death were neonatal sepsis and pulmonary hypoplasia. Thus, the perinatal survival rate was 55%—a number comparable with most previous studies.[9,10] Surprisingly, a survival rate of 41.7% was found when the ruptured membranes

occurred before 21 weeks of gestation. The 82% survival rate at 24 weeks of gestation might be due to the administration of antenatal antibiotics, corticosteroids, and improved antenatal care. Such a high survival rate has been reported in very few studies among infants born at 24–26 weeks of gestation. In 1988, 118 cases of PPROM were evaluated by Moretti and Sibai.[9] They recorded 67.7% perinatal mortality. Based on gestational age at the onset of PPROM, the survival rate was 13% (8 of 60) at less than 23 weeks of gestation, and 50% (32 of 64) at 24–26 weeks of gestation. Furthermore, Taylor and Garite reported a neonatal survival rate of 25%, and a 58.5% maternal morbidity rate.[11]

A study on 73 pregnant women, complicated with PPROM between 16 and 26 weeks, suggested that gestational age at PPROM is the main contributing factor for perinatal survival.[12] This study revealed that neonatal complications and poor outcomes from PPROM before 23 weeks of gestation are high. However, when the fetus is at the appropriate gestational age (24 weeks or above), the immediate perinatal survival rate was 100%. Indeed, RDS was noticed in 19 (79.2 %) surviving infants while 68.4% suffered from bronchopulmonary dysplasia. In the current study, the number of neonatal complications was higher compared to previous studies.[12–14] The incidence of neonatal sepsis was 50% (12 of 24), which is higher than numbers reported elsewhere (2% to 19%). We can suggest that the complications and the high figures noticed in our study might be due to premature birth instead of the PPROM.

Conclusion

Despite progress in medical services in Oman, and especially those in obstetric and neonatal care, perinatal outcome in pregnancies with second trimester PROM occurring between 16 and 26 weeks of gestation remains a difficult challenge. In our study, PPROM was associated with adverse perinatal outcomes in deliveries between 16 and 26 weeks gestation. Early use of antibiotics played a significant role in prolonging the latency period and minimised maternal and neonatal complications.

Thus, it is the physician's responsibility to counsel the parents about the poor outcomes that may be expected in neonates after extreme PPROM. However, this study was a small-scale retrospective study which had some limitations; therefore, the results should be interpretated with caution. Indeed, further studies dealing with long-term neonatal morbidity, including larger sample sizes and covering more hospitals should be the focus of future studies.

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