Neonatal and Maternal Outcomes of Previable Preterm Prelabour Rupture of Membranes: a 10-Year Retrospective Cohort Study

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Introduction: To evaluate the neonatal survival rate and maternal and neonatal morbidities after conservative treatment for previable preterm prelabour rupture of membranes (PPROM) at our hospital over the past 10 years.
Methods: Maternal and neonatal records of women with PPROM before 24 weeks who delivered at Princess Margaret Hospital between 1 April 2007 and 31 March 2017 were retrospectively reviewed. Patients with PPROM before 20 weeks of gestation were compared with those with PPROM between 20 and 23+6 weeks of gestation. The primary outcome was neonatal survival rate until discharge. Secondary fetal/neonatal outcomes included the live birth rate, latency period, gestational age at delivery, and short- and long-term neonatal complications of survivors. Secondary maternal outcomes included chorioamnionitis, placental abruption, cord prolapse, caesarean section, postpartum haemorrhage, maternal intensive care unit admission, hysterectomy, and maternal death.
Results: Of 80 women (77 singleton and 3 twin pregnancies), 30 opted for pregnancy termination and 50 opted for conservative management. Of the latter, 18 and 32 had PPROM before 20 weeks and between 20 and 23+6 weeks of gestation, respectively. Maternal characteristics of the two groups were comparable. The mean gestational age at PPROM was 20.2 weeks and the mean latency period was 16 days. The overall neonatal survival rate until discharge was 32.1% (n=17); it was lower in women with PPROM before 20 weeks of gestation than after 20 weeks of gestation (10.5% vs. 44.1%, p=0.012). The surviving neonates had various neonatal complications including respiratory distress syndrome (100%), probable or confirmed neonatal sepsis (81.8%), bronchopulmonary dysplasia (59.1%), and intraventricular haemorrhage (31.8%). Maternal complications included caesarean section (71.4%) and chorioamnionitis (26%).
Conclusions: The prognosis of PPROM remains grave, with only one third of neonates surviving to discharge. The neonatal complication rate remains high for survivors.

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Introduction

Preterm prelabour rupture of membranes (PPROM) is an uncommon obstetric complication, occurring in <1% of pregnancies[1]. Neonatal survival is generally poor, with great variation from 4.8% to 56%[2-10]. Fetal and neonatal complications include spontaneous miscarriage, stillbirth, preterm delivery, neonatal sepsis, pulmonary hypoplasia, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, limb contractures, and other complications of prematurity. Chorioamnionitis is a major maternal morbidity, with a rate of 20% to 71%[2-4,7,8]. Other maternal and obstetric complications include placental abruptio, cord prolapse, postpartum haemorrhage, caesarean section, and hysterectomy[11].

Although advances in neonatal intensive care have increased neonatal survival, management of PPROM before 24 weeks of gestation remains challenging. There is no consensus on the optimal option between pregnancy termination and conservative management with close monitoring. Counselling of parents is often difficult, owing to the great variation of neonatal and maternal complication rates and lack of local data. This study aimed to evaluate the neonatal survival rate and maternal and neonatal morbidities after conservative management for previable PPROM at our hospital over the past 10 years.

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Methods

This retrospective cohort study was approved by the Kowloon West Cluster Research Ethics Committee. Using the Obstetrics Clinical Information System and Clinical Data Analysis and Reporting System, patients with a diagnosis of 'PPROM' or 'miscarriage' before 24 weeks of gestation between 1 April 2007 and 31 March 2017 at Princess Margaret Hospital were identified, and maternal and neonatal records reviewed. Patients with unknown timing of membrane rupture were excluded, as were those who delivered within 12 hours of membrane rupture (likely to be the process of inevitable miscarriage rather than PPROM). Patients with pregnancy termination were also excluded.

Gestation was calculated from the patient's estimated date of delivery and verified by a dating scan. In two patients with no dating scan, gestation was confirmed by ultrasonography on admission. Membrane rupture was established with either leaking on a sterile speculum examination (with pool of liquor, positive cough impulse or positive Actim PROM test) or oligohydramnios on ultrasonography on admission (with normal fetal size and anatomy), together with a reported leaking sensation. A high vaginal swab was collected for bacteriological examination. All patients were prescribed either ampicillin or clindamycin (for those allergic to penicillin) for 7 to 14 days. Patients were hospitalised and the presence of any infection investigated including a regular maternal temperature chart, white cell count, and C-reactive protein level. Ultrasonography was used to assess liquor volume weekly and fetal growth bi-weekly.

Patients were counselled about the possible neonatal and maternal mortalities and morbidities associated with previable PPROM; options of pregnancy termination and conservative management were discussed. Neonatal resuscitation was carried out in all fetuses delivered at or after 24 weeks of gestation and in selected cases at 23 weeks of gestation depending on the patient's wish. Antenatal steroid (two doses of betamethasome 12 mg every 24 hours) was given at delivery. In one exceptional case, antenatal steroid was given at 22 weeks of gestation because the parents strongly opted for neonatal resuscitation at 22 weeks despite counselling by neonatologists.

The primary outcome was neonatal survival rate until discharge. Secondary fetal/neonatal outcomes included the live birth rate, latency period, gestational age at delivery, and short- and long-term neonatal complications of survivors. Secondary maternal outcomes included chorioamnionitis, placental abruptio, cord prolapse, caesarean section, postpartum haemorrhage, maternal intensive care unit admission, hysterectomy, and maternal death.

Chorioamnionitis was defined as maternal fever (≥37.8°C) on two occasions at least 4 hours apart and two or more of the following: uterine tenderness, foul smelling vaginal discharge, maternal tachycardia of >100 beats per minute, maternal leukocytosis of >15,000/μl, and fetal tachycardia of >160 beats per minute[12]. Neonatal sepsis was defined as a positive culture from blood or cerebrospinal fluid. Neonatal sepsis was suspected in the presence of (1) one or more clinical signs of infection (neonatal fever or hypothermia, respiratory or circulatory compromise, altered level of consciousness), and (2) one or more abnormal blood test results (elevated or low white cell count of >30 or <5 x10^9/l, elevated C-reactive protein, low platelet count of <100,000/ml), despite administration of antibiotics for ≥5 days[13-15]. Miscarriage was defined as fetal demise before 24 weeks of gestation, whereas stillbirth was defined as fetal demise before birth at or beyond 24 weeks of gestation.

Patients with PPROM before 20 weeks of gestation were compared with those with PPROM between 20 and 23+6 weeks of gestation, using the Chi squared test for categorical variables and the Student's *t* test or Mann-Whitney *U* test for continuous variables. A p value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS (version 23; IBM, Armonk [NY], US).

Results

During the study period, there were 48 139 deliveries at our hospital in which 95 women with PPROM before 24 weeks of gestation were identified. Of these, 13 with spontaneous miscarriage within 12 hours of PPROM and two with uncertain timing of PPROM were excluded, and the remaining 80 women (77 singleton and 3 twin pregnancies) were included (Figure). Of these, 30 opted for pregnancy termination and 50 opted for conservative management. Of the latter, 18 and 32 had PPROM before 20 weeks and between 20 and 23+6 weeks of gestation, respectively. Maternal characteristics of the two groups were comparable (Table 1).

The overall live birth rate was 41.5% (22 of 53 cases); it was lower in women with PPROM before 20 weeks of gestation than in women with PPROM between 20 and 23+6 weeks of gestation (10.5% [n=2] vs. 58.8%

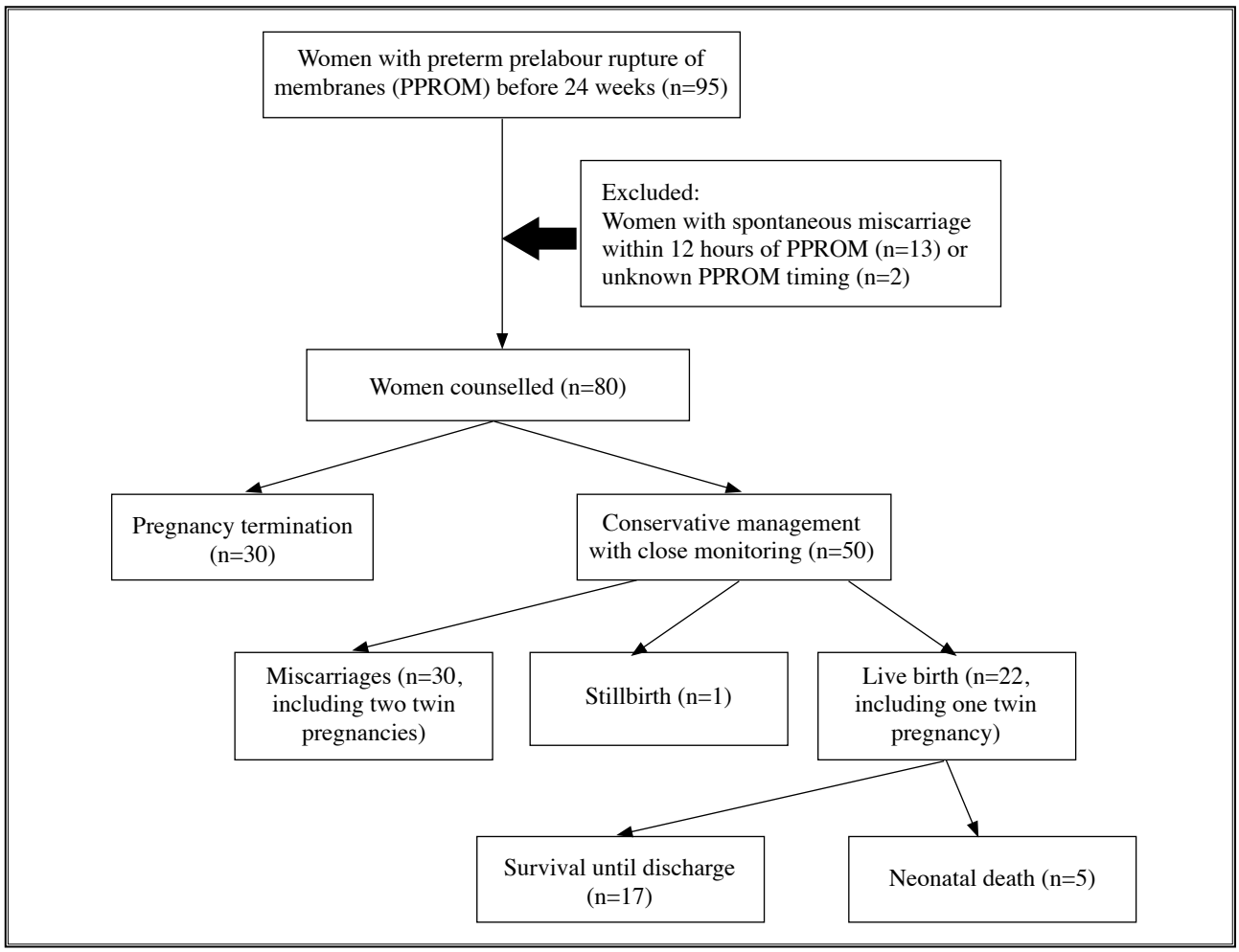

Figure. Flowchart of maternal and neonatal outcomes

[n=20], p=0.001, Table 1). Most miscarriages or stillbirths occurred in the first week of PPROM (n=26). Only two babies whose mothers had PPROM before 20 weeks of gestation were born alive. In one case, PPROM occurred at 18 weeks of gestation and delivery was at 25+6 weeks by caesarean section owing to chorioamnionitis. In another case, PPROM occurred at 12+5 weeks and delivery was at 29+2 weeks by caesarean section owing to fetal distress. All babies were delivered before 34 weeks; the median gestational age at delivery for babies born alive was 25.2 (range, 22+5 to 33+3) weeks. One woman with twin pregnancy by in-vitro fertilisation had PPROM at 21+3 weeks of gestation; she had spontaneous onset of labour at 22+5 weeks and opted for active neonatal resuscitation, but both babies died on day 1 and 4. The other two twin pregnancies had spontaneous miscarriage within one week of PPROM. All babies required neonatal intensive unit admission.

The overall neonatal survival rate until discharge was 32.1% (n=17); it was lower in women with PPROM before 20 weeks of gestation than after 20 weeks of gestation (10.5% [2/19] vs. 44.1% [15/34], p=0.012, Table 1). The neonatal survival rate was 34.8% (8/23) during the period from April 2007 to March 2012 and 30.0% (9/30) during the period from April 2012 to March 2017 (p=0.712). All five cases of neonatal death occurred within four days of birth. Among 23 cases that were delivered at least one week after PPROM, the overall neonatal survival rate until discharge was 56.5% (13 of 23).

Regarding neonatal complications, seven neonates had intraventricular haemorrhage (one grade 3 and six grade 1 or 2), 12 had retinopathy of prematurity (six of whom were of stage III and required laser therapy), and two had necrotising enterocolitis (none required surgery). Only four neonates survived without major neonatal morbidities (of neonatal sepsis, bronchopulmonary dysplasia, grade III or IV intraventricular haemorrhage, stage III or above retinopathy of prematurity, necrotising enterocolitis requiring surgery, and patent ductus arteriosus requiring surgery).

Table 1. Maternal characteristics and neonatal outcome after conservative management for preterm prelabour rupture of membranes (PPROM)

Variable	Overall (n=50)*	PPROM at <20 weeks of gestation (n=18)*	PPROM at 20 to 23+6 weeks of gestation (n=32)*	p Value
Maternal characteristics				
Age, y	33.2	33.4	33.0	0.802
Smoking	4	5.56	3.13	0.674
Race				0.782
Chinese	82	83.3	81.2	
Others	18	16.7	18.7	
Parity				0.706
Primigravida	48	44.4	50	
Multigravida	52	55.6	50	
History of miscarriage	24	22.2	25	0.825
History of preterm birth	6	0	9.4	0.180
Pregnancy				0.921
Singleton	94	94.4	93.8	
Twins	6	5.6	6.2	
Cervical cerclage/Arabin ring before PPROM	6	11.1	3.1	0.254
Invasive procedures before PPROM	4	0	6.2	0.279
Oligohydramnios at PPROM	73.5	77.8	71.0	0.603
Oligohydramnios (persistent or new onset) during conservative management	88.9	71.4	95	0.088
Gestational age at PPROM, w	20.2±2.6	17.3±1.8	21.9±1.1	-
Latency period, d	16±23.4	14.1±28.3	17.2±20.6	0.686
Neonatal outcome	(n=53)	(n=19)	(n=34)	
Live birth rate	22 (41.5)	2 (10.5)	20 (58.8)	0.001
Gestational age at delivery, w	25.7±2.9	27.4±2.5	25.6±2.9	0.493
Birthweight, g	829±395	817.0±231	830.3±413	0.424
Apgar score at 1 min	4.2±2.6	3.5±3.5	4.3±2.5	0.603
Apgar score at 5 min	6.5±2.9	5.5±2.1	6.6±3.0	0.354
Need for cardiopulmonary resuscitation at birth	7/22 (31.8)	0 (0/2)	7/20 (35.0)	0.311
Survival until discharge	17 (32.1)	2 (10.5)	15 (44.1)	0.012
Morbidities of liveborn neonates until discharge	(n=22)	(n=2)	(n=20)	
Nursery stay for survivors, d	122.6±91.3	88.5±34.6	127.1±97.1	0.551
Probable neonatal sepsis	14 (63.6)	1 (50)	13 (65.0)	0.674
Confirmed neonatal sepsis	4 (18.2)	1 (50)	3 (15.0)	0.221
Respiratory distress syndrome	22 (100)	2 (100)	20 (100)	-
Neonatal jaundice	18 (81.8)	2 (100)	16 (80.0)	0.484
Persistent pulmonary hypertension	7 (31.8)	0 (0)	7 (35.0)	0.311
Bronchopulmonary dysplasia	13 (59.1)	1 (50)	12 (60.0)	0.784
Intraventricular haemorrhage	7 (31.8)	1 (50)	6 (30.0)	0.563
Retinopathy of prematurity	12 (54.5)	1 (50)	11 (55.0)	0.892
Disseminated intravascular coagulopathy	3 (13.6)	1 (50)	2 (10.0)	0.116
Anaemia of prematurity	14 (63.6)	1 (50)	13 (65.0)	0.674
Necrotising enterocolitis	2 (9.1)	0 (0)	2 (10.0)	0.639
Patent ductus arteriosus requiring surgery	1 (4.5)	0 (0)	1 (5.0)	0.746
Survival without major morbidities	4/17 (23.5)	1/2 (50)	3/15 (20.0)	0.347

* Data are presented as mean, mean±standard deviation, %, or No. (%) of subjects

The 17 survivors were followed up for 10 years. Eight underwent surgery for inguinal hernia, hydrocoele, or hypospadias. Seven had varying degrees of developmental delay. One failed to thrive. One had retinal detachment of the right eye. Nine had no developmental delay or major morbidities. Nonetheless, further observation of their future development is required.

Gestational age at PPROM or latency period had no significant impact on obstetric or maternal complication rates (Table 2). The overall incidence of chorioamnionitis was 26% (n=13). Of 21 women with a live birth, 15 (71.4%) required caesarean section, mostly because of chorioamnionitis or fetal distress. Five (23.8%) had a classic caesarean section because of extreme prematurity with the lower segment not yet formed. The incidence of caesarean section was higher when the latency period was ≥14 days compared with 1 to 13 days (84.6% vs. 37.5%, p=0.026). Two women required intensive care unit admission due to severe maternal sepsis after spontaneous miscarriage (n=1) and massive postpartum haemorrhage (4500 ml) during classic caesarean section for placental abruptio and chorioamnionitis (n=1). There was no case of maternal death or hysterectomy.

Higher neonatal survival rate until discharge was associated with higher gestational age at PPROM, higher gestational age at delivery, higher latency period, lower white cell count at PPROM, and lower C-reactive protein level before delivery (Table 3).

Discussion

Previable PPROM occurred in <2 per 1000 pregnancies at our hospital. Parents were always counselled about the poor neonatal outcome. In our study, the overall neonatal survival rate was 32.1%, which was higher than the 18%[3] and 23%[5] reported in two studies in 2006 and 2008, respectively, and was similar to the 34.3%[7] reported in a 2012 study of 31 cases with PPROM at a mean gestational age of 19 weeks. However, it was lower than the 47%[2] and 56%[6] reported in two studies in 2004 and 2009, in which the mean gestational age at PPROM was 22 weeks and 21.4 weeks, respectively. In our hospital, the perinatal and neonatal mortality rates were 3.6 and 0.8 per 1000 births, respectively, which were comparable with the mean of 4.5 and 1.5 per 1000 births reported by seven other public hospitals in Hong Kong. The neonatal survival rate until discharge was lower in women with PPROM before 20 weeks than after 20 weeks (10.5% vs. 44.1%, p=0.012). This finding was comparable with that of a study reporting a neonatal survival rate of 18% in women with PPROM at 14 to 19 weeks and 53% in women with PPROM at 20 to 24 weeks[7]. This information provides parents a realistic estimate of the neonatal outcome based on gestational age at PPROM.

Table 2. Maternal complications by gestational age at preterm prelabour rupture of membranes (PPROM) and by latency period

Maternal complication	Gestational age at PPROM				Latency period			
	Overall (n=50)*	<20 weeks (n=18)*	20 to 23+6 weeks (n=32)*	p Value	Overall (n=50)*	1-13 days (n=36)*	≥14 days (n=14)*	p Value
Chorioamnionitis	13 (26)	4 (22.2)	9 (28.1)	0.648	13 (26)	8 (22.2)	5 (35.7)	0.329
Cord prolapse	2 (4)	2 (11.1)	0 (0)	0.054	2 (4)	2 (5.6)	0 (0)	0.368
Placental abruptio	2 (4)	0 (0)	2 (6.3)	0.279	2 (4)	2 (5.6)	0 (0)	0.368
Caesarean section†	15/21 (71.4)	2/2 (100)	12/19 (63.2)	0.293	15/21 (71.4)	3/8 (37.5)	11/13 (84.6)	0.026
Classic caesarean section†	5/21 (23.8)	0/2 (0)	5/19 (26.3)	0.406	5/21 (23.8)	2/8 (25)	3/13 (23.1)	0.920
Postpartum haemorrhage	3 (6)	0 (0)	3 (9.4)	0.180	3 (6)	1 (2.8)	2 (14.3)	0.124
Retained products of gestation requiring surgery	4 (8)	2 (5.6)	3 (9.4)	0.633	4 (8)	3 (8.3)	1 (7.1)	0.889
Hysterectomy	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	-
Intensive care unit admission	2 (4)	1 (5.6)	1 (3.1)	0.674	2 (4)	2 (5.6)	0 (0)	0.368
Mortality	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	-

* Data are presented as No. (%) of subjects

† Only liveborn cases were considered (caesarean section was not required for miscarriage or stillborn)

Table 3. Factors associated with neonatal survival until discharge after conservative management for preterm prelabour rupture of membranes (PPROM)

Variable	Survivors (n=17)*	Non-survivors (n=36)*	p Value
Maternal age, y	34.1±5.3	32.6±4.5	0.334
Smoker	1 (5.9)	1 (2.8)	0.580
History of miscarriage	5 (29.4)	7 (19.4)	0.614
History of preterm delivery	1 (5.9)	2 (5.6)	0.681
Oligohydramnios at PPROM	12 (70.6)	26/34 (76.5)	0.650
Oligohydramnios (persistent or new onset) during conservative management	12/13 (92.3)†	14/16 (87.5)†	0.672
Latency period, d	33.88±31.9	6.83±8.4	<0.001
Gestational age at PPROM, w	21.4±2.7	19.7±2.4	0.029
Gestational age at delivery, w	26.2±3.1	20.6±2.7	<0.001
White cell count at PPROM, $x10^9$/l	10.8±3.6	14.1±4.5	0.005
White cell count before delivery, $x10^9$/l	14.1±4.5	16.9±6.0	0.127
C-reactive protein at PPROM, mg/dl	20.5±25.0	22.6±17.8	0.203
C-reactive protein before delivery, mg/dl	22.7±36.6	40.3±71.8	0.002
Presence of chorioamnionitis	6 (35.3)	8 (22.2)	0.314
Chorioamnionitis on placental section	14 (82.4)	30/35 (85.7)	0.753
Birth weight, g	896.4±428.7	600.4±67.0	0.066

* Data are presented as mean±standard deviation or No. (%) of subjects

† The remaining patients had spontaneous miscarriage or delivery within 1 week of PPROM

Severe oligohydramnios significantly affects neonatal survival, as the risk of pulmonary hypoplasia increases with decreasing liquor volume[1,16-18]. Such finding was not observed in our study or other studies[2,5]. Instead, the white cell count at PPROM and C-reactive protein level before delivery were predictors of neonatal survival. Nonetheless, a larger sample is needed to determine the threshold for action. Most miscarriages occurred within one week of membrane rupture. If the fetus could survive the first week after PPROM, >50% would survive until discharge. This information is useful for patients who remain well during close observation.

In our study, the incidence of neonatal complications was slightly higher than that reported in other studies[2,4,7]. This could be due to the lack of a unified definition for these complications. Our data were extracted from neonatal discharge records produced by the paediatricians in charge. Pulmonary hypoplasia and limb contracture were unique complications of mid-trimester PPROM and were seldom documented by paediatricians in neonatal records. Hence, the exact incidence of these two complications may have been under-reported. Most surviving neonates required a prolonged hospital stay, 3 months on average. Even after discharge from the neonatal unit, most still required long-term follow-up for various residual problems, particularly developmental delay that occurred in seven of 17 surviving neonates.

The maternal complication rate plays an important role in counselling. One in seven women with previable PPROM has significant maternal morbidity[11]. Over 70% of our patients required caesarean section for suspected chorioamnionitis or fetal distress, compared with 20% to 25% of the general population in our unit. One third of the total were classic caesarean section, as the lower segment was not yet formed owing to the extreme prematurity. Classic caesarean section has major implications for future pregnancies and may affect a women's decision on pregnancy termination or conservative management. Most studies did not report the rate of caesarean section; it is unknown if such a high caesarean section rate in our unit is common among women with previable PPROM or if it is due to obstetrician anxiety and preference for a quicker and 'safer' way of delivery. The rate of caesarean section increased significantly when the latency period was ≥14 days compared with 1 to 13 days. One reason could be that the risk of chorioamnionitis and other obstetric complications increases with increasing duration of PPROM, although this was not observed in our study. Another reason could be that a shorter latency period was

associated with miscarriage or stillbirth, hence eliminating the need for caesarean section. Although 26% of our patients had chorioamnionitis (comparable with that reported in other studies[2-4,7,8]), only one woman had severe sepsis and required intensive care unit admission. There was no case of maternal death or hysterectomy.

Limitations of our study included the small sample size and the retrospective nature. Our study cannot provide a long-term prognosis of PPROM, which is important in making decisions about pregnancy termination or conservative management. 37.5% of our patients opted for pregnancy termination. If they had opted for conservative management, the overall neonatal and maternal outcomes could have been changed. A multicentre randomised controlled trial of conservative management versus pregnancy termination is needed to determine the optimal option but this is ethically not feasible. It is uncertain whether the low neonatal survival rate was mainly due to extreme prematurity at delivery or PPROM that worsens the prognosis. Nonetheless, our findings provide local data to help parents and doctors in decision making.

Conclusion

The prognosis of PPROM remains grave, with only one third of neonates surviving to discharge. The neonatal complication rate remains high for survivors.

Declaration

All authors have no conflicts of interest to disclose.

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