

## Maternal and neonatal morbidity and mortality associated with preterm premature rupture of membranes prior to 34 week gestation at Kigali University Teaching Hospital: A retrospective and prospective study

**Authors:** V. Dusingizimana<sup>1,3</sup>, M. Small<sup>1,4,5</sup>, R. Teteli<sup>2,3</sup>, S. Rulisa<sup>1,3</sup>, U. Magriples<sup>1,4,\*</sup>

**Affiliations:** <sup>1</sup>Department of Obstetrics and Gynecology, College of Medicine and Health Sciences/University of Rwanda, Kigali, Rwanda; <sup>2</sup>Department of Pediatrics, College of Medicine and Health Sciences/University of Rwanda, Kigali, Rwanda; <sup>3</sup>University Teaching Hospital of Kigali, Kigali, Rwanda; <sup>4</sup>Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut, USA ; <sup>5</sup>Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, North Carolina, USA.

### ABSTRACT

**BACKGROUND:** Preterm premature rupture of membranes is an obstetric complication which has adverse perinatal effects and long-term morbidity and mortality. There is no published outcome data in Rwanda.

**OBJECTIVES:** To assess maternal and neonatal outcomes at 24 to 34 weeks gestational age with preterm premature rupture of membranes (PPROM).

**METHODS:** Retrospective chart review of patients admitted with PPRM from 2011 to 2014 in the largest teaching hospital in Rwanda. Prospective data collection was performed in the last year (2015). Overall maternal and neonatal outcomes were documented as well as a comparison of neonatal outcomes stratified into 3 gestational age groups (24 to 28 weeks, 29 to 31 weeks and 32 to 34 weeks).

**RESULTS:** The study group was 109 patients. The mean gestational age at PPRM and delivery were  $28.9 \pm 2.8$  weeks and  $30.0 \pm 2.8$  weeks, respectively. The majority (62.4%) delivered within one week of PPRM. Chorioamnionitis was present in 9.2%, placenta abruption in 4.6% and the cesarean delivery rate was 42.2%. The overall perinatal death rate was 38.5% and neonatal mortality rate was 30.9%. Perinatal mortality was highest in the 24 to 28 weeks gestational age group (73.5%) and in infants weighing less than 1 kg (67.9%).

**CONCLUSION:** PPRM in our setting carries significant maternal morbidity and high neonatal mortality below 28 weeks. Parents should be thoroughly counseled about potential adverse maternal complications and poor neonatal outcome and be involved in decision-making regarding cesarean delivery and intensive neonatal care.

**Keywords (MeSH):** Preterm premature rupture of membranes; neonatal morbidity; perinatal mortality; Rwanda

**\*Corresponding author:** Urania MAGRIPLES, urania.magriples@yale.edu; **Potential Conflicts of Interest (Col):** All authors: no potential conflicts of interest disclosed; **Funding:** All authors: no funding was disclosed; **Academic Integrity.** All authors confirm that they have made substantial academic contributions to this manuscript as defined by the ICMJE; **Ethics of human subject participation:** The study was approved by the local Institutional Review Board. Informed consent was sought and gained where applicable;

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## INTRODUCTION

Preterm premature rupture of membranes (PPROM) is defined as spontaneous rupture of the membranes at less than 37 weeks gestational age at least 1 hour before onset of uterine contractions [1]. It is an obstetric complication which is responsible for many adverse effects on maternal health, fetal development, perinatal and long-term morbidity and mortality [2]. It occurs in approximately 3-10% of all pregnancies and constitutes a leading cause of preterm births [3,4].

Fetal and neonatal morbidity and mortality risks are significantly affected by gestational age, duration of latency, and neonatal management after delivery. Fetal and neonatal complications include prematurity and its associated morbidities, placental abruption, fetal distress due to cord compression or prolapse, fetal deformities, infection, fetal and neonatal death. PPRM carries a risk of fetal death of 1 to 2% [5,6]. In addition, it exposes the mother to the increased risk of infection, abruption, cesarean section, and prolonged hospital stay [4].

Numerous risk factors for PPRM have been investigated. Subclinical intrauterine infection likely constitutes a major predisposing factor for PPRM and is highly correlated with the maternal and neonatal morbidities. In addition, trauma, low socioeconomic status, inadequate antenatal care, poor nutrition during pregnancy, vaginal bleeding, smoking, race, genetic predisposition, and uterine over distention comprise other associated risk factors for PPRM [1,4].

In the absence of indications for prompt delivery, expectant management is tailored to gestational age at presentation, and includes antibiotics, steroids, and magnesium sulfate for neuroprotection, especially when the gestational age is below 32 weeks without evidence of imminent delivery [3].

In our setting, data on maternal morbidity and neonatal outcome associated with PPRM is limited. Clinical outcomes in low resource settings are useful in developing appropriate counseling strategies for parents and providers and for establishing appropriate expectations for neonatal survival. In addition, this level of data can be useful for developing quality improvement programs to help reduce maternal and neonatal morbidity and mortality from PPRM.

**Objectives:** The aims of this study were to assess maternal and neonatal morbidity and mortality associated with PPRM between 24 to 34 weeks gestational age.

## METHODS

**Study design:** The current study is a mixed retrospective and prospective descriptive study

**Study site:** CHUK represents the largest teaching and referral hospital in Rwanda. There are 2500 annual deliveries and it is the site for transfer for the predominance of mothers with PPRM with public health insurance. The overall cesarean section rate at CHUK is 54%.

**Participants:** Pregnant women admitted for PPRM between 24 weeks and 34 weeks gestational age were eligible for inclusion. Patients were excluded from data analysis if they had maternal complications (hypertension, diabetes, HIV) or fetal complications (multifetal pregnancies, known congenital anomalies, intrauterine growth restriction) and other conditions not related to PPRM which might influence the outcome.

**Procedures:** Retrospective chart review of patients admitted with PPRM from 2011 to 2014 was performed. Prospective data collection was performed from 1st January, 2015 to 31st December 2015. All of the patients with PPRM during the entire study period had chart review of maternal and neonatal records and the hospital computerized database. All patients admitted for PPRM in 2015 had informed written consent and were prospectively enrolled. They also had direct patient interviews. After delivery, neonatal follow up was obtained until discharge or death. Information after discharge was unavailable. Direct interview of the treating pediatricians was obtained if necessary for clarification.

**Variables and questionnaire:** Maternal demographics, gestational age of rupture of membranes, treatments and delivery information was recorded as well as the hospital course and complications. Neonatal demographics and complications were recorded until discharge.

**Data collection, management and analysis:** Data was collected from the retrospective chart review for the first four years of the study and prospectively for the fifth year from enrolment until discharge. A standardized form was used for all patients. Data were captured in EpiDATA v.3.1 and analyzed with STATA v. 13 software. Descriptive statistics such as frequency distribution, mean, standard deviation, minimum and maximum values were used to describe the studied variables. We also compared neonatal outcome in three main gestational age groups, 24/7 - 27/7 weeks, 28/7 - 31/7 weeks and 32/7 - 34/7 weeks. Chi-square test was used to describe qualitative variables among groups and t-test was used for comparing quantitative variables.

**Ethical clearance:** The study received ethics approval from CHUK Research & Ethics Committees and from the Institutional Review Board (IRB) of the College of Medicine and Health Sciences/University of Rwanda (No 35/CMHS IRB/2016).

## RESULTS

From 2011 to 2015, a total number of 112 women with pregnancies complicated by PPRM at 24 to 34 weeks met the inclusion criteria and were included. Ninety-one patients were in the first study period (retrospective) and twenty-one were in the second time period (prospective). Three women were transferred to other institutions after a few hours of admission and therefore 109 patients had complete information for analysis.

**Maternal characteristics and outcomes:** Maternal demographics are shown in Table 1. Most women were housewives (43.7%), 65.2% were multigravida and 82.2% had community-based health insurance. The mean gestational age (GA) at rupture of mem-

branes was  $28.9 \pm 2.8$  weeks and the mean gestational age at delivery was  $30.0 \pm 2.8$  weeks. The overall mean latency period was  $7.8 \pm 8.5$  days, while the maximum latency period was 7 weeks. The majority of women (62.4%) delivered within one week and only 9.2% had pregnancies prolonged beyond two weeks. A latency of more than two weeks was more common in the group of patients who ruptured their membranes between 24 to 28 weeks gestational age compared to other groups ( $p=0.013$ ). The most common indication for delivery was spontaneous labor (60.9%), followed by induction of labor at 34 completed weeks (14.6%). Maternal morbidities included: fever which was recorded in 14.9% of 101 patients, clinically diagnosed chorioamnionitis (9.2%), and placenta abruption (4.6%). The overall cesarean delivery rate was 42.2%. Most cesareans were performed for abnormal fetal presentations (29%) or non-reassuring fetal heart rates. Of 71 patients with available information on prior history of infection, 60.6% reported a prior history of urogenital infection. In the 78 multigravidas, 6.3% reported history of prior PPROM whereas 7.6% had history of preterm labor.

**Table 1. Maternal characteristics and outcomes (n=109)**

Variables	Mean	Std. dev.
Age (yrs)	29.7	6.6
Gestational age at PPROM (wks)	28.9	2.8
Gestational age at delivery (wks)	30.0	2.8
Variables	frequency	%
Latency		
< 1 week	68	62.4
1-2 weeks	31	28.4
>2 weeks	10	9.2
Clinical diagnosis of chorioamnionitis	10	9.2
Abruption	5	4.6
Cesarean Section	46	42.2

**Management:** Most patients (83.9%) were transferred from district hospitals. Of the transfers, 31.9% did not receive antibiotics before transfer, 75.5% were treated for fetal lung maturation with dexamethasone and 13% of received an inappropriate dose of dexamethasone. Tocolytics were not frequently used; they were given only in 31% of transferred patients.

At CHUK, the use of antibiotics is standardized and there were 99 patients who were eligible for antibiotics including patients who received incomplete courses or did not receive antibiotics before transfer. At CHUK, 91.9% received Ampicillin intravenous for 48 hours followed by amoxicillin and erythromycin orally for 1 week. The use of antibiotics regardless of the dose was significantly associated with prolonged latency ( $p=0.011$ ). Ninety-five patients were eligible for steroid administration for fetal lung maturation and 87.3% were treated with dexamethasone 6 mg 12 hourly for 48 hours according to our protocol. A rescue dose was given in 24.2% of those who spent two weeks or more after the initial lung maturation therapy. The use of magnesium sulfate for neuroprotection in CHUK was introduced in 2013 and

since that time 51 patients were eligible and 58.8% received magnesium sulfate. Tocolytics were used for 48 hours in 48 patients (43.2% of total population) who had uterine contractions before fetal lung maturation therapy.

**Neonatal outcomes:** There were 97 live born infants and 11% of infants were stillbirths at delivery (Table 2). The overall mean infant birth weight was  $1427.1 \pm 471.5$  grams and the mean NICU stay was  $19.2 \pm 19.4$  days. Neonatal infection was diagnosed by positive blood culture (7%) or increased C-Reactive Protein (17%) while others were based on abnormal white blood cell count or

**Table 2. Neonatal morbidity**

Variables	n	%
Liveborn	97	89.0
Stillbirth	12	11.0
Immediate neonatal death	2	
NICU admission	93	95.9
<b>NICU STAY</b>		
≤ 4 weeks	75	80.7
≥ 4 weeks	18	19.4
<b>APGAR</b>		
1-6	26	26.8
≥ 7	71	73.2
<b>MAJOR MORBIDITY IN NICU</b>		
Hypoxic Ischemic Encephalopathy	4	4.3
Respiratory problems	56	60.2
Early neonatal infection	67	72.0
Necrotizing enterocolitis	4	4.3
Intraventricular hemorrhage	3	3.2
<b>MINOR MORBIDITY IN NICU</b>		
Hypoglycemia	2	2.2
Hypothermia	3	3.2
Anemia	12	12.9
Jaundice	30	32.3
Feeding disorders	6	6.5

The overall perinatal mortality was 38.5% and the neonatal mortality was 23.8%. Mortality was significantly associated with GA at delivery. Mortality was significantly higher in infants born between 24- 28 weeks (73.5%) compared to infants born at 29-31 weeks (35.1%) and infants born at 32- 34 weeks (10.5%) ( $p=0.001$ ). Overall, the risk of mortality was also significantly related to birthweight with the highest risk noted in the extreme low birthweight group (< 1 kg) compared to infants weighing between 1 to 1.5 kg and between 1.5 to 2.5 kg (67.9%, 48.6% vs. 13.6%, respectively;  $p<0.0001$ ).

The probable cause of infant death in this study was established by clinical review by neonatology. It was possible to have more than one cause attributed to the infant's death. Among 42 cases of infant death that were registered, infectious morbidity was the most common probable cause of death (59.5%), followed by respiratory problems (45.2%).

## DISCUSSION

The aims of this study were to assess maternal and neonatal morbidity and mortality associated with PPRM between 24 to 34 weeks gestational age in Rwanda. PPRM is associated with significant maternal and neonatal morbidity. Our sample is from a large referral population; therefore, it is difficult to extrapolate the overall population risk factors for PPRM in Rwanda from this study. In the current study, the majority of patients who ruptured membranes were below 35 years old with a mean gestational age of 29 weeks. Prior research has not demonstrated an association of maternal age and PPRM [7]. The predominance of our cohort were multigravidas. This finding was in accordance with the study by Dars et al from Pakistan [4].

Most literature associates infectious morbidity with PPRM and preterm labor even though the exact mechanism remains unclear. In our study, a history of prior urogenital infection was recorded in 61%. Previous studies have shown a correlation between vaginal tract flora and organisms grown in amniotic fluid or blood of neonates with early onset sepsis [8]. It is reported that intrauterine infection is found in two thirds of patients who present with PPRM [8-10]. In our setting, although we are not equipped to diagnose intrauterine infection by amniocentesis, early diagnosis and treatment of urinary or vaginal tract infection may reduce the risks of infection and its complications.

In our referral center, 91% of patients were treated with 48 hours of intravenous Ampicillin plus oral Erythromycin (IV Erythromycin is unavailable) then Amoxicillin/Erythromycin for 7 days as a modification of the regimen studied by Mercer, et al [10, 11]. We observed significantly prolonged latency in the group that received antibiotics regardless of the dosing. There was no difference in latency period between referred patients and those who presented immediately to CHUK after PPRM ( $p=0.82$ ), this was likely due to a small number of those who consulted CHUK directly after PPRM. The mean latency period was 7.8 days and we found that the majority (62.4%) of women delivered within one week. This is consistent with previous findings in developed countries which state that 50 to 60% of women will deliver within one week [3, 4, 11, 12]. We also found that earlier gestational age of rupture of membranes was associated with longer latency which is similar to what has been reported in developed countries [3, 11].

With expectant management of patients with PPRM, the most common maternal complication is chorioamnionitis. This risk increases with the duration of PPRM and decreases with advancing gestational age [3]. In our study, we found a chorioamnionitis rate of 9%. This rate is lower than reported in the literature where 13-60% of patients develop chorioamnionitis [3]. The diagnosis of chorioamnionitis in Rwanda is only based on the occurrence of overt clinical signs such as fever, uterine tenderness and fetal tachycardia and is not based on laboratory tests, amniocentesis or placental pathology and therefore is likely under-diagnosed. In addition, infection is thought to be the primary cause of spontaneous labor in patients with PPRM which may explain why the majority of patients in our study (61.9%)

went into labor spontaneously. Only 14% of patients who were expectantly managed delivered at 34 weeks either by induction or cesarean section to reduce the risks of maternal and neonatal infectious morbidity. There is controversy in the literature regarding the practice of delivering patients with PPRM who reach 34 weeks gestational age. Recent studies suggest that in the absence of overt signs of infection or fetal compromise, a policy of expectant management at this gestational age should be continued with appropriate surveillance of maternal and fetal wellbeing [12], [13]. This practice may be difficult in low resource settings where continuous fetal monitoring is unavailable and use of ultrasound may be limited.

In our study, we reported an abruptio placentae rate of 5% which is consistent with the literature where abruption after PPRM affects 4-12% of patients [3]. Placental pathology is not the standard of care in our institution and therefore the diagnosis was made on clinical findings. The reported rate of cesarean section of 42% is also consistent with the literature [2]. In our cohort, there was no difference in Cesarean rate by gestational age group ( $p=0.3$ ). There has been debate about the increased neonatal benefits with cesarean delivery prior to 30 weeks' gestation [14, 15]. In our low resource setting, cesarean section is associated with significant post-operative maternal infectious morbidity and mortality, and is therefore performed for obstetric indications [16].

We noted high perinatal and neonatal mortality particularly at the earliest gestational ages. Almost 60% of the fetal and neonatal deaths were observed in the group of patients with ruptured membranes at 24 to 28 weeks of gestation. The neonatal mortality in this group was 73.5%. Birth weight was also an independent prognostic factor of neonatal survival and 67.9% of extremely low birth weight babies (less than 1 kg) died before 28 days of life and less than half of infants (43%) who weighed less than 1.5 kg survived. We did not control for potential confounding factors of morbidity as estimated fetal weight and gestational age are generally the only information available to the obstetrician for patient counseling.

Though short-term maternal complications in our cohort are similar to the literature from developed countries, the neonatal mortality at early gestational ages and with low birthweight in our setting is much higher than in industrialized countries [14-17]. This is likely due to the lack of advanced neonatal care and technology such as surfactant, mechanical ventilation and parenteral feeding. In our setting, respiratory support is limited to continuous positive airway pressure (CPAP) and oxygen. There were no changes in the neonatal management protocols during the study period.

The International Federation of Obstetricians and Gynecologists (FIGO) has stated that infants born between 22 to 28 weeks are at the threshold of viability. Providers should consult with their neonatology staff and use country specific data to counsel parents on outcomes. In our setting, neonatal viability may be considered at a higher gestational age than in developed countries and cesarean section should be undertaken only after thorough parental counseling about the potential poor neonatal outcome.

Limitations of this study: This is the first study in Rwanda to document the outcomes of PPROM. To obtain an adequate sample size, a mixed retrospective and prospective cohort was studied over 5 years. Data collection over the retrospective portion (first 4 years) was limited by chart abstraction. We have not surveyed long-term maternal or neonatal morbidity and mortality of PPROM which are likely high. Maternal outcomes were limited to the immediate postpartum period, therefore delayed complications from infection and cesarean delivery are likely underrepresented. Chronic medical and developmental concerns in premature neonates were beyond

the scope of this study but need to be documented in order to improve parental counseling.

## CONCLUSION

PPROM at 24 to 34 weeks in our setting carries significant maternal morbidity and high neonatal mortality at early gestational ages (below 28 weeks). Parents must be involved in decision-making regarding delivery and intensive neonatal care. Consideration should also be given to counseling patients in low resource setting on the option of pregnancy termination at peri-viable gestational ages.

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