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Maternal and fetal outcome of term pre labour rupture of membrane in a regional referral hospital in Bhutan from 2018-2020: a retrospective cross sectional study

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ABSTRACT

Introduction: Term premature or prelabour rupture of membrane (PROM) refers to the disruption in fetal membranes before the onset of labor, after 37 weeks of gestation. PROM is commonly encountered in our practice but there is no published study on PROM in our country. This study was conducted to determine the incidence, clinical profile and it's association with maternal and fetal outcome in term PROM in our hospital. **Methods:** A retrospective cross sectional study, carried out at a regional referral hospital in Bhutan. Medical records-based data was collected from clinically diagnosed cases of term PROM, from 1st January 2018 to 31st December 2020. **Results:** The incidence of term PROM among deliveries was 5.5 %. Unfavourable maternal outcome was seen in Primigravida (*p*-value=0.05), PROM duration ≥24 hours (*p*-value= 0.007), Prolonged latency period of 24 hours or more (*p*-value=0.03), prophylactic antibiotics after 18 hours (*p*-value=0.05) and vaginal delivery (*p*-value=0.0001). Unfavourable fetal outcome was observed in cases referred in from regional health centres (*p*-value=0.01). **Conclusions:** Early initiation of appropriate prophylactic antibiotics, Early induction of labour as opposed to expectant management, Prompt referral of all PROM cases from primary health centres and district hospitals and availability of appropriate prophylactic antibiotics at all health centres may improve maternal and fetal outcome in term PROM.

Keywords: Clinical profile; Fetal outcome; Maternal outcome; Term PROM.

INTRODUCTION

Premature or prelabour rupture of membrane (PROM) refers to the disruption in fetal membranes before the onset of labor with spontaneous leakage of amniotic fluid. PROM after 37 weeks of gestation is referred to as Term PROM. PROM occurs in approximately 5% – 10% of all pregnancies, of which approximately 80% occur at term[1] but the prevalence of preterm PROM may be as high 50% in referral centres with Neonatal Intensive Care Unit (NICU) facilities[2]. PROM adversely affects maternal and fetal outcome and risk of maternal and fetal infection is related to factors like duration of the rupture of membrane and the latency period[3].

The etiology of PROM may be multifactorial. Some of the risk factors include previous history of PROM, multiple pregnancy, polyhydramnios, cervical incompetence, smoking, poor nutritional status and genital infection [4]. The infection is most commonly polymicrobial with organism such as Trichomonas vaginalis (TV), bacterial vaginosis (BV), Gardnerella vaginalis, Neisseria gonorrhea, chlamydia trachomatis, and candidiasis and Group B streptococcus.

PROM has significant maternal and neonatal complications especially infection. Maternal complications include chorioamnionitis, surgical site infection in patients who underwent caesarean section, puerperal sepsis and prolonged hospital stay. Chorioamnionitis is thought to be the result of microbial invasion of the amniotic cavity. Clinical signs include maternal fever, uterine tenderness, maternal tachycardia and a foul smelling liquor associated with fetal tachycardia[5]. Fetal complications include cord prolapse with fetal distress and infection with neonatal sepsis. PROM is major cause of neonatal mortality due to prematurity and sepsis. Prompt diagnosis and appropriate management is crucial to reduce maternal and fetal complications, mainly infections. The study TERM PROM found that prostaglandin analogues such as misoprostol shortens the latency period compared with expectant management especially when the cervix is unfavourable. However the risk of hyper stimulation, fetal distress and caesarean section may increase. Broad spectrum antibiotics are recommended for treatment considering the polymicrobial nature of the infection. Treatment with antibiotics reduces the risk of maternal and fetal complications when duration of rupture is more than 18 hours. Ampicillin and Azithromycin are some of the commonly used antibiotics[6]. Maternal C-reactive protein (CRP) is good marker for chorioamnionitis. Chorioamnionitis increases the risk of EONS (early onset neonatal sepsis) and is an indication for

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prompt delivery. Group B streptococcus is the commonest cause of EONS and antibiotics are usually directed against it[7,8].

PROM frequently complicates pregnancy in our practice but there is no published study on maternal and fetal outcome of PROM in Bhutan. With this study we aimed to describe the incidence of term PROM, clinical profile and its association with maternal and fetal outcome in pregnant women admitted to the central regional referral hospital.

METHODS

After obtaining ethical clearance from Research Ethics Board of Health vide letter number REBH/Approval/2021/007 dated 02nd February 2021, a retrospective study was conducted in Central Regional Referral Hospital (CRRH) .The CRRH is a 150 bedded multispecialty hospital and serves as referral center for five districts in central and southern part of Bhutan.

PROM after 37 weeks of gestation, confirmed by clinical examination, were included in the study. All preterm PROM were excluded from the study as prematurity was a major confounder for the outcomes in our study. There were 2920 deliveries during the 3 year period from 2018 to 2020 and 162 cases fulfilled the criteria of Term PROM. Assuming prevalence of 10% as reported in most studies (since we do not have data for Bhutan), standard normal variation of 1.96 at 95% confidence interval, and precision of 5%, the minimum sample size required was 70. Convenience sampling method was used and all 162 cases fulfilling the eligibility criteria were included in the study.

A structured data collection sheet was used to collect information on patient and pregnancy characteristics such as age, occupation, gravidity, Antenatal care, referral status and clinical profile related to PROM such as past history and duration of PROM, onset of labour, latency period and time of initiation of antibiotic prophylaxis.Variables for maternal outcome included duration of hospital stay, chorioamnionitis, and surgical site infections. Fetal outcome variables included admission to NICU for neonatal sepsis. For the purpose of analysis we categorized maternal and fetal outcomes as favourable and unfavourable. Unfavourable maternal outcome was defined as Presence of chorioamnionitis, SSI (surgical site infection) or duration of hospital stay of four days or more. Unfavourable fetal outcome was defined as admission in NICU for neonatal sepsis (we did not want admission in NICU as a criteria for unfavourable fetal outcome since many babies were admitted in NICU for various reasons such as observation, neonatal jaundice etc.). Latency period in PROM is defined as the interval between PROM and onset of labour[9].

Data entry was done using Epidata Version 3.1 and analyzed in Epidata Analysis Version 2.2.2.182 (Epidata Association, Odense, Denmark). Descriptive analysis and findings were presented in percentages. Inferential statistics such as Chi- square test, Fisher's exact test and Relative risk with 95% confidence intervals were calculated to test the significance of differences of proportions of categorical variables. A *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Overall, among 2920 deliveries during the study period, 162 presented with PROM at term. The incidence of term PROM among deliveries in CRRH was 5.5 %. Table 1 shows the socio-demographic and clinical profile. Of the total cases, (92%) were between age group of 18 to 35 years and 62.3% were Primigravida ,2.4% had past history of PROM. The duration of PROM was 24

Table 1. Socio demographic and clinical profile of 162 women with term PROM* admitted to central regional referral hospital, Bhutan, from 1st January 2018 to 31st December 2020

		n	percentage
Age	< 18 years	3	1.9
	18-35	149	92
	> 35 years	10	6.2
Occupation	Blue collar	124	76.5
	White collar	38	23.5
ANC† booking	booked	157	96.9
Gravidity	Primigravida	101	62.3
	Multi gravida	61	37.7
History of PROM*	yes	4	2.4
Duration of PROM*	≥ 24 hours	92	56.8
Initiation of antibiotic prophylaxis	≤ 18 hours	112	69.1
	> 18 hours	50	30.9
Onset of labour	Spontaneous	60	37.0
	induced	99	61.1
Latency period§	≥ 24 hours	66	45.5
Duration of hospital stay	≥ 4 days	82	50.6
Chorioamnionitis	Yes	2	1.20
Surgical site infection	yes	0	0
Mode of delivery	Vaginal	119	73.4
	Caesarean section	43	26.5
Admission to NICU‡ for neonatal sepsis	yes	36	22.2
Referred in	yes	66	40.7

**Prelabour rupture of membrane*
†Antenatal care
‡Neonatal Intensive care unit
§Latency period: n=145, as information on latency period was missing in 17 samples

Table 2. Association between socio-demographic and clinical profile with maternal outcome of 162 women with term PROM* admitted to central regional referral hospital, Bhutan, from 1st January 2018 to 31st December 2020

Variables		Favourable (*n*=80)	Unfavourable (*n*=82)	*p*-value	Relative Risk
Age	≤ 35 years	75(49.3)	77 (50.7)	0.96†	
	>35 years	5 (50.0)	5(50.0)		
occupation	Blue collar	63 (50.8)	61 (49.2)	0.51†	
	White collar	17 (44.7)	21 (55.3)		
Gravidity	Primigravida	44 (43.6)	57 (56.4)	0.05†	1.38 (0.97-1.95)
	Multigravida	36 (59.0)	25 (41.0)		
ANC§	booked	79 (50.3)	78 (49.7)	0.18‡	
	Unbooked	1 (20.0)	4 (80.0)		
History of PROM*	Yes	1(25.0)	3 (75.0)	0.62‡	
	No	79 (50.0)	79 (50.0)		
PROM* duration	≥ 24 hours	37 (40.2)	55 (59.8)	0.007†	1.55 (1.10-2.18)
	< 24 hours	43 (61.4)	27 (38.6)		
Latency period‖	≥ 24 hours	29 (43.9)	37 (56.1)	0.03†	1.48 (1.04-2.10)
	<24 hours	49 (62.0)	30 (38.0)		
Time of Initiation of prophylactic antibiotics	≤ 18 hours	61 (54.5)	51 (45.5)	0.05†	1.36 (1.01-1.83)
	> 18 hours	19 (38.0)	31 (62.0)		
Mode of delivery	vaginal	79 (66.3)	40 (33.7)	0.0001‡	1.47(1.28-1.80)
	caesarean	42 (97.7)	1 (2.32)		

**Prelabour rupture of membrane*
†denotes chi-square test, ‡denotes Fisher's Exact Test, §Antenatal care
‖Latency period: favourable (n=78), unfavourable (n=67) as information on latency period was missing in 17 samples

Table 3. Association between socio-demographic and clinical profile with fetal outcome of 162 women with term PROM* admitted to central regional referral hospital, Bhutan , from 1st January 2018 to 31st December 2020

variables		Favourable (*n*=126)	Unfavourable (*n*=36)	*p*-value	Relative Risk
Age	≤ 35 years	119 (78.3)	33 (21.7)	0.69‡	
	>35 years	7 (70.0)	3 (42.9)		
Occupation	Blue collar job	96 (77.4)	28 (22.6)	0.84†	
	White collar job	30 (78.9)	8 (21.1)		
Gravidity	Primigravida	79 (78.2)	22 (21.8)	0.86†	
	Multigravida	47 (77.0)	14 (23.0)		
ANC§	Booked	121 (77.1)	36 (22.9)	0.58‡	
	Un booked	5 (100.0)	0		
History of PROM*	Yes	3 (75.0)	1 (25)	1.00‡	
	No	123 (77.8)	35 (22.2)		
PROM* duration	≥ 24 hours	69 (75.0)	23 (25.5)	0.32†	
	<24 hours	57 (81.4)	13 (18.6)		
Latency period‖	≥ 24 hours	47 (71.2)	19 (28.8)	0.11†	
	<24 hours	65 (82.3)	14 (17.7)		
initiation of prophylactic antibiotics	≤ 18 hours	88 (78.6)	24 (21.4)	0.71†	
	>18 hours	38 (76.0)	12 (24)		
Referred in	Yes	45 (68.2)	21(31.8)	0.01	0.49 (0.27-0.88)
	No	81 (84.4)	15(15.6)		

**Prelabour rupture of membrane*
†denotes chi-square test,‡denotes Fisher's Exact Test, §Antenatal care
‖Latency period:favourable (n=112), unfavourable (n=33) as information on latency period was missing in 17 samples

hours or more in 56.8% and the latency period 24 hours or more in 40.7% of cases. In 69.1% of cases prophylactic antibiotics was started within 18 hours of onset of PROM. Chorioamnionitis was seen in two (1.2%) women and none had surgical site infection. Looking at the mode of delivery, 26.5% were by caesarean section. Prolonged hospital stay (duration of hospital stay ≥4 days) was seen in 50.6% of the cases. Overall 40.7% of the PROM cases were referred in from other health centres in the region.

Table 2. Shows association of socio-demographic and clinical profile with maternal outcome. 56.4% of Primigravida had unfavourable maternal outcome compared to 41% in multigravida which was statistically significant at *p*-value 0.05. The risk of unfavourable maternal outcome was 1.55 times higher in cases where the duration of PROM was 24 hours or more (95% CI 1.10-2.18; *p*-value= 0.007). Prolonged latency period of 24 hours or more (RR=1.48, 95% CI 1.04-2.10; *p*-value=0.03) and initiation of prophylactic antibiotics after 18 hours (RR=1.36, 95% CI 1.01-1.83; *p*-value=0.05) were also associated with unfavourable maternal outcome. Vaginal delivery was also associated with unfavourable maternal outcome (RR=1.47, 95% CI 1.28-1.80; *p*-value=0.0001).

Table 3. Shows association between socio-demographic and clinical profile, with fetal outcome. Term PROM cases referred in from regional health centres were also associated with unfavourable fetal outcome (RR=0.49, 95% CI 0.27-0.88; *p*-value=0.01).

DISCUSSION

This retrospective cross sectional study on term PROM was undertaken to determine basic socio-demographic and clinical profile, and its association with maternal and fetal outcome. Even though PROM is frequently encountered in our practice, this is the first study on PROM in our hospital and in Bhutan. The incidence of term PROM among deliveries in our hospital was 5.5%. Incidenceof 2.7 to 7% in China and 5 - 15% in America was reported in some studies10 . Our findings suggest higher incidence of PROM in the Primigravida (63%) than in the multiparous women and a caesarean section rate of 26.5% which was similar to findings of a prospective case control study conducted in Kosova[11]. Contrary to our findings, a study of 13927 women with PROM in east china found higher caesarean section rate of 55.1% in term PROM[12]. In our study only 2 (1.2%) women developed chorioamnionitis and none had surgical site infection. A review of 14 randomized clinical trials, a systematic review, and a meta analysis found that Intra-partum antibiotic treatment was associated with a significant reduction in the frequency of neonatal sepsis (0.0% vs. 31.6%, *p*= 0.046), hospital stay, and maternal febrile days[13].In our hospital the protocol for management of PROM includes initiation of Prophylactic antibiotics (IV ampicillin 2g 6 hourly and Tab azithromycin 1g stat PO) and all 162 women in our study had received antibiotics, which may in part, account for the low incidence of chorioamnionitis and surgical site infection.

Prolonged PROM is usually associated with increased maternal and neonatal morbidity and mortality. We observed that the risk of unfavourable maternal outcome was 1.55 times higher ((95% CI 1.10-2.18; *p*-value= 0.007) when the duration of PROM was 24 hours or more. Similar findings of unfavourable maternal outcome was also seen in other studies done in Telangana, India and Bangladesh[14,15]. A retrospective study conducted at Jordan University Hospital found neonatal sepsis in 25.5% of cases with prolonged PROM[16]. However there was no significant difference in our study.

Contrary to findings of study of 1455 women with PROM in Uganda, which found that caesarean section was associated with unfavourable maternal and fetal outcome, we found that vaginal delivery was associated with unfavourable maternal outcome but there was no significant impact on fetal outcome[17]. Prophylactic antibiotics plays an important role in prevention of both maternal and fetal infection and in our hospital antibiotic prophylaxis is given to all patients but the time of initiation varied between 12 to 18 hours depending on clinicians. We found that initiation of prophylactic antibiotics after 18 hours and beyond was associated with unfavourable maternal outcome but there was no difference in fetal outcome. A 2015 meta analysis of randomized clinical trial concluded that antibiotic prophylaxis in women with latency period more than 12 hours significantly reduces rates of chorioamnionitis by 51% and endometritis by 88%[19]. Similar to our finding, a RCT carried out in Lisbon university hospital found that antibiotic prophylaxis reduces the rate of maternal infection in women with term PROM. However there was no significant effect on neonatal infection rate[18].

A higher risk of unfavourable fetal outcome or neonatal sepsis (RR=0.49, 95% CI 0.27-0.88; *p*-value=0.01) was seen among patients referred in from other primary health centres and district hospitals in the region. This could be related to longer PROM duration, delay in initiation of antibiotic prophylaxis and non-availability of certain antibiotics such as azithromycin in the primary and district health centres.

CONCLUSIONS

Early initiation of appropriate prophylactic antibiotics, induction of labour as opposed to expectant management, prompt referral of all PROM cases from primary health centres and district hospitals, and availability of appropriate prophylactic antibiotics at all health centres may improve maternal and fetal outcome in term PROM.

However our findings may not be representative of the whole country as it was a retrospective study conducted in one hospital. There were other limitations such as inadequate records or information which did not allow us to explore certain

factors of interest such as causal factors. Due to intermittent shortages of reagent in the laboratory and non-availability of tests such C-reactive protein in many of the cases, the diagnosis of chorioamnionitis was based on clinical parameters only. Certain cases of subclinical chorioamnionitis could have been missed as histological examination of placenta was not performed routinely. However, this being the first study on PROM in our country, we have been able to provide certain baseline data.

We recommend multi-centric prospective case control studies and randomized trials in the future to improve the reliability of our findings and also to address important issues such as risk factors, antibiotic prophylaxis, and induction of labour in PROM.

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AUTHORS CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

NG: Concept, design, data collection and analysis, manuscript writing and review.

RR: Concept, design, data collection and analysis, manuscript writing and review

Author agree to be accountable for all respects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

None

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