Original Article

Lower genital tract infections in preterm premature rupture of membranes and preterm labor: a case-control study from Vietnam

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Abstract
Introduction: This study aimed to determine the incidence of lower genital infections and related factors in preterm premature rupture of membranes (PPROM) and preterm labor.
Methodology: A case-control study was conducted on pregnant women who were admitted to the Hospital of Hue University of Medicine and Pharmacy, Vietnam between November 2017 and May 2019. Cases from 22 to 36 gestational weeks were included as group 1 (patients with preterm labor and intact membranes) or as group 2 (those with PPROM). The control group included women with singleton pregnancies who were matched on gestational age and recruited concurrently with the study cases. Gram stain was perfomed to identify *Lactobacillus*, *Gardnerella*, mobiluncus, Candida, and leucocytes. *Trichomonas vaginalis* was detected by wet mount. Cultures of vaginal secretions and aminotic fluid were performed to identify aerobic bacteria.
Results: Bacterial vaginosis was higher in group 1 (28.9%) compared to control (11.4%). The incidence of isolated aerobic bacteria was 44.1% in group 2, 11.1% in group 1, and 12.7% in the control group ($p < 0.001$). Fungal infection was not shown to be a risk factor for preterm labor ($p = 0.990$), whereas, bacterial vaginosis was (OR = 3.16; 95%CI = 1.23-8.15; $p = 0.016$). Isolated aerobic bacteria were associated with premature rupture of membranes (OR = 5.45; 95%CI = 2.11-14.05; $p < 0.001$).
Conclusions: Bacteria vaginosis increased the risk of preterm labor and preterm premature rupture of membranes. Isolated aerobic bacteria were related to PPROM, while fungal infection was not associated with preterm labor.

Key words: Bacterial vaginosis; preterm premature rupture of membranes; preterm labor.

Introduction

Preterm birth (PTB), defined as delivery before 37 weeks of pregnancy according to the World Health Organization, is the most common cause of perinatal neonatal morbidity and mortality worldwide [1]. It has been estimated that the prevalence of PTB is 11.1%, which is equivalent to 15 million preterm babies, resulting in about 1 million babies who have died each year because of PTB [2]. Despite advances in obstetric management and neonatal care, PTB in the United States accounts for about 70% of neonatal mortality and about 50% of long-term neurological disorders in children [3]. PTB can be classified as idiopathic or medical and obstetric complication. Pregnant women presenting with regular uterine contractions before 37 weeks of gestation are diagnosed with preterm labor (PL) [4]. Preterm premature rupture of membranes (PPROM) is defined as the rupture of the fetal membranes before the onset of labor before 37

gestational weeks and related to PTB [3]. Approximately 40% to 50% PTB are due to idiopathic preterm births with intact membranes, 25% to 40% result from PPROM, the remaining 20 – 30% occur due to indications for intervention because of a variety of maternal or obstetric complications [3]. Among the risk factors and etiologies for PTB that have been reported, microbiological studies have linked genital tract infections to 25 – 40% of PTB [5,6]. Infections have been shown to increase neonatal complications [7]. Bacterial vaginosis (BV), present in 15 – 42% of pregnant women [8], has been shown to lead to a four-fold increase in the risk of PTB and spontaneous PPROM [9]. The rate of PTB in an untreated group infected with BV was higher than the groups of pregnant women before 20 weeks of gestational with intermediate and normal bacteria [10]. In addition, BV has been reported to have negative effects on infants such as low birth weight [11], and to increase the risk

of postpartum infection [12]. According to a study in 2019, the individual prevalence of *Fusobacterium sp.* (21%), *Mubiluncus mulieris* (18.4%) and *Mycoplasma hominis* (19.5%) was found to be higher in the preterm women compared to their term counterparts (*p* < 0.0001) [13]. Besides that, the prevalence of *Trichomonas vaginalis* infection among 200 preterm labor women was reported 5%, while the rate of this infection among 200 non-preterm labor women was 1%. There was statistically significant association between the Trichomonasis and preterm labor (sig. = 0.0062, *p* < 0.01) [14]. According to a systematic review in 2014, the overall rate of PTB has been reported as 5-9% in Vietnam [15]. The rate of genital tract infection was also high [16,17], even with sexually transmitted infections [18,19]. Based on the real condition of clinical practice in a developing country, some of pathogens were not indicated routinely for screening of infection in cases with PL or PPROM, such as Mycoplasma hominis or HPV. This study aimed to evaluate the impact of lower genital tract infections on PL and PPROM.

Methodology
Patient population
This case-control study was conducted at the Hospital of Hue University of Medicine and Pharmacy, Vietnam from November 2017 to May 2019. Inclusion criteria were singleton pregnancies from 22 to < 37 gestational weeks women with preterm labor (PL) and intact membranes (group 1) and women with preterm premature rupture of membranes (PPROM) within 6 hours before hospitalization (group 2). Control group participants were recruited at the same time from women who had singleton pregnancy and were at the same gestational age having routine prenatal follow-ups. We used a convenient sample size for analysis. Exclusion criteria were cases treated with antibiotics within past 2 weeks, being treated with vaginal progesterone, cervical cerclage, and cervical pessary; diagnosed with placenta previa, placenta abruption, fetal death or decline to participate in the study. This work was approved by the Hue University of Medicine and Pharmacy Ethics Committee, approval number H2017/296. Written informed consent was obtained from all participants.

Diagnostic methods
The diagnosis of PL with intact membranes have been relied on clinical markers, such as: cervical change detected manually or by ultrasound, vaginal bleeding, combinations of preexisting and developing risk factors, regular or frequent contractions or uterine tightening, often painless and fetal behavioral states affected by labor [20]. PPROM was suggested by a history of watery vaginal discharge and confirmed on sterile speculum examination: (1) visual pooling of clear fluid in the posterior fornix of the vagina or leakage of fluid from the cervical os; (2) an alkaline pH of the cervicovaginal discharge, which is typically demonstrated by seeing whether the discharge turns yellow nitrazine paper to blue (nitrazine test); and/or (3) microscopic ferning of the cervicovaginal discharge on drying [21]. General characteristics including age, geography (rural/urban), education, occupation, history of disease, gestational age and pregnancy follow-up were collected. Subjects were examined for rupture of membrane. The cotton swabs was inserted into the vagina to obtain samples of vaginal discharge for Gram stain (in cases with PB but intact membrane) and culture. Gram stain was perfomed to identify *Lactobacillus*, *Gardnerella* and bacteroides, mobiluncus, fungi, and white blood cells in only PL group and control group. *Trichomonas vaginalis* was determined by wet mount. Cultures of vaginal secretions (PL group and control group) and aminotic fluid from the vaginal fornix in PPROM group in an aerobic environment were performed to identify aerobic bacteria. A vaginal swab was used to collect amniotic fluid in PPROM group and vaginal secretions in PL group and control group. On the Gram staining samples, bacterial vaginosis was evaluated according to Nugent score [22]. A score of 0-10 was determined by combining three other scores. At least 10–20 high power (1000× oil immersion) fields were counted and an average were determined. Lactobacillus morphotypes: Score 0 for >30, score 1 for 5–30, score 2 for 1-4, score 3 for < 1, score 4 for 0; Gardnerella / Bacteroides morphotypes: score 0 for 0, score 1 for < 1, score 2 for 1–4, score 3 for 5–30, score 4 for > 30; curved Gram variable rods (this factor is less important — scores of only 0–2 are possible): score 0 for 0; score 1 for 1-4, score 2 for ≥ 5. A total score of 7 to 10 is compatible with BV, a score of 0-3 is assumed negative for BV, and a score of 4–6 is considered indeterminate for BV [23]. We only evaluated Nugent score for the PL group and intact membranes, but not the PPROM. Amniotic fluid could dilute these agents when gram staining is performed, therefore Nugent score results would not have been accurate. The vaginal swab was stretched out on blood agar, Drigalski lactose agar, and chocolate agar plates (Liofilchem s.r.l., Teramo, Italy) were used to culture the aerobic bacteria and yeasts in 24 hours and 48 hours. Candidiasis caused the typical

cottage cheese-like discharge and presence of blastopores or pseudohyphae were identified by microscopic examination with normal saline. In Trichomoniasis, the motile protozoa were detected from the wet mount of the vaginal samples under microscopic observation.

Data analysis

All analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were compared between groups using an independent sample t-test for normally distributed data or the Mann–Whitney U-test for skewed data. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) or two-sided p-values. Results with $p < 0.05$ were considered statistically significant.

Results

Demographic and general characteristics of patients in the study and control groups are shown in Table 1. There were 45 patients with PL and 34 with PPROM. The most common age group were 20 to 35 years in both groups (78.4% and 89.9%, respectively). Gestational age of 32 to < 37 weeks accounted for the highest rate in the two groups with 75.9%. History of

miscarriage was seen in 11.4% of the study group and 19.0% of the control group. The proportion of patients who had suffered from PL in the study group was 11.4%, whereas only 5.1% had PL in the control group. History of lower genital tract infection was seen in 10.1% of the study group and 13.9% of the control group. There were no significance differences in baseline variables between the study and control groups. Table 2 shows the results of vaginal discharge Gram staining in PL group (group 1) and control group. *Lactobacillus* was positive in 23/45 PL cases (51.1%), whereas *Gardnerella vaginalis* was seen in 71.1%. Candidiasis and Gram – positive cocci accounted for 64.4% and 48.9%, respectively. The rate of Gram – negative bacilli in PL patients was only 4.4%. We found no *Trichomonas* in any of the women with PL. There were no significant difference between PL group and control group in the pathogens detected by vaginal discharge Gram staining, except the Gram – positive cocci. The presence of these organisms were significantly higher in PL than in control group (48.9% vs. 29.1%, $p = 0.028$). Table 3 demonstrated the results of vaginal microbiology culture in PL group (group 1), PPROM group (group 2) and control group.

Table 1. Demographic and baseline characteristics of patients.

Factors		Study group		Control group		Total	p value
		N = 79	%	N = 79	%		
Age	< 20	4	5.1	3	3.8	47	
	20 - 35	62	78.4	71	89.9	61	
	≥ 35	13	16.5	5	6.3	18	0.09
	$\overline{X} \pm SD$	27.89 ± 5.83		27.56 ± 4.27			
	(Min-Max)	(18 – 40)		(20 – 39)			
Gestational age	$22^{0/7} – 27^{6/7}$	5	6.3	5	6.3	10	
	$28^{0/7} – 31^{6/7}$	14	17.7	14	17.7	28	1.00
	$32^{0/7} – 36^{6/7}$	60	75.9	60	75.9	120	
Geography	Rural	45	57.0	34	43.0	79	
	Urban	34	43.0	45	57.0	79	0.08
Occupation	Officer	22	27.8	21	26.6	43	
	Seller	9	11.4	13	16.5	22	
	Worker	16	20.3	14	17.7	30	
	Farmer	4	5.1	7	8.9	11	0.85
	Housewife	22	27.8	19	24.1	41	
	Other	6	7.6	5	6.3	11	
History of miscarriage	Yes	9	11.4	15	19.0	24	
	No	70	88.6	64	81.0	134	0.18
History of preterm birth	Yes	9	11.4	4	5.1	13	
	No	70	88.6	75	94.9	145	0.15
Number of children	No	41	51.9	42	53.2	83	
	1	24	30.4	31	39.2	55	0.15
	≥ 2	14	17.7	6	7.6	17	
History of lower genital tract infection	Yes	8	10.1	11	13.9	19	
	No	71	89.9	68	86.1	139	0.46

Table 2. Gram staining results of vaginal discharge in preterm labor and the control group.

Agents	PL		Control		p	OR	95% CI$_{OR}$
	N = 45	%	N = 79	%			
Lactobacillus	23	51.1	53	67.1	0.08	0.51	0.24 - 1.09
Gardnerella vaginalis	32	71.1	44	55.7	0.09	1.96	0.90 - 4.28
Mobiluncus	0	0.0	3	3.8	0.55		
Fungi	29	64.4	51	64.6	0.99	0.99	0.46 - 2.14
Gram – negative bacilli	2	4.4	2	2.5	0.62	1.79	0.24 - 13.17
Gram – positive cocci	22	48.9	23	29.1	0.03	2.33	1.09 - 4.98

PL: preterm labor; OR: Odds ratio.

Table 3. Results of vaginal microbiology culture.

Bacteria	Study group (N = 79)				Control group (N = 79)		p value
	PL (N = 45)		PPROM (N = 34)				
	n	%	n	%	n	%	
Enterococcus spp	1	2.2	4	11.8	2	2.5	0.064
S. aureus	4	8.9	5	14.7	7	8.9	0.607
Escherichia coli	0	0.0	2	5.9	1	1.3	0.140
Proteus mirabilis	0	0.0	1	2.9	0	0.0	0.160
Pseudomonas	0	0.0	1	2.9	0	0.0	0.160
Staphylococus Coagulase(-)	0	0.0	1	2.9	0	0.0	0.160
E. coli + S. aureus	0	0.0	1	2.9	0	0.0	0.160
Culture negative	40	88.9	19	55.9	69	87.3	<0 .001
Culture positive	5	11.1	15	44.1	10	12.7	

PL: preterm labor; PPROM: preterm premature rupture of the membrane.

Table 4. Evaluation of bacterial vaginosis by Nugent score.

Nugent score	PL Group		Control Group		p value
	n	%	n	%	
0-3 (Normal)	15	33.3	36	45.6	
4-6 (Intermediate)	17	37.7	34	43.0	0.009
7-10 (BV positive)	13	28.9	9	11.4	
Total	45	100	79	100	

PL: preterm labor; BV: bacterial vaginosis.

Table 5. The relation between some pathogens with preterm labor and premature rupture of membranes.

Pathogens	Study group		Control group		p	OR	95%CI$_{OR}$
	n	%	n	%			
PL (N = 45)							
Candida (+)	29	64.4	51	64.6	0.99	0.99	0.46-2.14
Candida (-)	16	35.6	28	35.4			
Total	45	100	79	100			
BV (+)	13	28.9	9	11.4	0.01	3.16	1.23 - 8.15
BV (-)	32	71.1	70	88.6			
Total	45	100	79	100			
Bacterial culture (+)	5	11.1	10	12.7	0.79	0.86	0.28 - 2.70
Bacterial culture (-)	40	88.9	69	87.3			
Total	45	100	79	100			
PPROM (n=34)							
Bacterial culture (+)	15	44.1	10	12.7	< 0.001	5.45	2.11 - 14.05
Bacterial culture (-)	19	55.9	69	87.3			
Total	34	100	79	100.0			
Trichomonas (+)	2	5.9	0	0	0.089	NA	NA
Trichomonas (-)	33	94.1	79	100			
Total	34	100	79	100			

PL: preterm labor; PPROM: preterm premature rupture of the membrane; NA: Non-applicable.

Aerobic bacteria was found more in the PPROM group compared with either the PL group or the control group (44.1% vs. 11.1% and 12.7%, respectively). The difference was statistically significant with $p < 0.001$. The rates of *Staphylococcus aureus* positive in PL, PPROM and control group were 8.9%, 17.6%, and 8.9%, respectively ($p = 0.607$). *Enterococcus spp* positive was identified in 2.2% of PL group, 11.8% of PPROM group, and 2.5% of control group ($p = 0.064$). The rate of *Escherichia coli* positive in PPROM group was also highest with 8.8%, whereas this value in control group was 1.3% ($p = 0.140$). We found no *Escherichia coli* positive case in PL group. Aerobic bacteria was significantly higher in PPROM group than the control group (44.1% vs. 12.7%, $p < 0.001$, OR = 5.45, 95%CI OR: 2.11-14.05). The evaluation of bacterial vaginosis by Nugent score in PL group and control group was shown in Table 4. BV was significantly higher in PL group compared with the control group (28.9% vs. 11.4, $p = 0.009$). Table 5 showed the relation between some pathogens with preterm labor and premature rupture of membranes. There was no significant difference of Fungi positive between PL and control group ($p = 0.99$, OR = 0.99, 95%CI OR: 0.46-2.14), but there was a significant difference in BV between PL and control group ($p = 0.014$, OR = 3.16, 95%CI OR: 1.23-8.15). *Trichomonas* positive was seen in 5.9% of PPROM cases and none in the control group.

Discussion

Genital tract infection is one of the main causes associated with preterm birth, which can result in an increased morbidity and mortality in neonates. This study aimed to determine the incidence of lower genital infections in preterm premature rupture of membranes (PPROM) and preterm labor. Nugent score is only used for quantification of *Lactobacillus, Gardnerella,* and *Mobiluncus* in the PL group, but not the PPROM group because in case of the ruptured membrane, amniotic fluid could dilute the vaginal fluid and the gram stain is no longer accurate. We have found a significant association with 3.16 time higher risk ($p = 0.014$) of PL when BV (+). Previous published study also reported the proportion of PTB, PPROM were 25% and 29.7%, respectively among 64 pregnant women with BV, with 2.7 times higher rate of preterm birth and 6.8 times of PPROM [11]. Similarly, high incidence of PTB (23.5%) and PPROM (14.3%) in women with BV was also reported compared to those with term pregnancies with only 2% and 0.3%, respectively [12]. Our data confirmed the adverse outcomes of BV in relation to PL

in a different population. Our data has revealed that aerobic bacteria were found mostly in PPROM group compared with PL group and control group with the highest proportion being *Staphylococcus aureus.* The rate of *Escherichia coli* positive in PPROM group was also highest with 8.8%, whereas we found no *Escherichia coli* positive case in the PL group. Previously, Nahar et al. in 2019 reported similar results in 200 patients that included pregnant and non-pregnant women, 41.07% of cases were positive with *Staphylococcus aureus,* 12% with *Enterococcus spp* and 21% with *Escheriachia coli* [24]. Specifically, the aerobic bacteria positive was related to PPROM ($p < 0.001$, OR = 5.45, 95%Ci OR: 2.11-14.05), but not to PL ($p = 0.799$). Since interleukin (IL) -1, IL-6, and IL-8 have been shown to be increased in pregnancy, aerobic bacteria may increase the risk of PTB, infection of aminotic membranes, and infection of the connective tissue of the umbilical cord [25]. Amniotic fluid is a very favorable environment for the growth of bacteria due to its rich nutrients and pH. We collected amniotic fluid through the vaginal tract; therefore, the assessment of aerobic bacteria in amniotic fluid was limited in our study. The relationship between aerobic bacteria and PTB and PPROM remains unclear, and more research is needed both in terms of diagnosis and its impact on pregnancy [26]. Among 45 cases with PL, *Lactobacillus* was positive in 23 (51.1%), whereas *Gardnerella vaginalis* was 71.1%. Research has indicated that *Lactobacillus* vaginal flora (CST 4) may be negative related with gestational age at birth ($p = 0.0039$) and that the risk of PTB was associated with the presence of *Gardnerella* or *Ureaplasma* [27]. Petricevic *et al.* showed that 44% of full-term women giving birth and 92% of preterm women had only one species of *Lactobacillus* spp. It is clear that the more types of *Lactobacillus spp* present in vaginal discharge, the better the pregnancy outcomes [28]. *Candida albicans* is an opportunistic pathogen; hormonal changes that lead to changes in vaginal pH allow for favorable conditions for fungal growth, especially in pregnancy. Although there is no reliable evidence to suggest an impact of fungal infection on pregnancy, asymptomatic recurrent vaginal yeast infections in the early stages of pregnancy may increase the rate of PTB and low birth weight [29]. Treating asymptomatic vaginal yeast infections has been shown to lower the risk of PTB (RR = 0.36, 95% CI = 0.17 – 0.75) [30]. In the present study, the rate of fungi positive in PL group and control group were 64.4% and 64.6%, respectively, and there was no significant difference of fungi positive between PL group and control group ($p = 0.99$, OR =

0.99, 95%CI OR: 0.46-2.14). The only significant difference in vaginal discharge Gram staining between PL and control was just observed in the Gram – positive cocci group (48.9% vs. 29.1%, *p* = 0.028). The most common gram – positive cocci in the vagina have been shown to be *alpha-hemolytic Streptococcus, beta-hemolytic Streptococcus A, C, G, Staphylococcus aureus, Streptococcus agalactiae,* and *Neisseria gonorrhea.* Our study showed a significantly higher rate of BV in PL than in control group (28.9% vs. 11.4, *p* = 0.009). A previous study on 64 pregnant women indicated that the rate of BV diagnosed by Nugent score was 26%, whereas the proportion of pregnant women with intermediatie Nugent score and normal Nugent score were 33.5% and 40.5%, respectively [11]. Other research has shown BV in pregnant women as diagnosed by Nugent score to be 19.6% [12] and 20.5% [31]. Adverse outcomes such as preterm birth, PROM and other complications were found more frequently in pregnant women with BV [31]. The discrepancy between our results and others may be due to studies having been conducted in different places and at different times. This partly reflects the epidemiological complexity of BV, especially in pregnant women. The limitation of the present study concerns in the cross-sectional descriptive design but not a longitudinal follow-up. We did not mention on the pregnancy outcomes, especially the neonatal condition. The future work should focus on the relationship between lower genital infection in PL and/or PPROM and the evidence of neonatal sepsis as well as neonatal outcomes.

Conclusions

Our data did not reveal an association between aerobic bacteria positive and PL but this infection did increase the risk of PPROM. BV is approved to be a considerable risk of PL. Isolation of aerobic bacteria may be an important risk factor for preterm premature rupture of membranes, while fungal infection does not seem to have any relationship with PL or PPROM.

Acknowledgements

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