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Microbial Profile of Women with Preterm Premature Rupture of Membrane in Saudi Arabia: A Retrospective Study

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ABSTRACT

This work aimed to establish the incidence of Preterm premature rupture of membrane (PPROM) and to identify the microbial organisms colonizing pregnant women with PPROM in the Western Province of Saudi Arabia. This retrospective study included all Saudi pregnant women diagnosed with PPROM who delivered at ≥27 weeks at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia, from January 2016 to December 2020. To detect routine microbial pathogens, cultures were analyzed from maternal specimens. PPROM cases accounted for 1.07%. O of all deliveries during the study period. The predominant pathogen isolated was Group B streptococcus (GBS) (72.9%), followed by Candida (18.6%). Advanced maternal age, primiparity, and neonatal morbidity were associated with PPROM (P=0.001). There is a low incidence of PPROM in Saudi Arabia. GBS was the most common microbial pathogen isolated from Saudi women admitted to KAUH with PPROM. This profile, which differs from the findings from other regions, highlights a clear need to determine the PPROM-associated pathogens in each country or region to establish suitable management with antibiotics. More advanced techniques are needed to detect genital infections and prevent subsequent complications.

Keywords: *Isolated microorganisms, Genital infection, Premature rupture of membrane, Saudi Arabia, Vaginal swab*

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INTRODUCTION

Premature rupture of membranes (PROM), the term used to refer to the bursting of the amniotic sac prior to the onset of labor, occurs in 5-10% of all pregnancies (Dayal & Hong, 2022). When this rupture of the fetal membranes occurs before the 37th week of pregnancy, the term preterm premature rupture of membranes (PPROM) is used (Mercer, 2005; Dayal & Hong, 2022). This significant complication impacts 2-4% of pregnancies and is implicated in one-third of preterm births (Mercer, 2005; Dayal & Hong, 2022). Given its link to preterm birth and associated complications, PPROM has been the focus of numerous clinical and epidemiologic studies (Dayal & Hong, 2022). Although no clear-cut etiology has been identified, research on this topic has suggested some association between PPROM and certain gynecologic and obstetric factors, including multigravida, history of miscarriage, premature labor or PROM, excessive amniotic fluid, and previous cervical procedures (Mercer, 2005; Dayal & Hong, 2022).

Genital infections are another factor linked to PPROM (Owens *et al*., 2020). Studies suggest these infections can weaken membranes' tensile strength, making rupture more likely (Brown *et al*., 2018). One such infection is candidiasis. Although older studies found no correlation between infection with candidiasis and PPROM, more recent research suggests that infection treatment is associated with a lower incidence of PPROM (Maki *et al*., 2017), giving indirect evidence of a link between this pathogen and PROM. Another microorganism, group B streptococcus (GBS), makes up the majority of vaginal-rectal pathogens in women with PPROM in the US and Canada (Brigtsen *et al*., 2022), with subsequent recommendations in both countries to give women with PPROM ampicillin prophylactically (Chen *et al*., 2022). Research has found that vaginal microbiomes vary according to ethnicity (Fettweis *et al*., 2019), underscoring the need for more studies to map the distribution of these microorganisms in different groups to facilitate effective management strategies.

While studies in some countries have thoroughly investigated the prevalence of different organisms in patients with PPROM, data from Saudi Arabia are inadequate. Few studies on this area have been published recently, and most were limited by small sample size. To fill this gap, the present study aims to investigate the incidence of PPROM in pregnancy and to record the range of microorganisms found in this group of patients in a tertiary care hospital in the Western Province of Saudi Arabia.

MATERIALS AND METHODS

In this retrospective study, we included all women with a PPROM diagnosis in their 27th week of pregnancy or later who delivered in the obstetric unit of King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia, during a 5-year period (from January 1, 2016, to December 31, 2020). Labor ward registers were used to identify eligible patients. Detailed participant data were extracted from the obstetric database and clinical management system used by KAUH and evaluated. Included in the evaluation were maternal demographics (e.g., age and parity), delivery mode, gestational age at delivery, birth

weight, and gender of the newborn. Exposure variables were those identified during laboratory tests that were carried out to detect genital infections. Selected for the study were singleton pregnancies of women at least 18 years old diagnosed with PPROM, no evidence of chorioamnionitis at admission, and no record of antibiotics use before cultures were taken. Excluded from the study were cases with complications related to the fetus (congenital or chromosomal fetal abnormalities, fetal growth restriction, or intrauterine hypoxia) or mother (gestational or pregestational diabetes, gestational hypertension, preeclampsia, or significant vaginal bleeding).

Diagnosis of PPROM was made through sterile speculum examination to confirm the pooling of amniotic fluid in the vagina. If clinical doubts persisted, the detection of insulin-like growth factor binding proteins in the vaginal fluid was used as confirmation that amniotic fluid was leaking. Following department protocol, microbiological analysis was conducted on all women diagnosed with membrane rupture by the attending physician following universal standard precautions. This included high vaginal, low vaginal, and rectal swabbing and mid-stream urine samples. Samples were tested to identify the microorganisms present.

Genital flora

Culture and antimicrobial susceptibility testing for GBS

Vaginal and rectal swab samples from pregnant women were obtained following universal standard precautions. In the laboratory, swabs were initially incubated in either a 5% sheep blood agar plate (BAP) with enrichment media or colistin–nalidixic acid agar at 37°C for 24 hours. Gram-positive cocci and bacilli can both be cultured in this way. Subsequently, gram-positive Streptococci were differentiated from gram-positive Staphylococci using a catalase reaction test. The presence of GBS was confirmed through the latex agglutination test, CAMP test, or automated identification machine.

Wet mount, gram staining, and vaginal cultures

Vaginal samples collected using sterile cotton-tipped swabs were placed in a transport medium and delivered to the laboratory, where they were aliquoted into two different tubes: one to be examined using direct wet-mount microscopy and the other to undergo Gram staining. These were then inoculated onto blood and MacConkey agar plates. Wet mount smears were used for the detection of yeast. The purpose of Gram staining was for the detection of inflammatory cells, yeasts, and pathogenic flora and to diagnose bacterial vaginosis through "clue cells" observation.

All women diagnosed with a rupture of the membrane were given 250 mg of erythromycin intravenously every 6 hours for 48 hours in addition to 2 gm of intravenous ampicillin every 6 hours. This was followed by oral antibiotics (amoxicillin 250 mg) every 8 hours for 5 days until the onset of labor. Another appropriate antibiotic replaced Erythromycin if erythromycin-resistant bacteria appeared in the cultures. In spontaneous or induced labor cases, benzylpenicillin was given intravenously to curb GBS until delivery. Patients at <34 weeks of pregnancy were managed conservatively, bearing evidence of acute chorioamnionitis or the onset of preterm labor. Women who had reached 34 weeks or more were advised that labor induction was possible. Delivery by cesarean section was avoided unless strongly indicated.

Statistical analysis

Data from the investigation was recorded and analyzed using SPSS version 20.0. Descriptive statistical analyses were carried out using means with standard deviations and medians with ranges and frequencies with corresponding percentages. Continuous variables were compared using the t-test, while discrete variables were compared using the Chi-square test. A P-value of <0.05 was deemed statistically significant.

RESULTS AND DISCUSSION

Of a total of 21,763 women who delivered at the KAUH obstetric unit during the study period, 232 women with PPROM and 969 women with PROM were eligible and included in the study, giving an overall incidence of PPROM of 1.07% (232/21,763) and 4.45% (969/21,763) of PROM. Across the 5 years, the incidence of PPROM ranged from 1.45 % in 2016 to 1.6% in 2020, with the lowest rate observed in 2019 (1.02%). The incidence of PROM ranged from 4.02% in 2016 to 7.06% in 2020, with the lowest rate observed in 2018 (3.88%).

Table 1 outlines the demographics and birth outcomes of the participants with PROM and PPROM. The age of the women ranged from 18–43 years, with an overall mean age of 28.43 ± 5.62 years. Advanced maternal age (defined as being 35 or older) and primiparity were more frequent in PPROM women than in those with PROM. Babies were born earlier to women with PPROM (32.7 vs. 39.2 weeks; P=0.001) and weighed less (2012 vs. 3030 g; P=0.001) than those born to women with PROM. More cesarean sections were performed on women with PPROM than on those with PROM (38.4% vs. 18%; P=0.001), and neonatal mortality was higher in the PPROM group as well (5.2% vs. 0.5%; P=0.001).

Table 1. Demographics and pregnancy outcomes of women with PROM and PPROM

Variable	PROM (n=969)	PPROM (n=232)	P-value
Maternal age (years)	28.17 ± 5.52	29.50 ± 6.12	0.001*
Advanced maternal age ≥ 35 years	163 (16.9%)	53 (22.8%)	0.001*
Primiparous	416 (42.9%)	154 (66.3%)	0.001*
Multi parous	553 (57.1%)	78 (33.6%)	0.001*
Gestational age at delivery (weeks)	39.18 ± 1.25	32.70 ± 3.57	0.001*
Cesarean delivery	174 (18%)	89 (38.4%)	0.001*
Baby weight at birth (g)	3030 ± 406	2012 ± 703	0.001*
Baby gender (male/female)	474/495	105/127	0.001*
Neonatal death	5 (0.5%)	12 (5.2%)	0.001*

Abbreviations; n=number; PROM = premature rupture of membrane; PPROM = preterm PROM

* Data are shown as mean ± standard deviation or No. (%); * Significant difference at P<0.05

Of the 1,201 women approached, 969 (80.7%) women were swabbed, and 768 (79.3%) were culture-positive. Types of microorganisms isolated from mothers with PPROM and PROM are shown in **Table 2**. Positive cultures were observed in 76.3% of PPROM women, with GBS accounting for most of the microorganisms (72.9%), followed by Candida albicans (C. albicans) (18.6%). In women with PROM, the culture positivity rate was 76.9%, similar to the rate among women with PPROM, with GBS accounting for approximately half of the microorganisms (50.8%), followed by C. albicans (30.6%).

Table 2. Microbiology investigation results in women with PROM and PPROM

Type of microorganism	PROM (n=591)	PPROM (n=177)	P-value
GBS	300 (50.8)	129 (72.9)	0.000*
C. albicans	181 (30.6)	33 (18.6)	0.000*
GBS & C. albicans	25 (4.2)	2 (1.1)	0.006*
CoNS	19 (3.2)	3 (1.7)	0.001*
Staphylococci saprophyticus	14 (2.4)	2 (1.1)	0.017*
Klebsiella pneumoniae	14 (2.4)	4 (2.3)	0.001*
Gardnerella vaginalis	11 (1.9)	0 (0)	-
Haemophilus influenza	11 (1.9)	1 (0.6)	0.001*
Enterococcus saprophyticus	9 (1.5)	2 (1.1)	0.036*
Pseudomonas aeruginosa	7 (1.2)	1 (0.6)	0.008*

Abbreviations, n=number; PROM = premature rupture of membrane; PPROM = preterm PROM

* Significant difference at P<0.05

The prevalence of PROM reported worldwide is inconsistent, ranging from 5–10% of all deliveries (Dayal & Hong, 2022). These disparities may result from variations in study populations. In women at ≥ 37 weeks of gestation who were admitted to KAUH in Jeddah, Saudi Arabia, from 2016–2020, the PROM rate ranged from 3.88 to 7.06%. These findings are similar to results from other Saudi regional studies (Mahdi *et al*., 2016) and lie within the range for PROM globally (Mercer, 2005; Dayal & Hong, 2022). However, it is noteworthy that the present findings are slightly higher than those from prior studies conducted in the same region and other developing countries. Yamani *et al*. (1999), for example, reported that 3.2% of 6,347 women who delivered at KAUH (37–41 weeks of gestation) over a three-year period (1993–1995) presented with PROM. Our findings are significantly lower, however than those reported by Byonanuwe *et al*. (2020) in Uganda (13.8%), Hailemariam *et al*. (2017) in Ethiopia (14.6%), and Zhuang *et al*. (2020) in China (18.7%). Disparities in quality of service and socioeconomic level of study participants may explain these variations in rates. In our study, the PPROM rate ranged from 1.02 to 1.6%, slightly higher than rates observed in other Saudi regional studies (Mahdi *et al*., 2016). In Mahdi *et al*. (2016) retrospective study of 380071 pregnancies at King Abdullah Medical City, Makkah, from 2014-106, 429 cases of PPROM (0.11%) were recorded, prompting the author to conclude that the rate of PPROM is low in our region (Mahdi *et al*., 2016). Although the present findings are slightly higher than those found in Makkah, they are lower than reported rates in other studies (Li *et al*., 2019). The determinants for PPROM identified in the literature include advanced maternal age, primiparity, and multigravida. Our study found that PPROM cases had higher rates of preterm births, lower birthweight babies, and increased neonatal death, substantiating a correlation between PPROM and significant neonatal morbidity and mortality.

In pregnancy, the prevalence of vaginal microorganisms doubles. This rise in colonization is linked to higher concentrations of estrogen in circulation and vaginal deposits of glycogen and other substrates (Amabebe & Anumba, 2018). In the current study, GBS was the most common pathogen in the cases of PROM and PPROM (55.8%). This differs dramatically from the results of a study in Abha, in the southern part of Saudi Arabia, where CoNS was the most prevalent pathogen (24.2%) found in women with PROM (Asindi *et al*., 2002). However, our findings on GBS's prevalence align with prior research in other countries. In a study of 212 women with PROM conducted in Brazil, Lajos *et al*. (2008) reported GBS as the most common pathogen. In their study in Trinidad and Tobago, Orrett *et al*. (2003) found GBS in 32.9% of vaginal and rectal samples from 201 women in their last trimester. A larger study in Iran on 1,197 pregnant women found a 9.1% rate of rectovaginal GBS colonization, and among those colonized with GBS, the incidence of PROM was elevated (Namavar *et al*., 2008).

GBS was also found to be the most commonly isolated organism in some studies conducted in Saudi Arabia. In a study done in Makkah, Mohamed *et al*. (2020) determined a GBS colonization rate of 15% in 400 Saudi women in their third trimester (Mohamed *et al*., 2020). A similar study in Alkhobar, Saudi Arabia, found that 19% of the women admitted to the hospital in labor were colonized with GBS (Musleh & Al Qahtani, 2018). In this Saudi context, the GBS colonization rate in pregnant women documented in the present study is higher than that found in other studies, especially the Abha study, where just one case was isolated from the 7,713 cases examined (Asindi *et al*., 2002). However, these disparities are not surprising since maternal GBS colonization is known to vary geographically (Sahuquillo-Arce *et al*., 2020). Although no recent studies have been conducted in Jeddah, the location of the present study, a 2011 study at the same hospital, isolated GBS in 31.6% of women in their third trimester diagnosed with PROM (Zamzami *et al*., 2011). It is impossible to know if the elevated GBS prevalence in the present study stems from an actual rise in GBS colonization. It is perhaps more plausible that differences in sampling and culturing methods account for the higher rate found in our study.

However, this predominance of GBS has not been reported in all countries. In a systematic review of research on the pathogens linked to PROM in China, Zeng *et al*. (2014) found that Staphylococcus and Escherichia made up the majority of microorganisms isolated in PROM cases. Besides suggesting regional variation as the reason for the low prevalence of GBS in their study population, the researchers pointed out that prenatal screening for GBS is not done on a large scale in China. Studies conducted in India and Iran found E. coli to be the predominant pathogen seen in PROM cases (38.2%, 24.2%; respectively), with GBS being the least prevalent (0.9%, 2.1%; respectively) (Kerur *et al*., 2006; Saghafi *et al*., 2018; AlShehri *et al.,* 2022). Other potential factors for such disparities in PROM-related pathogen prevalence beyond geographical variations

include different techniques involved in collecting, transporting, and storing samples (Vieira *et al*., 2019).

In our study, C. albicans was found in 181 cultures (30.6%) of PROM and 33 cultures (18.6%) of PPROM women. While the correlation between vaginal Candida colonization and PROM is not fully understood, one suggested mechanism is that the release of inflammatory cytokines observed with candidiasis can lead to the rupture of membranes (Camilli *et al*., 2020; Sumantri *et al.,* 2022). Other studies have documented fungal infections (Albeaik *et al*., 2020; AlHussain *et al.,* 2022). In Japan, Maki *et al*. (2017) reported Candida as the most frequent microbial organism (25%) found in women with PROM. In a meta-analysis of randomized controlled trials that involved a total of 685 pregnant women with asymptomatic vaginal Candida infection, treatment of the infection was found to be associated with decreased rates of preterm birth and PROM (Roberts *et al*., 2015), giving indirect evidence that candidiasis is associated with a higher risk of PROM. However, Rasti *et al*. (2014) found no significant association between colonization with Candida and the risk of PROM in Iran. In contrast, Nakubulwa *et al*. (2015) found Candida colonization to be protective against PROM, with a statistically significant number of PROM cases being less likely to have candidiasis than women who did not develop PROM, a finding in line with that reported by Karat *et al*. (2006). As these findings differ from those of other studies, Nakubulwa *et al*. (2015) have speculated that perhaps the amniotic fluid in patients whose membranes had already ruptured rinsed out the Candida cells, resulting in negative cultures, but this hypothesis has not been proved.

While the relationship between Candida colonization and PROM clearly warrants further elucidation, bacterial colonization makes up the majority of microorganisms reported in women with PROM and thus deserves most of our attention. In the United States, the rate of maternal colonization with GBS has dropped progressively over time to its current range of 20–25%. Better access to health care for women at high risk for GBS colonization and better treatment of urinary tract and/or other infections in pregnant women may account for earlier declines (Morgan *et al*., 2022). This suggests that similar reductions in the prevalence of GBS in Saudi Arabia could be achieved by improving access to health care for those at high risk, raising awareness about the importance of regular prenatal care, and providing appropriate treatment of infections during pregnancy.

CONCLUSION

GBS is the predominant pathogen isolated from Saudi women with PPROM and PROM, which is different from patterns reported in Western countries but similar to those reported in other geographical regions, highlighting the need to determine the microorganisms associated with PPROM in each country or region to tailor antibiotic treatment to the specific microorganism.

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