

# Risk factors of Premature Rupture of the Membranes: Case Control Study

**Comment [MK1]:** Can write investigation of risk factors.....

## Abstract :

**Background:** premature rupture of the membranes is a common condition with large contribution to preterm delivery and serious maternal and fetal morbidities. **Aims:** To investigate the risk factors of preterm premature rupture of membrane. **Methods:** Case-

control study included review of records of sample cases delivered in Benghazi medical center during the year 2021. Statistical analysis was done using SPSS 23.0 with appropriate tests.

**Results:** A total of 120 participants were enrolled with 60 patients in each group. Maternal age was statistically significant only when considering categories. The rate of mothers in advanced maternal age was in case group, 23.3% and for control group, 43.3%. Also, higher proportion of nullipara among group of cases; 30.0% and Control; 13.3%, higher rate of mothers with previous caesarean was found among case group (31.7% against 10.0%), vaginal discharge was reported among all of cases (100.0%) while rate among controls was only 45.0% and high CRP was reported only among case group in a proportion of 23.3% but not among control group. Those differences were all statistically significant. Blood group and Rhesus factor,

history of abortion among controls, urinary tract infection, early pregnancy bleeding and male fetus had statistically insignificant differences. **Conclusion and recommendations:** Premature rupture of the membranes is associated with primiparity, history of vaginal discharge

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and clinical as well as laboratory manifestations of inflammation and further multicenter prospective study to verify outcomes of premature rupture of membranes are recommended.

## 1. INTRODUCTION

Preterm prelabor rupture of the membranes (PPROM) is defined as rupture of the fetal membranes prior to 37 weeks of completed gestation. This significant obstetric problem occurs in about 3-4% of all pregnancies and is directly associated with 40% to 50% of all preterm births.<sup>1,2</sup>

It increases the risk of prematurity and leads to a number of other perinatal and neonatal complications, including a 1 to 2 percent risk of fetal death.<sup>3</sup>

One of the most common complications of preterm PROM is early delivery. The latent period, which is the time from membrane rupture until delivery, generally is inversely proportional to the gestational age at which PROM occurs.<sup>3</sup>

When PROM occurs too early, surviving neonates may develop sequelae such as malpresentation, cord compression, oligohydramnios, necrotizing enterocolitis, neurologic impairment, intraventricular hemorrhage, and respiratory distress syndrome.<sup>3</sup>

The number of pPROM cases exceeds that of preeclampsia and gestational diabetes and other iatrogenic preterm births. In addition, neonatal mortality and morbidities are higher in the pPROM group than any other subclasses of preterm births. Yet, pPROM is an often-ignored and understudied adverse outcome of pregnancy. Despite remarkable improvements in prenatal care over the past three decades, rates of pPROM and subsequent preterm delivery have worsened.<sup>4</sup>

Regarding the pathophysiology of PROM, almost half of all preterm births are caused or triggered by an inflammatory process at the fetomaternal

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interfaceresultinginpreterm labor or rupture of membranes with or without chorioamnionitis ("first inflammatory hit"). Preterm babies have highly vulnerable body surfaces and immature organ systems. They are postnatally confronted with drastically altered antigen exposure including hospital-specific microbes, artificial devices, drugs, nutritional antigens, and hypoxia or hyperoxia ("second inflammatory hit").<sup>5</sup>

The diagnosis of PROM requires a thorough history, physical examination, and selected laboratory studies. Patients often report a sudden gush of fluid with continued leakage. Physicians should ask whether the patient is contracting, bleeding vaginally, has had intercourse recently, or has a fever. It is important to verify the patient's estimated due date because this information will direct subsequent treatment.<sup>1</sup>

The physician should perform a speculum examination to evaluate if any cervical dilation and effacement are present. When preterm PROM is suspected, it is important to avoid performing a digital cervical examination; such examinations have been shown to increase morbidity and mortality.<sup>1</sup>

If PROM occurs during term, immediate delivery is recommended, as it is associated with a significantly lower perinatal morbidity rate than expectant management.<sup>6-9</sup>

However, the management of women with preterm PROM (PPROM), accounting for 40% of the total preterm deliveries, is somewhat controversial. Immediate delivery may lead to complications resulting from fetal immaturity, but expectant management is associated with risks such as placenta abruptio, infection, fetal distress, and umbilical cord prolapse, causing a medical dilemma.<sup>7,10,11</sup>

In early PPRM, defined as PROM before 34.0 weeks of gestation, expectant management is strongly recommended because of adverse neonatal outcomes from prematurity

.InastudyofEkinetal.,althoughcomplicationsuch

as chorioamnionitis and placental abruption were increased, the overall adverse pregnancy outcomes were decreased in women managed expectantly.<sup>12</sup>

The optimal management of late PPRM, defined as PROM between 34.0 weeks and 36.6 weeks of gestation, remains inconclusive. Therefore, the management of late PPRM should be determined on the basis of a comprehensive acknowledgment of the risk of infection and possible complications from premature delivery. According to the 2018 American College of Obstetricians and Gynecologists (ACOG) guidelines, expectant management, including a combination therapy of intravenous ampicillin and erythromycin, administration of antenatal corticosteroids until 34.0 weeks of gestation and group B Streptococcus prophylaxis, is strongly recommended.<sup>6,13</sup>

The guidelines recommend prompt delivery after 34.0 weeks of gestation. However, the Cochrane review mentioned the lack of clinical evidence to support these guidelines.<sup>7,13</sup>

## **2. REVIEW OF THE LITERATURE:**

The etiology of PPRM is unclear. PPRM may be caused by cervical incompetence, genital infections, and uterine abnormality. Some studies have shown that a history of PPRM, race, smoking status, poor nutrition, and genital infection are risk factors for PPRM.<sup>14</sup>

The etiologies of genital infection include *Chlamydia trachomatis* (CT), *Ureaplasma urealyticum* (UU), *Candida albicans*, syphilis, *Neisseria gonorrhoea* (NG), group B streptococci (GBS), herpes simplex virus (HSV), and bacterial vaginosis (BV).<sup>15</sup>

Genital infections might cause a release of cytokines and other inflammatory mediators that may weaken the membrane and cause PPRM. Studies by Chow and Blas showed that CT infection was associated with the occurrence of PPRM.<sup>16,17</sup>

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Pregnant women with BV more readily developed PPROM than women without BV.<sup>16-19</sup>

Candidiasis infection in pregnant women with PPROM is controversial, and a recent study showed that the treatments for candidiasis might reduce the incidence of PPROM.<sup>20</sup>

Pregnant women who were infected with NG had a six-time higher risk of developing PPROM than women without NG infection. GBS might cause the activation of inflammatory cells in fetal membranes, which could lead to PPROM.

18,21

According to Bouvier D et al (2019) The specific risk factors for PPROM were body mass index (BMI) < 18.5 kg/m<sup>2</sup>, history of PPROM, nulliparity, gestational diabetes, and low level of education.<sup>22</sup>

Watts DH et al (1991)<sup>23</sup> determined CRP levels serially from 22 weeks' gestation until delivery in healthy pregnant women without antepartum complications; the median hs-CRP values ranged from 0.7–0.9 mg/dL for women who were not in labour and showed no significant change in serum levels of hs-CRP according to the gestational age.

Moghaddam Banaem L et al (2012)<sup>24</sup> found a significant relationship between elevated maternal serum hs-CRP levels in the first 20 weeks of pregnancy and the later occurrence of preterm premature rupture of membranes (PPROM) and preterm birth as well.

Nevertheless, a recent meta-analysis by Etyang AK et al (2020)<sup>25</sup> showed that the sensitivity and specificity for CRP ≥ 20 mg/L (5 studies, 252 participants) was 59% (95% CI 48-69) and 83% (95% CI 74-89) respectively. So, the use of CRP for predicting PPROM is limited.

### **Aims of the study**

To investigate the demographic and clinical risk factors for preterm premature rupture of membranes among the Libyan patients.

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## **Patients and methods**

### **1. Design of study and settings:**

Case control study in mothers admitted for delivery to labour room in AlJamhoria hospital /Benghazim medical center BMC during the period of the year 2021.

### **2. Group of the study:**

Group of cases were randomly selected cases of preterm premature rupture of the membranes.

Group of controls were mothers delivered normally without significant complications at the same time.

### **3. Data synthesis:**

Review of records for all patients with premature rupture of the membrane deliveries according to preformed data sheet includes data related to demographic and personal characteristics, past history, the present delivery.

### **4. Variables:**

Maternal

age Parity

Blood group Rhf

actor status

History of obstetric conditions.

History of vaginal discharge

History of urinary tract

infection. History of early pregnancy

bleeding. Vital signs

CRP (c-reactive protein)

### **5. Ethical considerations:**

All participants were consented for study performance. Confidentiality of data was assured using an anonymous form of data collection.

### **6. Statistical analysis:**

Data were analyzed using statistical package for social science (SPSS) version 23. Descriptive statistics as frequency and percentage.

Inferential statistics were used when needed Chi-square ( $X^2$ ), t test and Mann-Whitney U test to find the difference in the distribution of the variables between the two groups,  $P$ -values were considered significant when  $\leq 0.05$ .

Data were presented in form of tables and figures, were the figures done by Microsoft Excel 2010.

## **RESULTS**

A total of 120 participants were enrolled with 60 patients in each group. All of the cases in case group were diagnosed with history of painless leaking and positive speculum examination.

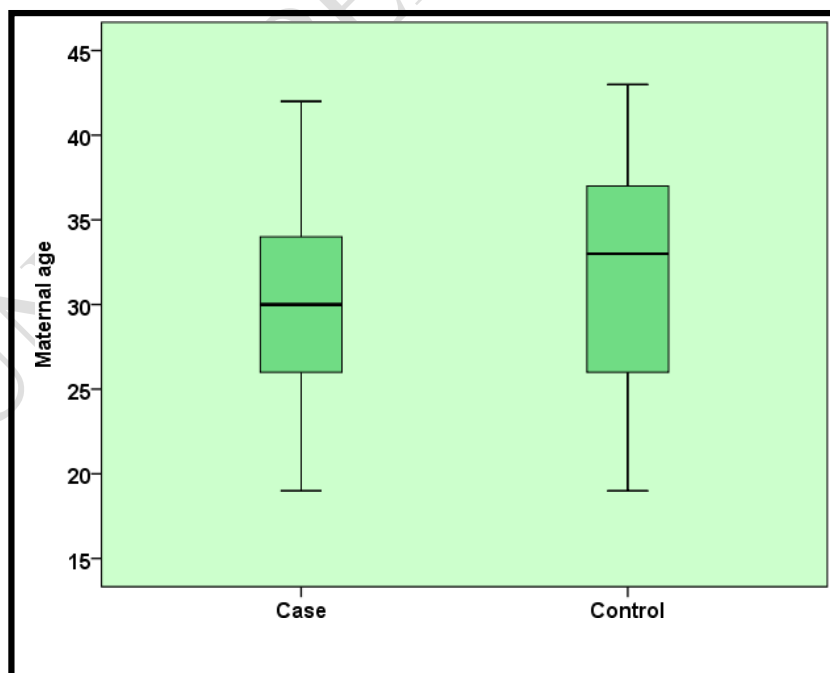
**Demographic and other risk factors:**

Maternal age tends to be lower among cases and rate of advanced maternal age is higher among controls. The difference was statistically significant. See figure 1 and table 1

Parity is also less among cases and a higher proportion of nullipara among this group. The difference was statistically significant. See figure 2 and table 2  
Larger proportion of mothers with history of abortion among controls, but the difference was not statistically significant. See table 3

Higher rate of mothers with previous was found among case group. The difference was statistically significant. See table 4

Maternal age



**Figure1: Comparison of maternal age across study groups**

Case Mean 30.53 (SD 5.622), Median 30.00 Range 19-42

Control Mean 31.92 (SD 6.692), Median 33.00 Range 19- 43

Mann-Whitney U 1545.0 P 0.180

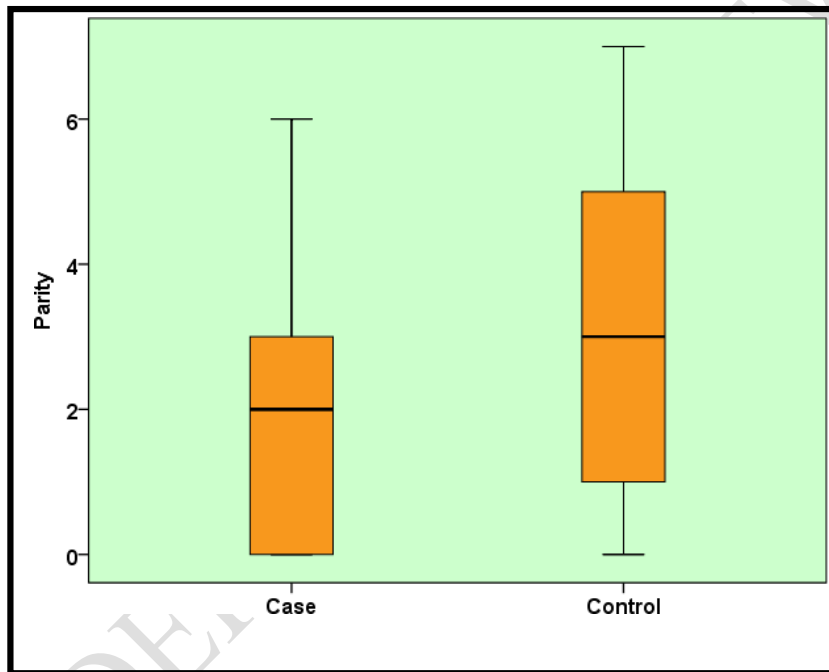
**Table 1: Group and Advanced maternal age**

			Advanced maternal age		Total
			Yes	No	
Group	Case	Count	14	46	60
		% within Group	23.3%	76.7%	100.0%
	Control	Count	26	34	60
		% within Group	43.3%	56.7%	100.0%
Total		Count	40	80	120
		% within Group	33.3%	66.7%	100.0%

Pearson Chi-Square 5.400 P=0.020

Parity

Figure2: Comparison of parity across study groups



Case Mean1.83(SD1.719),Median2.00Range0-6

Control Mean3.07(SD2.193), Median3.00,Range0-7

Mann-WhitneyU 1212.5,P0.002

**Table2:GroupandPrimi**

			Primi		Total
			Yes	No	
Group	Case	Count	18	42	60
		% within Group	30.0%	70.0%	100.0%
	Control	Count	8	52	60
		% within Group	13.3%	86.7%	100.0%
Total		Count	26	94	120
		% within Group	21.7%	78.3%	100.0%

Pearson Chi-Square 4.910 0.027

Abortion

**Table3:Groupandanyabortions**

			Anyabortions		Total
			Yes	No	
Group	Case	Count	16	44	60
		% withinGroup	26.7%	73.3%	100.0%
	Control	Count	19	41	60
		% withinGroup	31.7%	68.3%	100.0%
Total		Count	35	85	120
		% withinGroup	29.2%	70.8%	100.0%
PearsonChi-Square			.363	0.547	

Previous scars

**Table4: Group and any previous scars**

			Any previous scars		Total
			Yes	No	
Group	Case	Count	19	41	60

		% withinGroup	31.7%	68.3%	100.0%
	Control	Count	6	54	60
		% withinGroup	10.0%	90.0%	100.0%
Total		Count	25	95	120
		% withinGroup	20.8%	79.2%	100.0%

PearsonChi-Square 8.539 P=0.003

Maternalbloodgroup:

**Table5:GroupandMaternalbloodgroup**

Group	Case		Maternalblood group				Total
			A	B	AB	O	
		Count	24	11	1	24	60
		% withinGroup	40.0%	18.3%	1.7%	40.0%	100.0%
	Control	Count	31	9	2	18	60
		% withinGroup	51.7%	15.0%	3.3%	30.0%	100.0%

Total	Count	55	20	3	42	120
	% withinGroup	45.8%	16.7%	2.5%	35.0%	100.0%

PearsonChi-Square 2.281 0.516

MaternalRhfactor

**Table6:GroupandMaternalRh**

		MaternalRh		Total	
		Rh+	Rh -		
Group	Case	Count	55	5	60
		% withinGroup	91.7%	8.3%	100.0%
Control	Count	53	7	60	
	% withinGroup	88.3%	11.7%	100.0%	
Total		Count	108	12	120
		% withinGroup	90.0%	10.0%	100.0%

PearsonChi-Square 0.370 0.543

**Clinical characteristics:**

Most of cases (41/60; 68.3%) had duration of leaking < 72 hours.

Gestational diabetes was reported only among cases in small proportion. The difference was statistically insignificant. See table 7

Vaginal discharge was reported among cases in higher rates than controls. The difference was statistically significant. See table 8

Urinary tract infection and also early pregnancy bleeding were reported in high rate among cases, but the difference was not statistically significant. See tables 9 and 10

Fever and tachycardia were only documented among cases not in controls. The difference was statistically significant. See figures 3 and 4

CRP was only elevated among case group but not in control group. The difference was statistically significant. See table 11

History of obstetric conditions:

**Table 7: Group and GDM**

		Count	GDM		Total
			GDM	NoGDM	
Case			2	58	60

Group	Control	% withinGroup	3.3%	96.7%	100.0%
		Count	0	60	60
Total		% withinGroup	0.0%	100.0%	100.0%
		Count	2	118	120
		% withinGroup	1.7%	98.3%	100.0%
		Count			

Fisher's exact test  $P=0.496$

History of vaginal discharge:

**Table 8: Group and Vaginal discharge**

			Vaginal discharge		Total
			Reported	Not reported	
Group	Case	Count	60	0	60
		% withinGroup	100.0%	0.0%	100.0%
Control		Count	27	33	60
		% withinGroup	45.0%	55.0%	100.0%

Total	Count	87	33	120
	% within Group	72.5%	27.5%	100.0%

Pearson Chi-Square 45.517  $P < 0.001$

History of UTI:

**Table 9: Group and UTI**

			UTI		Total
			Reported	Not reported	
Group	Case	Count	22	38	60
		% within Group	36.7%	63.3%	100.0%
Control	Count	18	42	60	
		% within Group	30.0%	70.0%	100.0%
Total		Count	40	80	120
		% within Group	33.3%	66.7%	100.0%

Pearson Chi-Square 0.600  $P = 0.439$

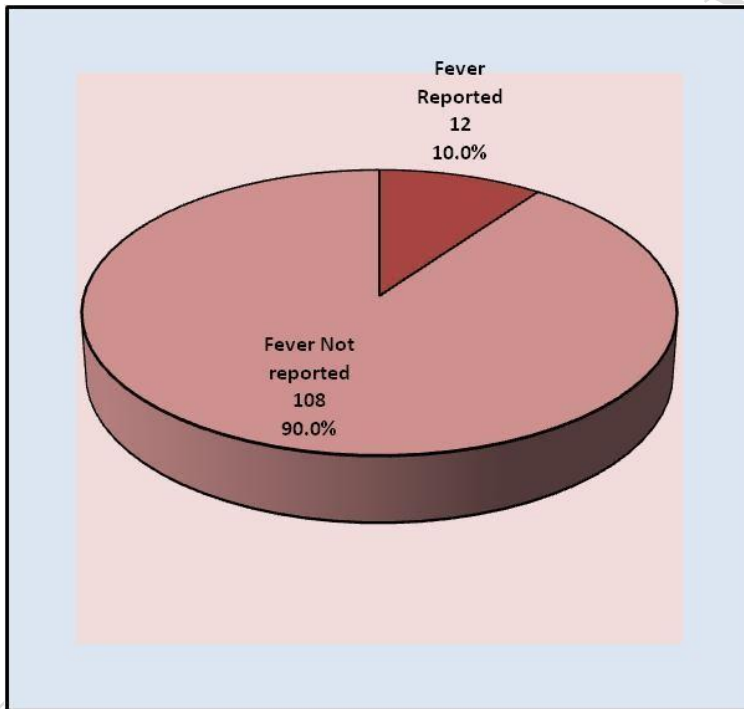
History of early pregnancy bleeding:

**Table 10: Group and early pregnancy bleeding**

			Bleeding		Total
			Reported	Not reported	
Group	Case	Count	3	57	60
		% within Group	5.0%	95.0%	100.0%
	Control	Count	0	60	60
		% within Group	0.0%	100.0%	100.0%
Total		Count	3	117	120
		% within Group	2.5%	97.5%	100.0%

Fisher's Exact Test  $P=0.244$

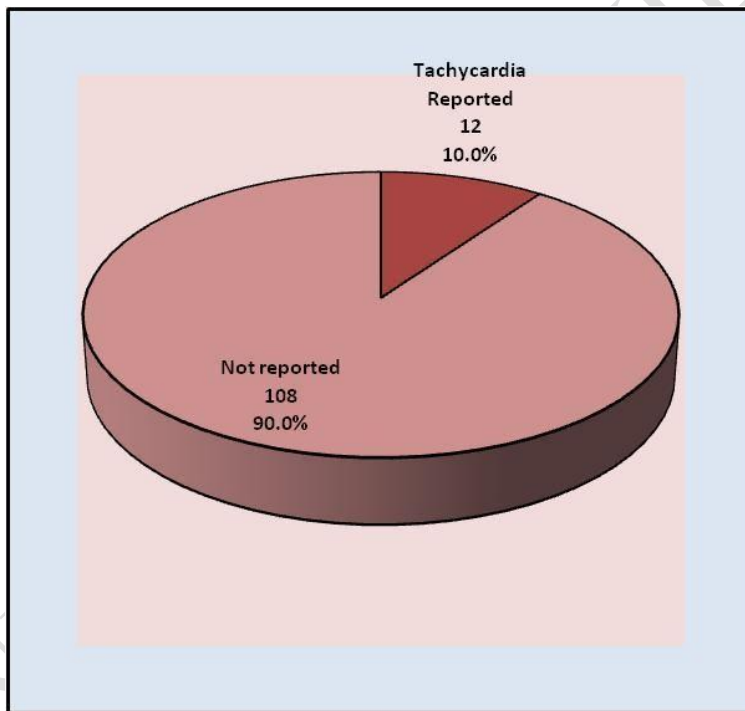
Hightemperature:



**Figure3:Distributionof PROMcasesaccordingtofever**

$\chi^2 = 13.3, P < 0.001$

High pulse rate:



**Figure 5: Distribution of PROM cases according to tachycardia**

$\chi^2 = 13.3, P < 0.001$

HighCRP:

**Table11:GroupandHigh CRP**

		CRPHigh		Total	
		YES	NO		
Group	Case	Count	14	46	60
		% withinGroup	23.3%	76.7%	100.0%
	Control	Count	0	60	60
		% withinGroup	0.0%	100.0%	100.0%
Total		Count	14	106	120
		% withinGroup	11.7%	88.3%	100.0%

PearsonChi-Square15.849  $P<0.001$

**Gender of the baby:**

Male gender of the neonate is higher among case group than in control group. The difference was not statistically significant. See table 12

**Table 12: Group and Gender of the baby**

			Gender		Total
			Male	Female	
Group	Case	Count	42	18	60
		% within Group	70.0%	30.0%	100.0%
	Control	Count	33	27	60
		% within Group	55.0%	45.0%	100.0%
Total		Count	75	45	120
		% within Group	62.5%	37.5%	100.0%

Pearson Chi-Square 2.880  $P=0.09$

## DISCUSSION

PPROM has unclear etiology. PPRM may be caused by multiple factors that involve inflammatory conditions.<sup>14</sup>

The present study investigated total of enrolled 120 participants with 60 patients in each group. All of the cases in case group were diagnosed with history of painless leaking and positive speculum examination.

Maternal age tends to be lower among cases and rate of advanced maternal age is higher among controls; Case group: Mean 30.53 years (SD 5.622), Median 30.00 and for Control group: Mean 31.92 years (SD 6.692),  $P = 0.180$ . The difference was statistically significant only when considering categories. The rate was in Case, 23.3% and for Control group, 43.3%;  $P = 0.020$

Parity is also less among cases and a higher proportion of nullipara among this group. Case; 30.0% and Control; 13.3%. the difference is statistically significant;  $P = 0.027$ . This confirms the finding of Bouvier D et al (2019)<sup>22</sup> which concluded primiparity as a risk factor for PPRM.

Also comparison of parity as a scale parameter showed significant difference, Case group; Mean 1.83 (SD 1.719) and in Control group; Mean 3.07 (SD 2.193). The difference was statistically significant;  $P = 0.002$ . The cause of this association is not yet clear. Anyhow, immunerelated mechanisms may partially explain this.

Larger proportion of mothers with history of abortion among controls, but the difference was not statistically significant.

Higher rate of mothers with previous caesarean was found among casegroup (31.7% against 10.0%). The difference was statistically significant;  $P = 0.003$

Maternal blood group and maternal Rh factor didn't show any significant association.

Regarding clinical characteristics, most of cases (41/60; 68.3%) had duration of leaking < 72 hours.

Gestational diabetes was reported only among cases in small proportion. The difference was statistically insignificant. This is discordant with Bouvier D et al (2019)<sup>22</sup> which stated GDM as a risk factor for PPROM. The smaller sample size and the probably under diagnosed GDM might be the cause.

Vaginal discharge was reported among all of cases (100.0%) while rate among controls was only 45.0%. The difference was statistically significant ( $P < 0.001$ ). This is concordant with several studies demonstrated that genital infections might cause release of cytokines and other inflammatory mediators that may weaken the membrane and cause PPROM. Pregnant women with BV more readily developed PPROM than women without BV.<sup>15</sup>

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As a consequence of infection, fever and tachycardia were only documented among cases (20.0% for each) not in controls. The difference was statistically significant ( $P < 0.001$ ).

Regarding CRP which is known inflammatory marker for several conditions and at cut-off level of 10 mg/L it was reported only among casegroup in a proportion of 23.3% but not among control group;  $P < 0.001$ . This is concordant with Moghaddam Banaem Letal (2012)<sup>24</sup> and Kahyaoğlu Setal

(2014) <sup>25</sup>. Anyhow, the sensitivity and specificity by the present study seems less than described by Etyang AK et al (2020) <sup>25</sup> in their meta-analysis. This might put limitation for the reliability of use of CRP.

Urinary tract infection and also early pregnancy bleeding were reported in high rate among cases, but the difference was not statistically significant.

Male gender of the neonate was higher among case group than in control group (70.0% versus 55.0%). The difference anyhow, was not statistically significant.

The limitations of the present study included retrospective design and difficulty in gathering complete data. Further large multicenter studies with prospective design and use of high sensitivity (hs)CRP as well as other inflammatory markers in sum to clinical predictors and outcome utility estimation are to be considered.

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## **Conclusion and Future**

### **Recommendations 1. Conclusion:**

Premature rupture of the membranes is associated with primiparity, history of vaginal discharge and clinical as well as laboratory manifestations of inflammation.

### **2. Recommendations:**

1. Enhancing clinical and laboratory evaluation of primigravid mothers before delivery in the time before term to expect PPROM and avoid complications.
2. Multicenter prospective study to verify risk factors and outcomes of premature rupture of the membranes cases in the Libyan population.

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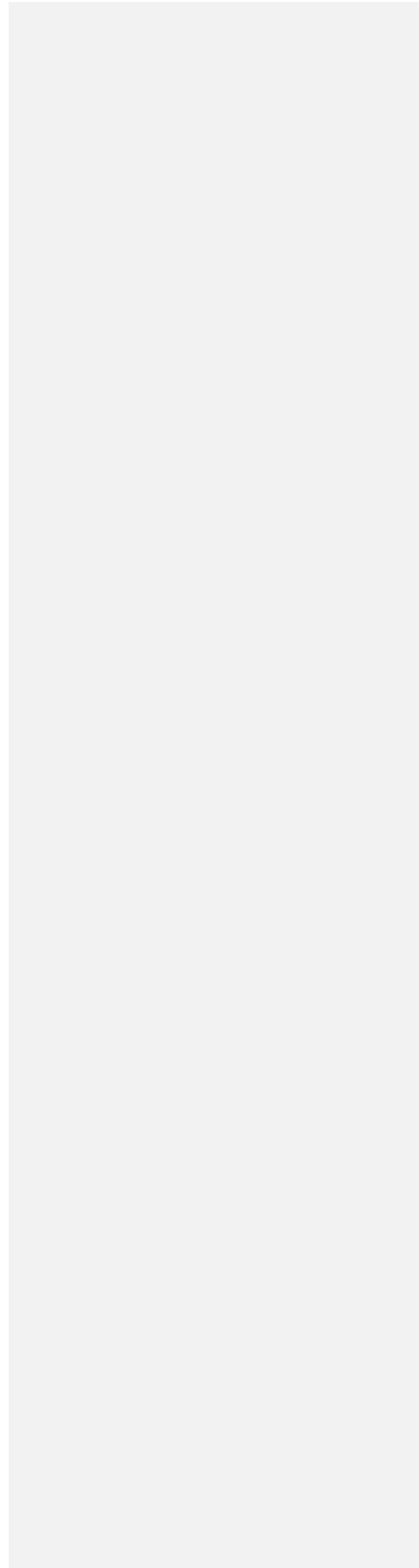
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**APPENDIX**

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**Appendix(Preformed data collectionsheet)**

**Arab Board of Health Specialties**

Epidemiology and outcomes of premature rupture of membranes

serial number			
1Maternal age			
2Parity	3Abortion	4Previous scars	
5Maternal blood group		6Maternal Rh	
7.Any chronic condition diagnosed before			
8.Any obstetric condition this pregnancy			
9.Painless Leaking?		YES	NO
10.SE		Confirmative	Not
11.Duration of leaking in hours before delivery (Latency period)			
Hx: 12.Vaginal discharge		YES	NO
13.UTI		YES	NO
14.Bleeding		YES	NO
15. Fever		YES	NO
16.Tachycardia		YES	NO
17.CRP High		YES	NO

UNDER PEER REVIEW

