Risk factors of Premature Rupture of theMembranes: Case Control Study

Abstract :

Background: premature rupture of the membranes is a common condition withlarge contribution to preterm delivery and serious maternal and fetal morbidities.**Aims:** To investigate the risk factors of preterm premature rupture of membrane.**Methods:**Case–controlstudyincludedreviewofrecordsofsamplecasesdelivered in Benghazi medical center during the year 2021. Statistical analysis wasdone using SPSS 23.0 with appropriate tests.**Results:** A total of 120 participantswereenrolledwith60patientsineachgroup.Maternalagewasstatisticallysignificant only when considering categories. The rate of mothers in advancedmaternal age was in case group,23.3%and for control group, 43.3%.Also,higherproportion of nullipara among group of cases; 30.0% and Control; 13.3%, higherrate 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%) whilerate among controls was only 45.0% and high CRP was reported only among casegroup in a proportion of 23.3% but not among control group. Those differenceswere all statistically significant. Blood group and Rhesus factor, history of abortionamongcontrols,urinarytractinfection,earlypregnancybleedingandmalefetushadstatisticallyinsignificantdifferences.**Conclusionandrecommendations:**Prematureruptureofthemembranesisassociatedwithprimiparity,history ofvaginal discharge and clinical as well as laboratory manifestations of inflammation and further multicenter prospective study to verify outcomes ofpremature ruptureofmembranesare recommended.

1.INTRODUCTION

Pretermprelaborruptureofthemembranes(PPROM)isdefinedasruptureof the fetal membranes prior to 37 weeks of completed gestation. This significantobstetric problem occurs in about 3-4% of all pregnancies and is directly associatedwith 40%to50%of allpretermbirths.[1,2]

It increases the risk of prematurity and leads to a number of other perinataland neonatal complications,including a1 to 2percent riskoffetal death.[3]

One of the most common complications of preterm PROM is early delivery.Thelatentperiod,whichisthetimefrommembraneruptureuntildelivery,generallyisinverselyproportionaltothegestationalageatwhich PROMoccurs.[3]

Comment [NS1]: Capital

Comment [NS2]: the method section seems to be deficient.
In an abstract, the method section should include a concise summary of the methodology or research design used in the study. It should provide enough information for readers to understand how the study was conducted, without going into excessive detail.
Provide a summary of the participants involved in the study, including relevant characteristics such as demographics, sample size, and any inclusion or exclusion criteria.
Briefly mention the statistical or analytical techniques used to analyze the data.

Comment [NS3]: this sentence seems to be inappropriate. This fact can be narrated in a better way. Such as, In the case group, 23.3% of mothers were categorized as advanced maternal age, whereas in the control group, this percentage was 43.3%.

Comment [NS4]: place a space.

Comment [NS5]: place a space

Comment [NS6]: instead of and, place a full stop and start next sentence to narrate recommendation.

Comment [NS7]: Overall review of introduction.
The word count is more than generally required for an introduction.
There should be three to four paragraphs. This introduction contains many paragraphs of one to two lines.
The heading of literature review and aim of study is not required, rather these two things should be merged under the one heading of introduction.
Overall, the introduction must include Background, Preliminary Literature Review and Significance of the Study): One paragraph related to global work on the subject, one paragraph related to local work and one paragraph related to institutional work with a total of 5 to 8 references. Last paragraph should indicate the importance of work and what information/gaps are missing on topic/subject and how this study will contribute to new knowledge. At the end describe your objective in a SMART fashion.

Comment [NS8]: 37 completed weeks of gestation

When PROM occurs too early, surviving neonates may develop sequelaesuchasmalpresentation,cordcompression,oligohydramnios,necrotizingenterocolitis, neurologic impairment, intraventricular hemorrhage, and respiratorydistress syndrome.[3]

The number of pPROM cases exceeds that of preeclampsia and gestationaldiabetes and other iatrogenic preterm births. In addition, neonatal mortality andmorbiditiesarehigherin pPROM group thanany other subclassesofpretermbirths.Yet,pPROMisanoften-ignoredandunderstudiedadverseoutcomeofpregnancy. Despite remarkable improvements in prenatal care over the past threedecades,ratesof pPROMandsubsequentpretermdeliveryhaveworsened.[4]

Regarding the pathophysiology of PROM, almost half of all preterm birthsare caused or triggered by an inflammatory process at the feto-maternal interfaceresultinginpretermlaborорruptureofmembraneswithorwithoutchorioamnionitis("firstinflammatoryhit").Pretermbabieshavehighlyvulnerable body surfaces and immature organ systems. They are postnatally confronted with adrastically altered antigen exposure including hospital-specific microbes, artificialdevices,drugs,nutritionalantigens,andhypoxiaorhyperoxia("secondinflammatoryhit").[5]

The diagnosis of PROM requires a thorough history, physical examination,and selected laboratory studies. Patients often report a sudden gush of fluid withcontinuedleakage.Physiciansshouldaskwhetherthepatientiscontracting,bleeding vaginally, has had intercourse recently, or has a fever. It is important toverifythepatient'sestimatedduedatebecausethisinformationwilldirectsubsequent treatment.[1]

The physician should perform a speculum examination to evaluate if

Comment [NS9]: these are the intrauterine sequalae and not included in neonatal period.

Comment [NS10]: other causes of

anycervicaldilationandeffacementarepresent.WhenpretermPROMissuspected,itis important to avoid performing a digital cervical examination; such examinationshavebeenshowntoincreasemorbidityandmortality.[1]

If PROM occurs during term, immediate delivery is recommended, as it isassociatedwithasignificantlylowerperinatalmorbidityratethanexpectantmanagement. [6–9]

However,themanagementofwomenwithpretermPROM(PPROM),accounting for 40% of the total preterm deliveries, is somewhat controversial.Immediate delivery may lead to complications resulting from fetal immaturity, butexpectant management is associated with risks such as placenta abruptio, infection,fetaldistress, andumbilicalcordprolapse,causingamedicaldilemma.[7,10,11]

InearlyPPROM,definedasPROMbefore34.0weeksofgestation,expectantmanagementisstronglyrecommendedbecauseofadverseneonataloutcomesfromprematurity.InastudyofEkinetal.,althoughcomplicationssuch as chorioamnionitis and placental abruption were increased, the overall adversepregnancyoutcomes weredecreasedin womenmanaged expectantly.[12]

The optimal management of late PPROM, defined as PROM between 34.0weeksand36.6weeksofgestation,remainsinconclusive.Therefore,themanagement of late PPROM should be determined on the basis of a comprehensiveacknowledgmentoftheriskofinfectionandpossiblecomplicationsfrompremature delivery. According to the 2018 American College of Obstetricians andGynecologists(ACOG)guidelines,expectantmanagement,includingacombination therapy of intravenous ampicillin and erythromycin, administration ofantenatal corticosteroids until 34.0 weeks of gestation and group B Streptococcusprophylaxis,isstronglyrecommended.[6,13]

The guidelines recommend prompt delivery after 34.0 weeks of gestation.However, the Cochrane review mentioned the lack of clinical evidence to

supportthese guidelines.[7,13]

2.REVIEWOFTHELITERATURE:

The etiology of PPROM is unclear. PPROM may be caused by cervicalincompetence,genitalinfections,anduterineabnormality.Somestudieshavesho wn that a history of PPROM, race, smoking status, poor nutrition, and genitalinfection are riskfactorsfor PPROM.[14]

The etiologies of genital infection include*Chlamydia trachomatis*(CT),*Ureaplasma urealyticum* (UU), *Candida albicans*, syphilis, *Neisseria gonorrhoea*(NG), groupB streptococci(GBS), herpes simplex virus(HSV), and bacterialvaginosis (BV). [15]

Genitalinfectionsmightcauseareleaseofcytokinesandotherinflammatorymedia torsthatmayweakenthemembraneandcausePPROM.Studies by Chow andBlasshowedthatCT infectionwas associatedwiththeoccurrenceof PPROM.[16,17]

Pregnant women with BV more readily developed PPROM than womenwithout BV. [16–19]

Candidiasis infection in pregnant women with PPROM is controversial, andarecentstudyshowedthatthetreatmentsforcandidiasismightreducetheincidenceof PPROM.[20]

Pregnant women who were infected with NG had a six-time higher risk ofdevelopingPPROM thanwomenwithoutNGinfection.GBSmightcausetheactivationofinflammatorycellsin fetalmembranes,whichcouldleadtoPPROM.
[18,21]

According to Bouvier D et al (2019) The specific risk factors for PPROMwerebodymassindex(BMI)<18.5kg/m^2,historyofPPROM,nulliparity,gestati onal diabetes,andlowlevelof education.[22]

Watts DH et al (1991) [23] determined CRP levels serially from 22 weeks' gestationuntildeliveryinhealthypregnantwomenwithoutantepartumcomplications; the median hs-CRP values ranged from 0.7–0.9 mg/dL for womenwho were not in labour and showed no significant change in serum levels of hs-CRPaccordingtothegestationalage.

Comment [NS11]: please describe hs-CRP when writing it for the first time.

MoghaddamBanaemLetal(2012)[24]foundasignificantrelationshipbetween elevated maternal serum hs-CRP levels in the first 20 weeks of pregnancyand the later occurrence of preterm premature rupture of membranes (PPROM) andpretermbirthaswell.

Nevertheless, a recent meta-analysis by Etyang AK et al (2020) [25] showedthat the sensitivity and specificity for CRP ≥ 20 mg/L (5 studies, 252 participants)was59%(95%CI48-69)and83%(95%CI74-89)respectively.So,theuseofCRPforpredictingPPROM islimited.

Aims ofthestudy

Toinvestigatethedemographicandclinicalriskfactorsforpretermprematureruptureme mbranesamongtheLibyanpatients.

Patientsandmethods

1.Designof studyandsettings:

Casecontrol study in mothers admitted for delivery to labour room inAlJamhoria hospital /Benghazimedical center BMC during the period oftheyear 2021.

2. Groupsof thestudy:

Groupofcaseswererandomlyselectedcasesofpretermprematureruptureof the membranes.

Groupofcontrolsweremothersdeliverednormallywithoutsignificantcomplications atthesame time.

3.Datasynthesis:

Reviewofrecordsforallpatientswithprematureruptureofthemembrane deliveries according to preformed data sheet includes data related todemographicandpersonalcharacteristics,pasthistory,thepresentdelivery.

4.Variables:

Maternal

ageParity

BloodgroupRhf

actorstatus

Historyofobstetricconditions.

Historyofvaginaldischarge

Comment [NS12]: Overview of material & Methods
it should be written in a continuous method without sub-headings.
ethical approval along with IRB number should be mentioned.
inclusion & exclusion criteria are missing.
define prePROM and diagnostic criteria in your methods.
describe when you conducted hs-CRP? before pre-PROM or after?
if before than it can be taken as risk factor. if yes, when you first conducted this test and how frwquently you performed this and in what percentage of cases leaking happened?
if you conducted it after leaking, then it will not be considered as risk factor but as outcome measure.

Comment [NS13]: A case-control study was conducted in the labour room of Al Jamhoria hospital……..l during the period of the year 2021.

Comment [NS14]: can be written in a more appropriate way.

History of urinary tract

infection.History of early pregnancy

bleeding.Vital signs

CRP (c-reactive protein)

5.Ethicalconsiderations:

Allparticipantswereconsentedforstudy performance.Confidentialityofdatawas assuredusinganonymousformof datacollection.

6.Statisticalanalysis:

Data were analyzed using statistical package for social science (SPSS)version 23.Descriptivestatistics as frequencyandpercentage.

Inferential statistics were used when needed Chi-square(X^2), t test andMann-Whitney U test to find the difference in the distribution of the variablesbetweenthetwogroups, *P*-valuewereconsideredsignificantwhen≤0.05.

Data were presented in form of tables and figures, were the figuresdonebyMicrosoftExcel2010.

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RESULTS

A total of 120 participants were enrolled with 60 patients in each group. All ofthe cases in case group were diagnosed with history of painless leaking andpositivespeculumexamination.

Comment [NS15]: write in a sentence describing all variables

Comment [NS16]: there are too many tables. the demogrhaic data can be merged in one table.

Demographicandother riskfactors:

Maternalagetendstobeloweramongcasesandrateofadvancedmaternalage is higher among controls. The difference was statistically significant. Seefigure1andtable1

Parity is also less among cases and a higher proportion of nullipara among thisgroup. The difference was statistically significant. See figure 2 and table 2Largerproportionofmotherswithhistoryofabortionamongcontrols,butthedifferencewasnotstatisticallysignificant.See table3

Higherrateofmotherswithpreviouswasfoundamongcasegroup.Thedifferencewasstatisticallysignificant.Seetable4

Comment [NS17]: previous? cesarean?

Maternalage

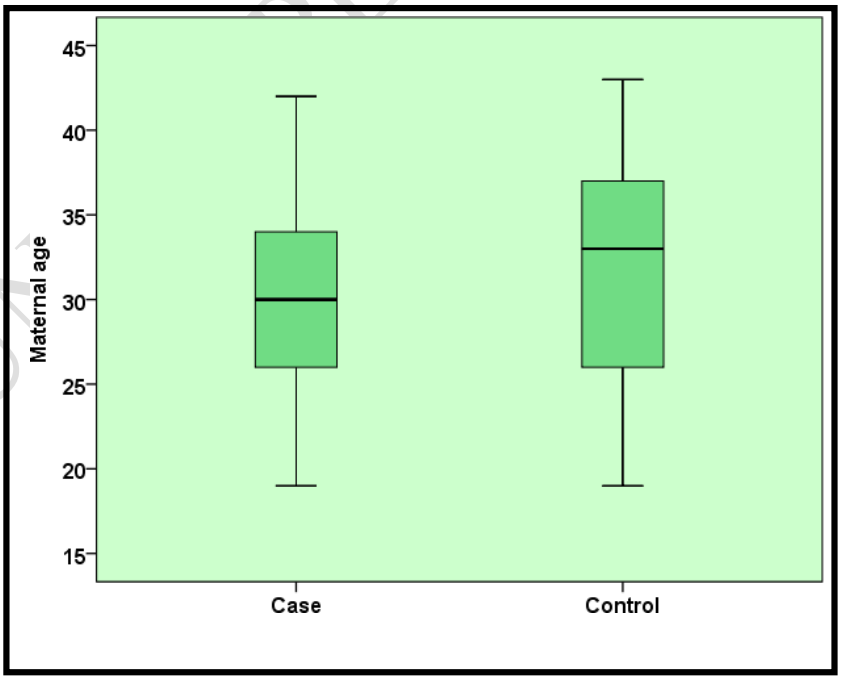


Figure1:Comparisonof maternalageacrossstudygroups

Case Mean30.53(SD5.622),Median30.00Range19-42

Control Mean31.92(SD6.692), Median33.00Range19- 43

Mann-WhitneyU 1545.0*P*0.180

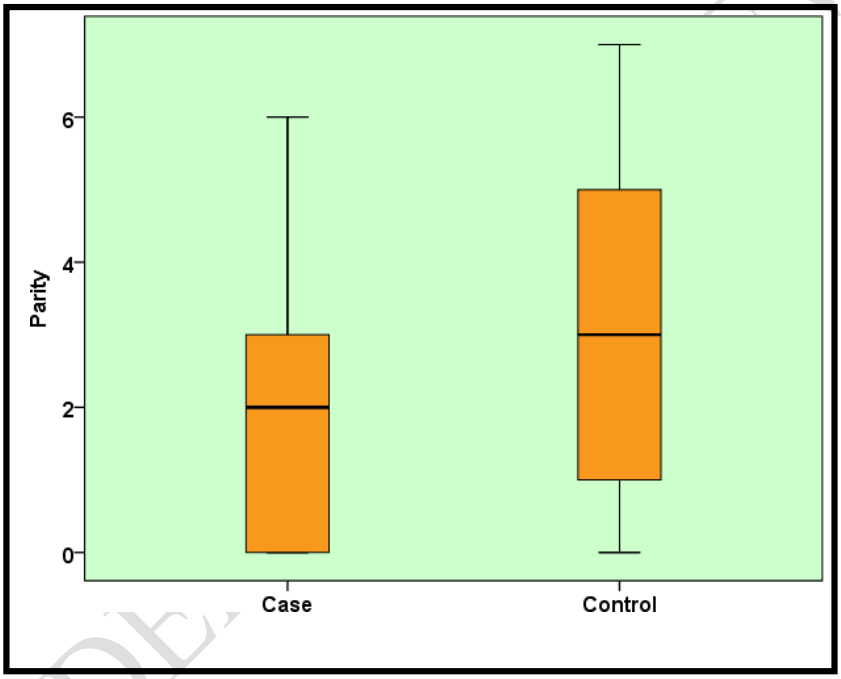
Table1:GroupandAdvancedmaternalage

			Advancedmaternalage		**Total**
			Yes	**No**	
Group	Case	Count	14	46	60
		%withinGroup	23.3%	76.7%	100.0%
	Control	Count	26	34	60
		%withinGroup	43.3%	56.7%	100.0%
Total		Count	40	80	120
		%withinGroup	33.3%	66.7%	100.0%

PearsonChi-Square 5.400 *P*=0.020

Parity

Figure2:Comparisonof parityacrossstudygroups



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

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

Mann-WhitneyU 1212.5,*P*0.002

Table2:GroupandPrimi

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

Previousscars

Table4:Groupandany previousscars

			Anyprevious 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

			Maternalblood group				**Total**
			A	**B**	**AB**	**O**	
Group	Case	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	

Clinicalcharacteristics:

Comment [NS18]: describe results in one table

Mostofcases(41/60;68.3%)haddurationofleaking<72hours.

Gestational diabetes was reported only among cases in small proportion. Thedifferencewasstatisticallyinsignificant.Seetable7

Vaginal discharge was reported among cases in higher rates than controls. Thedifferencewasstatisticallysignificant.Seetable8

Urinary tract infection and also early pregnancy bleeding were reported inhigherrateamongcases,butthedifferencewasnotstatisticallysignificant.See tables9and10

Fever and tachycardiawere only documented amongcases not incontrols.Thedifferencewasstatisticallysignificant.Seefigures3 and4

CRPwas only elevatedamong case group but notin control group.Thedifferencewasstatisticallysignificant.Seetable11

Historyofobstetricconditions:

Table7:GroupandGDM

			GDM		Total
			GDM	NoGDM	
	Case	Count	2	58	60

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

Fisher'sexacttest *P*=0.496

Historyofvaginaldischarge:

Table8:Group andVaginal discharge

			Vaginaldischarge		**Total**
			Reported	**Notreported**	
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
	%withinGroup	72.5%	27.5%	100.0%
PearsonChi-Square		45.517	*P*<0.001	

HistoryofUTI:

Table9:GroupandUTI

			UTI		**Total**
			Reported	**Notreported**	
Group	Case	Count	22	38	60
		%withinGroup	36.7%	63.3%	100.0%
	Control	Count	18	42	60
		%withinGroup	30.0%	70.0%	100.0%
Total		Count	40	80	120
		%withinGroup	33.3%	66.7%	100.0%
PearsonChi-Square			0.600	*P*=0.439	

Historyofearlypregnancybleeding:

Table10:Groupandearlypregnancybleeding

			Bleeding		Total
			Reported	Notreported	
Group	Case	Count	3	57	60
		%withinGroup	5.0%	95.0%	100.0%
	Control	Count	0	60	60
		%withinGroup	0.0%	100.0%	100.0%
Total		Count	3	117	120
		%withinGroup	2.5%	97.5%	100.0%

Fisher'sExactTest *P*=0.244

Hightemperature:

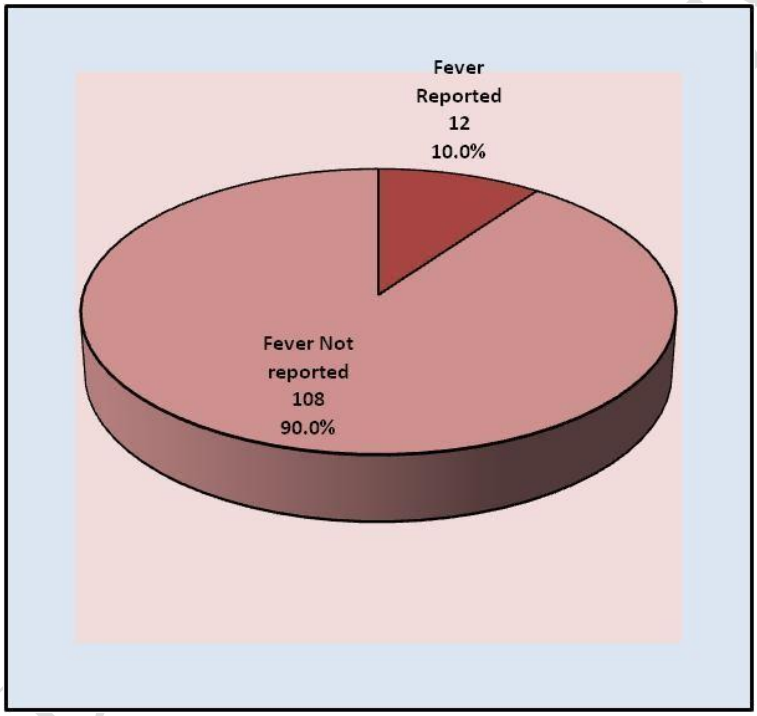


Figure3:Distributionof PROMcasesaccordingtofever

$X2 = 13.3$, $P < 0.001$

Highpulserate:

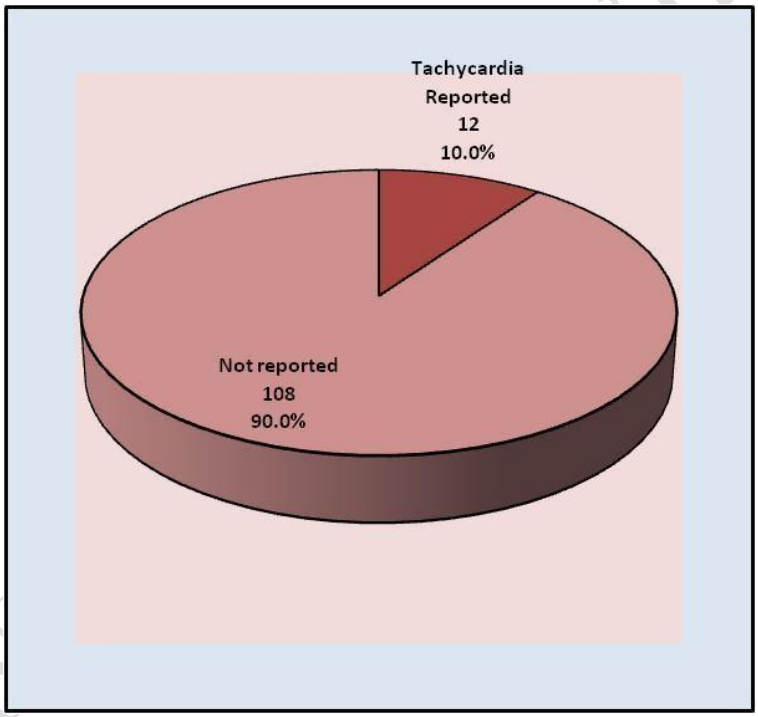


Figure5:Distributionof PROMcasesaccordingtotachycardia

$X2 = 13.3$, $P < 0.001$

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

Genderof thebaby:

Malegenderoftheneonateishigheramongcasegroupthanincontrolgroup.Thedifferen ce wasnotstatisticallysignificant.Seetable 12

Table12:GroupandGenderofthebaby

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

PearsonChi-Square 2.880 *P*=0.09

DISCUSSION

PPROM has unclear etiology. PPROM may be caused by multiple offactors thatinvolveinflammatoryconditions.[14]

The present study investigatedtotal of enrolled 120 participants with60 patients in each group. All of the cases in case group were diagnosed withhistoryofpainlessleaking and positivespeculumexamination.

Maternal age tends to be lower among cases and rate of advancedmaternal age is higher among controls; Case group: Mean30.53years(SD5.622),Median 30.00andforControlgroup:Mean31.92years(SD6.692),*P* 0.180.Thedifferencewasstatisticallysignificantonlywhenconsideringcategories. The rate was in Case, 23.3%and for Control group, 43.3%*; P* =0.020

Comment [NS19]: this is part of results not required here.

Parity is also less among cases and a higher proportion of nulliparaamongthisgroup.Case;30.0%andControl;13.3%.thedifferenceissatatistically significant; *P* = 0.027. This confirms the finding of Bouvier D etal(2019)[22]which concluded primiparityasariskfactorforPPROM.

Alsocomparison of parity as ascale parametershowed significantdifference,Casegroup;Mean1.83(SD1.719)andinControlgroup;Mean 3.07 (SD2.193). The difference was statistically significant *; P* =0.002.Thecauseofthisassociationisnotyetclear.Anyhow,immunerelatedmechanismsmaypartiallyexplain this.

Larger proportion of mothers with history of abortion among controls,but thedifference was notstatisticallysignificant.

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

MaternalbloodgroupandmaternalRhfactordidn'tshowanysignificantasso ciation.

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

Gestationaldiabeteswasreportedonlyamongcasesinsmallproportion. The difference was statistically insignificant. This is discordantwith Bouvier D et al (2019) [22] which stated GDM as a risk factor for PPROM.The smaller sample size and the probably under diagnosed GDM might be thecause.

Vaginal discharge was reported among all of cases (100.0%) while rateamongcontrols wasonly45.0%.Thedifferencewas statisticallysignificant(*P* < 0.001). this is concordant with several studies demonstrated that genitalinfectionsmightcausereleaseofcytokinesandotherinflammatorymediato rsthatmay weakenthemembraneandcausePPROM.PregnantwomenwithBVmorereadilyde velopedPPROMthanwomenwithoutBV.[15] [–19]

Asaconsequenceofinfection,feverandtachycardiawereonlydocumented among cases (20.0% for each) not in controls. The difference wasstatisticallysignificant(*P*< 0.001).

RegardingCRPwhichisknowninflammatorymarkerforseveralconditions 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 isconcordantwithMoghaddamBanaemLetal(2012)[24]andKahyaoğluSetal

(2014) [25]. Anyhow, the sensitivity and specificity by the present study seemsless than described by Etyang AK et al (2020) [25] in their meta-analysis. Thismight putlimitation for thereliabilityof useof CRP.

Urinary tract infection and also early pregnancy bleeding were reportedinhigherrateamongcases,butthedifferencewasnotstatisticallysignificant.

Male gender of the neonate was higher amongcase groupthan incontrolgroup(70.0%versus55.0%).Thedifferenceanyhow,wasnotstatisticallysignificant.

The limitations of the present study included retrospective design anddifficulty in gathering complete data. Further large multicenter studies withprospective designand use of highsensitivity (hs)CRP as wellas otherinflammatorymarkersinsumtoclinicalpredictorsandoutcomeutilityestimation aretobe considered.

Conclusion and Future Recommendations1.Conclusion:

Premature rupture of the membranes is associated with primiparity,history of vaginaldischarge and clinical as well as laboratory manifestationsofinflammation.

2.Recommendations:

1. EnhancingclinicalandlaboratoryevaluatingofprimigravidamothersbeforewithinthetimebeforetermtoexpectPPROMand avoidcomplications.

2. Multicenterprospectivestudytoverifyriskfactorsandoutcomesofprematureruptureofthe membranecasesinthe Libyan population.

Comment [NS20]: inappropriate grammar.

REFERENCES

Comment [NS21]: references are old.

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APPENDIX

Appendix(Preformeddatacollectionsheet)

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
7Any chronic condition diagnosed before
8Any obstetric condition this pregnancy
9.Painless Leaking? YES NO
10.SE Confirmative Ncl
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

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