

## ORIGINAL RESEARCH ARTICLE

# Association between genital tract infection and premature rupture of membranes: A retrospective case control study in Tunisia, North Africa

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## Abstract

Premature Rupture of Membranes is responsible for most cases of neonatal death. In most of these cases, the causes of PROM have not been established in Tunisia, although several risk factors have been described. Therefore, we set out to determine the presence of an association between genital infections and PROM among Tunisian women. A case-control study was conducted among 251 women to detect the presence of association between genital tract infection and Premature Rupture of Membranes. Cases had a premature membranes rupture and the controls had intact membranes or suffering from premature membrane rupture during the latent phase of labour. Data were collected from the medical register including socio-demographic characteristics, obstetrics, and medical history. Association between genital infections and premature rupture of membranes was estimated using the Odds Ratio and 95% CI. One risk factor was identified, including age. There is no association between the presence of *Group B streptococcus* (OR= 1.08; 95% CI 0.50-2.34), presence of *Trichomonas vaginalis* (OR= 2.45; 95% CI 0.15-39.83) and presence of *Candidiasis* (OR= 1.11; 95% CI 0.58-2.14) and premature rupture of membranes. Co-infection was not associated with premature rupture of membranes (OR= 0.43; 95% CI 0.45-6.07). There is no association between genital infections and PROM among pregnant Tunisian women. (*Afr J Reprod Health* 2021; 25[2]: 131-137).

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**Keywords:** Genital infections, premature rupture of membranes, risk factors, Monastir, Tunisia

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## Résumé

La rupture prématurée des membranes est responsable de la plupart des cas de décès néonatal. En effet, les causes de la RPM n'ont pas été établies en Tunisie, bien que plusieurs facteurs de risque aient été décrits. Par conséquent, nous avons cherché à déterminer la présence d'une association entre les infections génitales et la RPM chez les femmes tunisiennes. Une étude cas-témoins a été menée auprès de 251 femmes pour détecter la présence d'une association entre l'infection des voies génitales et la rupture prématurée des membranes. Les cas avaient une rupture prématurée des membranes et les témoins avaient des membranes intactes ou souffraient d'une rupture prématurée de la membrane pendant la phase latente du travail. Les données ont été recueillies à partir du registre médical, y compris les caractéristiques sociodémographiques, l'obstétrique et les antécédents médicaux. L'association entre les infections génitales et la rupture prématurée des membranes a été estimée à l'aide du OR et de l'IC à 95%. Un facteur de risque a été identifié, incluant l'âge. Il n'y a pas d'association entre la présence de *streptocoques du groupe B* (OR = 1,08; IC à 95% 0,50-2,34), la présence de *Trichomonas vaginalis* (OR = 2,45; IC à 95% 0,15-39,83) et la présence de candidose (OR = 1,11; 95% CI 0,58-2,14) et rupture prématurée des membranes. La co-infection n'était pas associée aussi à la rupture prématurée des membranes (OR = 0,43; IC à 95% 0,45 à 6,07). Il n'y a pas d'association entre les infections génitales et la RPM chez les femmes tunisiennes. (*Afr J Reprod Health* 2021; 25[2]: 131-137).

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**Mots-clés:** Infections génitales, rupture prématurée des membranes, facteurs de risque, Monastir, Tunisie

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## Introduction

Premature rupture of membranes (PROM) is an event that occurs during pregnancy when the sac containing the developing fetus and the amniotic

fluid bursts before the beginning of labour. Mostly, this event occurs at term, when labour usually begins<sup>1</sup>. Sometimes the membranes burst before 37 weeks gestations<sup>2,3</sup>. PROM increases the risk of prematurity and causes several other perinatal and

neonatal complications, including 20 à 40 % of premature birth and 10% of foetal death<sup>4</sup>. In general, the frequency of PROM varied between 2 and 10%<sup>5</sup>.

Many risk factors for PROM were identified including, oligohydramnios polyhydramnios, history of having a premature infant, multiparity, mother's hypertension, infant diabetes, placenta previa, anatomic abnormality of the uterus, history of the organic disorder (cardiac, renal, thyroid), cervical cerclage, uterine abnormality and blood group type A have a significant correlation with recurrence of premature labour<sup>6-8</sup>. Other factors were also implicated such as demographic elements (age of the mother). In fact, younger mothers of 17 and older than 35 years are at higher risk of PROM. Moreover, the low socioeconomic level was the result of poor nutrition as well as inadequate care during pregnancy<sup>9</sup>. Evenly, behavioral factors in the mother such as smoking are related to PROM. A study carried out in the US, have demonstrated that 10-20% of PROM were related to the mother being a smoker.

According to various studies, the roles of numerous risk factors such as lifestyle, and low weight gain during pregnancy have been recognized in preterm labour and intrauterine growth retardation. Other risk factors in previous studies include addiction to narcotics, use of alcohol, ambient poisons, prolonged standing, intensive work, activity, stress, lack of social support, illiteracy and poverty, first pregnancy, multiparity, hydramnios, abdominal surgery during pregnancy, abnormal uterus fever, disease during pregnancy, bleeding during pregnancy, history of pyelonephritis, history of having a low-weight infant, history of abortion, and hypertension<sup>10,11</sup>.

Past obstetric history and genital infections like *Candidiasis*, *Trichomonas (T.) vaginalis*, *Chlamydia trachomatis*, bacterial vaginosis, and *Group B streptococcus (SGB)* appear to play an important role in the etiology of PROM<sup>12</sup>. A study of<sup>13</sup>, found an association between *T. vaginalis* and PROM. The parasite of *T. vaginalis* can hurt membranes. In 2011, Roberts *et al.*<sup>14</sup>, proved a positive association of *candidiasis* with PROM and this by the reduction in the incidence of PROM across the treatment of *candidiasis*. Another study has demonstrated the fact that the *SGB* may be a cause of PROM by causing inflammatory responses at foetal membranes in experimental and epidemiological studies<sup>15</sup>. In general, genital

infections produce inflammatory cells that are implicated in the burst of the foetal membranes among pregnant women causing PROM<sup>16</sup>.

Despite all efforts made in the prevention of PROM, no study has been carried out in Tunisia to prevent this phenomenon. Although, the risk of development of PROM is still increasing<sup>15</sup>. This study aimed to detect the presence of an association between PROM and genital infections.

## Methods

### *Study design and participants*

This case-control study was conducted at the Center of Maternity and Neonatology of Monastir (CMNNM), between July and September 2017 to assess the presence of an association between PROM and genital infections. The Center has several departments, including obstetrics and gynecology that offer specialized clinical care. For inclusion in this study, we selected participants presenting to the antenatal wards at or above 37 weeks (w) of gestation and were women with confirmed PROM. The diagnosis of PROM at speculum examination was made if the trickle of amniotic fluid was observed leaving the cervix, or a pool of amniotic fluid collected behind the cervix<sup>17</sup>. Control group are women with or without PROM in the latent phase of labour (> 37 w) or who consult for maternal complications and met the inclusion criteria for controls.

### *Data collection*

Data collection sheet was used to collect socio-demographic characteristics such as age, marital status, origin, and biological characteristics like service, clinical information, pregnancy term, parity, and gestational age. Other exposure variables were results from laboratory investigations for detecting the presence of genital infections and associated infections. Incomplete patient files were excluded.

### *Statistical analysis*

Data were analyzed with SPSS version 20. To assess risk factors for PROM, we compared the presence of genital infections among the cases and controls using odds ratios and 95% CIs and their p values. p values less than 0.05 (p <0.05) were considered statistically significant.

## Results

Among the 251 women analyzed in this study, 73 were suffering from PROM (29%). The average ages of mothers with PROM were between 25 and 30 years. Most of them were housewives (99.6%), lived in rural areas (81.7%). Most pregnant women had PROM in a term upper than 37 weeks (55.4%) while the rest had PROM with a term lower than 37 weeks (44.6%). In Table 1, no significant difference between the case and control groups in any of the investigated variables except the variable age. Also, there is a significant difference in the age ( $p < 0.05$ ) as shown in Table 1.

Table 2, shows the absence of association between the presence of infection and having PROM (OR= 1.05, 95% CI 0.61-1.82). However, there is no association between *SGB* and PROM (OR= 1.08, 95% IC 0.50-2.34). Similarly, there is no association between *T. vaginalis* and PROM (OR= 2.45, 95% IC 0.15-39.83), or between *Candida sp* and PROM (OR= 1.11, 95% IC 0.58-2.14).

## Discussion

This is one of the few studies to determine the presence of an eventual association between genital infections and PROM in pregnant women, and in our knowledge, the first do this in Monastir, Tunisia. We found that 29% of pregnant women had a PROM. This rate is higher among women of lower socioeconomic status. We can ascribe this to lower quality of antenatal care (ANC), which can influence women's health, reducing their number of visits to the doctor and consequently their laboratory tests.

Afulani *et al*<sup>18</sup>, found that high-quality ANC can reduce maternal and neonatal morbidity and mortality and stillbirths through prevention, as well as early identification and management of pregnancy complications or preexisting conditions. Although, we increase attention to the domain of communication: often, women are not given enough information during ANC, hence, they do not understand the purpose of examinations and medicines and are not able to ask clarifying questions. Most studies have considered the role of spiritual and mental factors as important in the growth and development of the fetus.

Nabavizadeh *et al*<sup>19</sup>, observed a significant correlation between the incidence of preterm labour

and the general health status of mothers which is consistent with the findings of Ghosh *et al.*<sup>20</sup>, who reported that the fear of delivery and chronic stress increase the risk of preterm labour. In her study, Rondo pointed out the role of stress at the beginning of pregnancy, anxiety, and depression in the last months of pregnancy, and their effects on premature labour<sup>15</sup>.

Various mechanisms have been suggested for this correlation. A direct correlation between premature delivery and mothers' mental health status (level of stress, anxiety, depression) may be correlated with the release of catecholamines. As a result of the release of catecholamines and therefore reduction of placenta blood circulation, oxygen reduction and nutrients in the fetus lead to disorders in foetal growth and premature labour<sup>12,21</sup>. Given that stress increases corticotropin-releasing hormone, cortisol, and plasma levels, it may contribute to an increase in uterine contractions and consequently premature labour<sup>22</sup>. Unfortunately, we have no data about this factor to include it in our results.

The combination of PROM with pregnant women aged  $\geq 25$  years could be explained by endogenous modifications of the fetus and its appendices, the rates of foetal aneuploidy being all the higher as the age of the mother increases<sup>23</sup>. Mercer<sup>16</sup>, highlighted the role of multiparity, which in uterine distention can increase the risk of PROM by 7.4% in multiple pregnancies compared with 3.7% in single pregnancies. The findings of these studies are contrary to the results of studies performed by Shah<sup>24</sup> and Babinszkiet *al*<sup>25</sup> as those studies did not recognize multiparity and grand parity as a cause of the increased risk of premature labour, but are consistent with the results of Guoet *al*<sup>26</sup> who also mentioned this point and stated that the number of pregnancies is a risk factor for premature labour and found that prevalence of premature labour in women is 6% of the first pregnancy, 4.3% with the second pregnancy, 4% with the third, and 5.7% with fourth pregnancies. Also, Reimeet *al*<sup>27</sup> concluded that the risk of premature labour is increased by second pregnancy in comparison to the first<sup>27</sup>. Although the etiology in many cases is unknown and idiopathic. The findings of the present study show no association between parity and PROM. Also, no association was detected between the occurrence of PROM and the presence of *Candida sp* or *SGB*. Although this does not agree with several studies showing a

**Table 1:** Socio-demographic and biological characteristics of two groups (cases and control) at the Center of Maternity and Neonatology of Monastir during the period from July 1, 2017 to September 31, 2017

Factor	Case* N : 73	Controls* N : 178	P value*
<b>Age</b>			
19-24	8 (11%)	28 (15.73%)	0.43*
25-30	28 (38%)	67 (37.64%)	1
31-36	21 (29%)	60 (33.7%)	0.67
37-42	16 (22%)	17 (9.60%)	<b>0.02</b>
43-48	0(0.0)	6 (3.37%)	0.18**
<b>Civil status</b>			
Single	1 (1%)	0(0.0)	0.29
Married	72 (99%)	178 (100%)	1
<b>Origin</b>			
Rural	61 (83.6%)	144 (80.9%)	0.91
Urban	12 (16.4%)	34 (19.1%)	0.72
<b>Parity</b>			
P0	3 (4.1%)	8 (4.5%)	1
P1	38 (52.1%)	103 (57.9%)	0.72
P2	20 (27.4%)	31 (17.4%)	0.18
P3	10 (13.7%)	22 (12.3%)	0.83
P4	2 (2.7%)	13 (7.3%)	0.24
P5	0(0.0)	1 (0.6%)	1
<b>Pregnancy term</b>			
<37w*	56 (76.7%)	30 (16.9%)	7.44
≥37w	17 (23.3%)	148 (83.1%)	3.1
<b>Service</b>			
Risque	28 (38.3%)	54 (30.3%)	0.21
Maternity	30 (41.1%)	82 (46%)	0.47
Gynecology	8 (11%)	13 (7.3%)	0.34
Post operative	1 (1.4%)	0(0.0)	0.29
Reanimation anesthesia	0(0.0)	2 (1.1%)	1
Externalgynecology	3 (4.1%)	18 (10.1%)	0.13
Post partum	3 (4.1%)	9 (5%)	1
<b>Nature of sampling</b>			
Vaginal swab	46 (63%)	85 (47.8%)	0.24
Amnioticfluidswab	27 (37%)	17 (52.2%)	5.6

Case\*: women with PROM ≤ 37 week

Control\*: women with PROM > 37w or other abnormality during pregnancy follow-up

P\*: calculated by software Epi info 7

\*: comparison of the different modalities of each variable between the case and control groups

\*\* : calculated by Fisher's Exact Test

P\*: number of pregnancy

w\*: number of Week

significant association between the presence of these two germs and PROM, our results are consistent with those of Ekwo *et al*<sup>28</sup>. In fact, this study found no association between genital infections and PROM.

Contradictory results have been reported between the association of *SGB* and PROM. Kessous *et al*<sup>29</sup> showed a relation between the occurrence of PROM and the presence of *SGB*, where the prevalence of this bacteria in women with PROM was 10.7%, whereas in controls it was 7.9%. This phenomenon may be due to the release of cytokines and other inflammatory modulators

caused by the presence of germ and bacterial vaginosis<sup>30,31</sup>.

Previous studies reported that during the *Candida* infestation, inflammatory cytokines are released, causing membrane rupture<sup>32</sup>. But, studies of Nakubulwaet *al*<sup>16</sup> and Karat *et al*<sup>30</sup> demonstrated that patients with PROM were less likely to have candidiasis compared to those without PROM. These latter findings suggested the possibility that the liquor amnii in patients with PROM washed out the yeast cells leading to non-detection. Other studies have not found *Candida* as a risk factor for PROM<sup>32</sup>.

**Table 2:** Relationship between genital infections and PROM in case and control

Variable	Cases N= 73	Controls N= 178	P value	OR	(95%)IC
<b>Presence of infections</b>					
Yes	33	78	0.84	1.06	(0.59-1.90)
No	40	100		0.95	(0.53-1.70)
<b>Isolated Germs</b>					
<i>Escherichia coli</i>	1	6	0.67	0.40	(0.02-3.42)
<i>Candida sp</i>	17	38	0.73	1.12	(0.55-2.24)
<i>Proteus mirabilis</i>	0	1	1	-	-
<i>Staphylococcus aureus</i>	2	0	0.08	-	-
<i>Streptocoque B</i>	11	25	0.83	1.09	(0.47-2.48)
<i>Klebsiella pneumoniae</i>	0	4	0.32	-	-
<i>Enterococcus</i>	0	1	1	-	(0.00-42.69)
<i>Trichomonas vaginalis</i>	1	1	0.49	2.44	(0.03-193.73)
<i>Serratia mariansis</i>	1	1	0.49	2.44	(0.03-193.73)
<i>Acinetobacter</i>	0	1	1	-	-
<b>Associated Infections</b>					
No	69	172	0.48	0.60	(0.13-2.99)
Yes	4	6		1.65	(0.33-7.24)
<b>Avortements</b>					
Yes	20	39	0.35	1.34	(0.69-2.63)
No	53	139		0.74	(0.38-1.46)

In our study, no association was found between the presence of *Candida* and PROM. However, the association between *Candidosis* and PROM is still poorly exploited. According to the literature, the combination of *Candida* as a risk factor is not yet conclusive and needs to be further explored. Further studies recommend considering a urine culture with more than  $10^5$  CFU/ml as indicative of the presence of urinary tract in preterm labour women<sup>33</sup>.

Our study showed no significant association between PROM and *T. vaginalis*. However, Draper *et al*<sup>13</sup> has shown the existence of inflammatory proteases involved in the PROM induced by the parasite *T. vaginalis*. On the other hand, a prospective study in Kashan (Iran) on 450 pregnant women showed the association between *T. vaginalis* and PROM. Also, we can attribute this result to the fact that not all PROM cases have benefited from bacteriological examination in search of this parasite. However, in our study, we could not show with evidence that *T. vaginalis* is a risk factor for PROM. In this study, some important variables such as consanguineous marriage, eclampsia, pregnancy hypertension, diabetes, thyroid, cardiac disease of mothers were missed in the questionnaire design. These are the limitations of this study, so we suggest that other researchers

should attend to these in future studies of factors related to PROM.

## Ethics statements

The study was carried out according to the Declaration of Helsinki Principles and all Tunisian pertinent regulations. The samples were obtained for routine diagnostic purposes from pregnant women who were managed by the Centre of Maternity and Neonatology of Monastir at the request of the gynecologist. We confirmed that informed consent was obtained for all subjects. During consulting, the gynecologist informs pregnant women of the importance of biological analysis. Given the seriousness of the situation, the pregnant women are convinced of the importance of this analysis of their health as well as that of the baby. After acceptance, the gynecologist prescribes a request for analysis containing the different information (age of the patient, age of the pregnancy, date of seroconversion, origin).

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### Authors' contributions

This study was conceived and designed by D.S., N.S., and H.B. All execution and analysis were performed by D.S., and N.S. The manuscript was written by D.S., N.S., and H.B. The manuscript was revised by N.S., and H.B.

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