Effect of Using Prophylactic Antibiotics by Patients More than 34 Weeks with Premature Rupture of Membrane on Maternal and Neonatal Outcomes

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Abstract:
Background: Preterm premature rupture of membrane (PPROM) and premature rupture of membrane (PROM) are associated with various maternal and neonatal complications. Management guidelines regarding rupture of membrane before labour is still controversial.
Aim of the study: To measure the incidence of infection among patient with PROM and to compare the fetal and maternal outcomes between patients who used antibiotic and who did not use antibiotic following rupture of membrane after 34 weeks.
Methods: A prospective cohort study was conducted in Benghazi Medical center. Study population was 136 women with gestational age more than 34weeks. The participants were randomized into two groups one were used prophylactic antibiotics following premature preterm rupture of membranes and other women didn't use antibiotics. We used three type of antibiotics Erythromycin 250mg 6 hourly for ten days , rocephine 1gm /12hourly for ten days and combined rocephine and metronidazole 500mg/12h for one week. Blood sample was obtained for both mothers and her babies before and after birth and analyzed for W.B.C and C-reactive protein.
Results: The risk of occurrence of puerperal sepsis among the women with PROM, who do not receive prophylactic antibiotic is 88.1%. The relative risk (RR) of is 0.012. with 95% CI 0.002- 0.084.
Conclusion The study strongly suggests that prophylactic use of antibiotics in prelabor premature rupture of membranes occurring at 34 or more weeks of gestation reduces the risk of neonatal sepsis and probably maternal endometritis.
Keywords: Neonatal, Premature, Rupture of membrane, Sepsis.

Tob Regul Sci. ™ 2022;8(1): 3477-3489
DOI: doi.org/10.18001/TRS.8.1.262

Introduction:

Preterm premature rupture of membranes(PPROM) is the rupture of fetal membranes before 37weeks of gestation ,while Pre labor rupture of membranes (PROM) is the rupture of the fetal membranes before the onset of labor (1).

It occurs in approximately 10 percent of deliveries and results in the loss of the natural protection of fetus and intrauterine content from bacterial invasion consequently ,both the mother and her fetus are greater risk for infection. The longer time between rupture and delivery (defined as the latent period). The greater risk of infection ,especially if vaginal examination are performed frequently (2).

Procedures that may result in PROM include cerclage and amniocentesis,there appear to be no single etiology of PROM, choriodecidual infection or inflammation may cause PROM (3).
Infection appears to have an important role ,either as a cause or as a consequence of PROM ,some organisms produce collagenases ,mucinases and proteases which weaken the amnion and chorion and may lead to PROM ,on the other hand, infection may occur secondary to membranes rupture, Ascending infection may lead to occult deciduitis ,frank intra-amniotic infection or fetal infection. 80 percent of term pregnancies present in labor on admission ,95 percent of women experience spontaneous labor within 48 hours of premature rupture of membrane (4).
However, after 24 hours of premature rupture of membranes without delivery ,there is an risk of intrapartum fever,and after 72 hours, there is an increased risk of perinatal mortality .At admission ,about 40% of women at term who are in labor have positive bacterial cultures and this percentage increases over time (5).
Antibiotic therapy in PROM with strong link between infection and PROM, whereas antibiotics are effective for increasing the latent period. Antibiotic therapy could improve outcome in two ways, firstly, the prevention or treatment of infection may reduce maternal or fetal /neonatal morbidity. Secondly, by treating or preventing ascending infection, antibiotic therapy may prolong pregnancy and delay the progression of preterm birth (6).
Numerous studies have been performed in order to evaluate the benefit of antibiotics and significant evidence has been generated which shows that adjunctive antibiotics are beneficial in the conservative management of PROM (7).

Patients and methods:
136 Patients with premature rupture of membrane and with more than or equal 34 weeks of gestation, with singleton pregnancy >34weeks of gestation, primi and multigravida and leaking from cervix confirmed by speculum examination were included in the study. They were divided into study cohort: Women with PROM with a history of prophylactic antibiotic administration and Control cohort: Women with PROM who did not receive prophylactic antibiotic administration.
Patients with multiple pregnancies, maternal complications interfering with active management of PROM like PIH, Heart disease, previous LSCS, malpresentation, DM, IUGR, HIV infection, patients with congenital anomalies and patient use drugs like Digoxine ,carbamyzepine and antibiotic were excluded from the study.
An interview with every patient was undertaken by the investigator with aid of an interview performa. Assessment and follow-up was done on admission /during admission, at birth, at the end of the 2nd Week of delivery and at the end of the 42 days of delivery.
Assessment of the strength of association between antibiotics use and frequency of infections for both mothers and infants was measured by relative risk with 95% confidence interval. The attributed risk was also measured.

Ethical consideration: A formal letter: From department of Obstetrics and Gynaecology at university of Benghazi was send to every hospital requesting the director of hospital as applicable to allow the researcher to conduct the study. Patients were informed about the purpose of the study before conducting the interview and were told that participation is voluntary.

Results:

One hundred thirty-six women with PROM was included in the study, 42 of them was considered as a study cohort as they did not receive prophylactic antibiotics (un-exposed), and 94 was control cohort (exposed), one of the study cohort refused to complete the study, the attrition rate was 0.73% (Table 1).

Table 1: Distribution of the participants who completed the study according to type of cohort:

Type of cohort	Feature	Number (%)
Study cohort	Did not receive prophylactic antibiotics (not exposed to prophylactic antibiotic)	42
Control cohort	Receive prophylactic antibiotics (exposed to prophylactic antibiotic)	94
Total		136

The age of the women ranged from 18-44 years, the mean age of the women was 30 years with 5.9 years DS, and the median age is also 30 years. The most frequent age group was from 21-30 years, less than 21 years and more than 40 years form 3.7% and 4.4% respectively, fig (1).

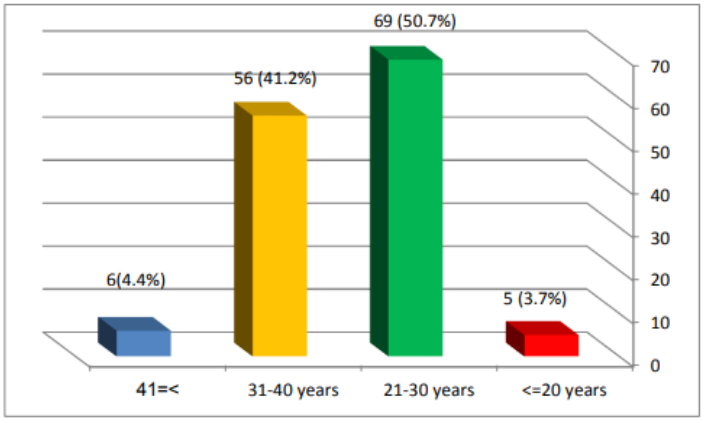

Fig (1): Distribution of the women according to their age group.

Table 2 Shows that there was no significant ($p>0.05$) difference between the study cohort and control cohort regarding the age, parity, gravidity, gestational age.

Table 2: Comparison between the study cohort and control cohort regarding their age and obstetric history.

	Study cohort (un-exposed) (NO. 42)	Control cohort (exposed) (NO. 94)	t	p- value
Age (±SD)	29.86 (± 5.7)	(±6)30.1	0.266	0.791
Parity	(± 1.5)1.71	(±1.9) 2.10	1.314	0.192
Gravidity	(±1.7)3.02	(±2.3) 3.60	1.653	0.101
Abortion	(± 0.6)0.40	(±0.9) 0.51	0.655	0.514
Gestational age	(±1.5) 37.17	(±1.6) 37.04	0.425	0.671

Table 3 shows that there was no significant (p>0.05) differences between the study cohort and control cohort regarding the feeling of fever, change in fetal movements, urinary tract symptoms, reduction in uterine size and abdominal pain.

Table 3: Comparison between the study cohort and control cohort regarding some symptoms/complains before delivery.

	Study cohort (un-exposed to prophylactic antibiotics) (NO. 42)	Control cohort (exposed to prophylactic antibiotics) (NO. 94)	X2	p-value
Fever	10 (23.8%)	25(26.6%)	0.118	0.731
Change in fetal movements	30 (71.4%)	60 (63.8%)	0.749	0.387
Urinary tract symptoms	1(2.4%)	11(11.7%)	3.135	0.077
Abdominal pain	25(59.5%)	60(63.8%)	0.230	0.632
Reduction in uterine size	22(52.4%)	32(34.5%)	4.553	0.103

From table 4 there was a significant difference between study cohort and control cohort regarding CPR result, where more positive cases among study cohort. Also no difference between the both groups regarding the existence of oligohydromios, Hb level, or WBCs count.

Table 4: Comparison between the study cohort and control cohort regarding results of some investigations before delivery.

	Study cohort (un-exposed) (NO. 42)	Control cohort (exposed) (NO. 94)	X2	p-value
Oligohydramnios by U/S	24 (57.1%)	47 (50%)	0.600	0.741
C.R.P (positive)	26 (61.9%)	14 (14.9%)	18.993	0.000
WBC				
Hb (< 11mg/dl)	17 (40.5%)	48 (51.1%)	1.304	0.253

Table 5 shows that no significant difference (p>0.05) in the birth weight between of the newborns to mothers who received prophylactic antibiotics and who did not receive.

Table (5): Distribution of the birth weight of the newborns and the receiving of prophylactic antibiotics by their mothers.

Birth weight	Study cohort (un-exposed) (NO. 42	Control cohort (exposed) (NO. 94)	X2	P
<2.5	0 (0%)	1 (1.10%)	1.138	0.566
2.5-4	37 (88.10%)	86 (91.50%)		
>4	5 (11.90%)	7(7.40%)		
Total	42 (100.00%)	94(100.00%)		

All the newborns (100%) had a normal Apgar score and blood sugar level. %2 %7 %91 Dysuria Groin pain No urinary symptoms 35 The C-reactive protein was performed in 122 (89.71%) newborns, Table (6) shows that there was a significant (P=0.000) increase in CRP-positive cases among newborns of mother who did not exposed to prophylactic antibiotics.

Table (6): Distribution of the women according to exposure to prophylactic antibiotics and the result of c-reactive protein test result.

CRP	Study cohort (un-exposed) (NO. 42	Control cohort (exposed) (NO. 84)	X2	P
Positive	32 (84.20%)	34 (40.50%)	20.153	0.000
Negative	6 (15.80%)	50 (59.50%)		
Total	38 (100.00%)	84(100.00%)		

Table (7) shows that the incidence of puerperal sepsis among the study cohort was 88.1% and the incidence among control cohort was 1.1%. The risk of occurrence of puerperal sepsis among the women with PROM, who do not receive prophylactic antibiotic is 88.1%. The relative risk (RR) of is 0.012. with 95% CI 0.002-0.084. This indicates a negative association between the exposure to prophylactic antibiotics and the occurrence of puerperal sepsis ; exposure is a protective factor.

The preventable fraction among the exposed (PFe) is 98.8% , so that the prophylactic antibiotics is able to prevent the puerperal sepsis by 98.8% among the women with PROM who receives them.

Table (7): Distribution of the women according to exposure to prophylactic antibiotics and occurrence of puerperal sepsis.

Exposure to prophylactic antibiotics	Puerperal sepsis		Total
	Yes	No	
Yes	1 (1.10%)	93 (98.90%)	94 (100.00%)
No	37 (88.10%)	5 (11.90%)	42 (100.00%)
Total	38 (28.00%)	98 (72.00%)	136 (100.00%)

Table 8 shows that no significant ($p > 0.05$) differences among between the study group and control group in occurrence of infection among their infants.

Table (8): Distribution of the women according to exposure to prophylactic antibiotics and occurrence of infection among their children.

Infection	Study cohort (un-exposed) (NO. 42	Control cohort (exposed) (NO. 94)	Total	X2	P
Yes	11 (26.2%)	31(33.0%)	42 (31.0%)	0.627	0.429
No	31 (73.8%)	63(67.0%)	94 (69.0 %)		
Total	42 (100.0%)	94 (100.0%)	136 (100.0%)		

The most frequently used antibiotics among the control group was erythromycin (58%), followed by Rosephin (39%) figure (2).

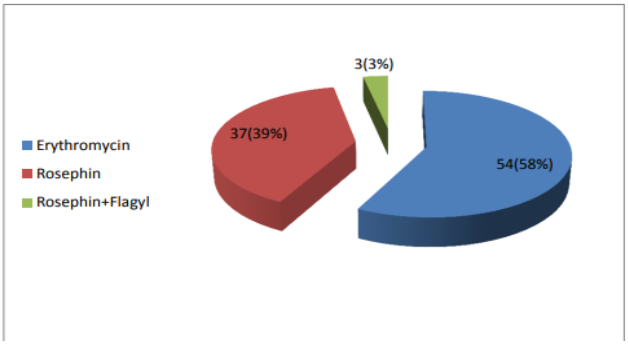

Figure 2: Distribution of women in control group according to the type of antibiotics they had received.

Discussion:

PROM is one of the most common obstetric complications and the most important difficulties in pediatrics, which puts the mother, and the fetus in danger and it counts as important causes of mortality in neonates. Despite its high incidence, there are not enough studies available to it (8).

PROM is accompanying the shortening stage of late labor and becoming infected Although there are multiple causes for PROM it seems that infections play a significant role in here (9).

In this study after equalizing both groups, a number of pregnancies and average gestational age both were according to the normal distribution (P 29 years can be explained by endogenous changes in the fetus and its annexes, as fetal aneuploidy rates are higher with increasing maternal age (10).

Studies retrieved in the literature did not identify age as risk factor for this disease, as they paired PROM cases with age-matched controls (11).this is similar to our results which showed there was no significant ($p>0.05$)difference between the cohort and control cohort regarding the maternal age ,parity and gravidity The lack of association between PROM and genitourinary infections during pregnancy in this study ($p>0.05$) may be attributed to the treatment completion for these infections by most women. Other studies have also identified higher values of mediators of infectious processes or bacteria after PROM (12).

The presence of uterine contractions during threatened preterm labor can weaken the amniotic membrane. Another study has also found an association between the presence of early contractions during pregnancy and PROM (13).

Other studies on premature rupture of the fetal membranes26and urinary and genital tract infections (14) also used self-reported information. Another limitation is the non-detection by the study of cases of asymptomatic genital infection. However, this type of infection appears to have no association with prematurity or PROM. For instance, screening for Streptococcus group B is recommended after the 35th week of gestation (15).

Maternal and fetal infection does not appear to be prior to the occurrence of PROM, but rather its consequence. The risk of PROM maternal and fetal infection could be increased by a longer time of rupture prior to birth in late preterm gestations (34 to 37 weeks) when compared to term pregnancies. Inflammatory responses in the body rapidly produce CRP, a reactive protein located in the blood plasma, the concentration of which is positively correlated with the severity of inflammation and tissue injury. Therefore, the monitoring of maternal CRP expression levels has important clinical value in the prevention of chorioamnionitis. The present study demonstrated that the maternal CRP expression levels ($p>0.05$) in the study cohort group were significantly higher than in the control group. Therefore, dynamic monitoring of CRP expression levels in pregnant patients with PROM may aid in the choice of suitable treatments, and the improvement of the outcomes of pregnancy (16).

According to **Ojaswini Patel (17)** and his colleague study conducted in 2017 that revealed Evaluation of CRP in blood has helped to predict development of chorioamnionitis and preterm delivery following PROM and 42 also perinatal morbidity and mortality., As expected, antibiotics

given to mothers that experience PROM serve to protect against infections during this lengthened latency period. Additionally, antibiotics increase the time that babies stay in the womb. Antibiotics don't seem to prevent death or make a difference in the long-term (years after the baby is born). But, because of the short-term benefits, routine use of antibiotics in PROM is still recommended (18).

In this study however, there was a strong association of puperial sepsis and neonatal infection among women who receiving antibiotic following PROM and women who did not receiving antibiotics, the incidence of puerperal sepsis among the study cohort was 88.1% and the incidence among control cohort was 1.1%. The risk of occurrence of puerperal sepsis among the women with PROM, who do not receive prophylactic antibiotic is 88.1%. The relative risk (RR) of is 0.012. with 95% CI 0.002- 0.084. however, the only one woman among 94 women who receiving antibiotics have puperial sepsis while 37 women from 42 women who did not receiving antibiotic they had puperial sepsis, This indicates a negative association between the exposure to prophylactic antibiotics and the occurrence of puerperal sepsis ; exposure is a protective factor .The the preventable fraction among the exposed (PFe) is 98.8% , so that the prophylactic antibiotics is able to prevent the puerperal sepsis by 98.8% among the women with PROM who receives them. We found The most frequently used antibiotics among the control group was erythromycin (58%), followed by Rosephin (39%) and about 3%combination of rocephine and metronidazole. Current study has examined the changes in microbiology and intra-amniotic inflammation in patients with preterm PROM treated with three different antimicrobial regimens. The first regimen was Erythromycin used by clinicians concerned with polymicrobial infections. The second regimen was ceftrixon developed and implemented based upon studies of the microbiology of amniotic fluid in patients with preterm PROM, the third regimen was combination of ceftrixon (Rochiphen) plus metronidazole , which showed that Ureaplasmas were a predominant species not treated 43 successfully with erythromycin (19).

The key finding of the current study is that antimicrobial therapy is more effective in eradicating intra-amniotic inflammation/infection than the antimicrobial therapy used in the past. The improved efficacy can be attributed to the improved bioavailability of antibiotics and expanded coverage. It is unlikely that the improved result can be attributed to the duration of therapy, as patients in both groups were treated from admission to delivery.is similar to JoonHo Lee85 et al. study conducted in 2016. The clinical benefit of this therapy is the subject of a separate communication. However ,Maternal mortality was not seen in this study. Maternal morbidity rate 38 cases (28.00%) are higher compared to study by **vermillion et al (20)** but is an agreement with that reported by **Yoon et al (21), by Egarter et al (22)** and **Davidson (23).**

Use of prophylactic antibiotic in PROM reduced maternal morbidity However despite the fact that the prophylactic antibiotic was used liberally in this study. Maternal morbidity rate was (28.00%) , and perinatal mobidity rate was 30.9% , Women with PROM are at increased risk of infection. According to W.H.O Recommendation, Erythromycin is recommended as the antibiotic of choice for prophylaxis in women with preterm prelabour rupture of membranes.but

If there is clinical evidence of chorioamnionitis or maternal sepsis, a septic work-up should be obtained and broad spectrum intravenous antibiotics commenced. The choice of antibiotics used can be determined locally but should include appropriate cover for GBS, E. coli, Listeria and anaerobes. Delivery is indicated in the management of chorioamnionitis. 94 (69%) of infants did not suffer from any infection during the first four weeks of birth, while 42(31%) of them suffered from different types of infections during the first four weeks of their life, in this study we found the most frequent infection was the chest infection 16 cases (38.1 %)in compared to **Hassan Boskadi. (24)** study which was 1.3%and **Medina et al. (25)** study was 0.9%, while septicemia was 11cases (21.4%) compared to **Niliand shain. (26)** study which was 18.4%, and the least frequent was the upper respiratory tract infection (14.3%).

Addidtion to that we noticed that neonatal 44 sepsis incidence was 30.9%. This number is very high compared to study conducted by **Van Der Ham et al. (27)** where neonatal sepsis occurred in 3.4% of all PROM cases. Similar study by **Popowski et al. (28)** showed neonatal sepsis incidence of 4.3%.

Based on the 2015 report of Department of Child Health at Cipto Mangunkusumo Hospital, neonatal sepsis incidence in the hospital was 13.01% (29).

In contrast, studies from several local referral hospital showed that neonatal incidence in Indonesia varied between 1.5% and 3.7% (30).

Regarding neonatal outcomes related to neonatal sepsis incidence, preterm pregnancy with gestational age of 34 to less than 37 weeks, neonatal sepsis was found in 20 subject (47,6%), Since 95% of neonatal sepsis occurred in preterm pregnancy, low birth weight of babies was expected. Babies with neonatal sepsis also had longer length of stay in the hospital, with median of 32 days, compared to 3 days in those without the condition. This finding might as well be related to the preterm gestational age. It is also consistent with the study by **Manuck et al. (31)** where duration of hospitalization is longer in preterm neonates It implies that prematurity is an important factor on the occurrence of neonatal sepsis. They also stated that preterm pregnancy of less than 37 weeks is the most frequent cause of neonatal morbidity.

The incidence of neonatal infection after rupture of membrane that persists for more than 24 hours is 1%, and after clinical inspection, the incidence mounts up to 3-5%. In general, tenfold increase in neonatal infection occurred in premature rupture of membrane cases without complications (32).

A multicenter study on PROM in term pregnancy, conducted in the US, Canada, UK, and Israel, found that prolonged rupture of membrane for ≥48 hours and 24 to 48 hours increases the risk of neonatal infection by 2.25 times (33).

Some studies on prelabor PROM showed no association between prolonged rupture of membrane with neonatal infection. However, a meta-analysis study found significant association between antibiotic administration in mothers with incidence of neonatal infection (OR 0.68 [0.53-0.87]) (34).

In majority (80%) of the participants the onset of PROM was acute (more than 24 hrs), while in 20% of them the 45 onset of PROM was since less than 24hrs. Our study shows that risk of neonatal sepsis is higher in longer duration of prolonged rupture of membrane as well as preterm pregnancy. There are several guidelines recommendation to use prophylactic antibiotics in women following preterm premature rupture of membranes to improve maternal and neonatal outcomes as follow; The Canadian Guideline. **(35)** recommends penicillins or macrolide antibiotics as the antibiotic of choice, administered intravenously, orally or in combination: either ampicillin 2 g + erythromycin250 mg every 6 hours for two days i.v., followed by amoxicillin 250mg + 333 mg erythromycin orally every 6 hours for 5 days or erythromycin 250mg orally every 6 hours for 10 days.

The German AWMF Guideline (36) recommends mezlocillin, piperacillin, clindamycin, ampicillin and erythromycin as suitable antibiotics to treat women with premature rupture of membranes. The Guideline offers no recommendations with regard to the duration of antibiotic treatment. The Guideline is currently being revised. WHO Recommendation Erythromycin is recommended as the antibiotic of choice for prophylaxis in women with preterm prelabour rupture of membranes (Conditional recommendation based on moderate –quality evidence) The use of a combination of amoxicillin and clavulanic acid ("co-amoxiclav") is not recommended.

Conclusion:

According to the results, antibiotics therapy for patients with preterm premature rupture of membranes was associoated with a decrease in the rate of endometritis and trend toword less and neonatal sepsis therefore, screening of high risk women for infection and treating them with antibiotics even prophylactically might help to reduce the risk of PROM in future pregnancies, particularly at extreme gestational age. To our knowledge, this is the first study conducted to determine the effect of antibiotic use following preterm premature rupture of fetal membranes to reduce maternal and neonatal morbidity and mortality in Benghazi.The finding of this study should increase awareness among obstetricians on the importance of screening and monitoring patients with PROM in future pregnancies, and therefore reduce maternal and fetal morbidy and mortality.

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