
Erythromycin Versus Placebo in Management of Preterm Premature Rupture of the Membranes

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Abstract:

Objective: To determine the efficacy of erythromycin on the latency period in preterm and premature spontaneous rupture of fetal membranes and improving fetal outcome compared with placebo.

Materials and methods: This study was a prospective non-randomized controlled trial (non-RCT) carried out in Tripoli Medical Center during the period between December-1-2009 and December-31-2010. Two hundred pregnant patients with gestational age Between 28 and 36 weeks were enrolled in this study. One hundred patients received erythromycin 250mg orally every 6 hours for 7 days, while the other one hundred patients received placebo. Dexamethasone two doses 12mg every 12 hours intramuscular injection was given to the patients with gestational age was between 28 and 34 weeks.

Results: There was a significant prolonged latency period in patients received erythromycin compared with patients received placebo ($p=0.001$). The erythromycin therapy was significantly reduced morbidity and mortality (31% vs. 36%) (10% vs. 20%) respectively. **Conclusion:** We concluded that erythromycin administration following PPSROM was associated with increased latency period and reduced in major markers of neonatal morbidity.

key words: PPSROM, diagnosis, complications, and treatment.

Introduction:

Preterm premature spontaneous rupture of membranes (PPSROM) is the rupture of fetal membranes during pregnancy before 37 weeks having gestation. It occurs in 3% of pregnancies and is the cause of approximately 40% of preterm deliveries.¹⁻³ It can lead to significant prenatal morbidity, including respiratory distress syndrome, neonatal sepsis, umbilical cord prolapse, placental abruption, and fetal death. In addition there are maternal risks associated with Chorioamnionitis.⁴ Ascending infections appear to be one of the major causes of PPSROM leading to a bacterial intrauterine infection, which activates the deciduas and fetal membranes to produce pro-inflammatory cytokines. This in turn leads to the release of prostaglandins, metalloprotease, and other bioactive substances. The prostaglandins stimulate uterine contractions, and metalloproteases soften the cervix and target the membranes, leading to rupture.⁵⁻¹² The diagnosis is made by a history suggestive of spontaneous rupture of membranes followed by a sterile speculum examination demonstrating pooling of fluid in the posterior vaginal fornix, a nitrazine test is not necessary.¹³⁻¹⁶ Ultrasound examination demonstrating oligohydramnios is used to confirm the diagnosis of PPSROM.¹⁷⁻²⁰ Digital vaginal examination is best avoided unless

there is a strong suspicion that the patient may be in labor. This is because micro-organisms may be transported from the vagina into the cervix, leading to intrauterine infection, prostaglandin release and preterm labor.²¹ Management of PPSROM varies depending on gestational age and includes consideration of delivery when rupture of membranes occurs at or after 34 weeks gestation.²²⁻²⁷ Once the decision to manage a patient expectantly has been made, the institution of broad-spectrum antibiotics should be considered. A meta-analysis showed that patients receiving antibiotics after PPSROM, compared with those not receiving antibiotics experienced reduced postpartum endometritis, chorioamnionitis, neonatal sepsis, neonatal pneumonia, and IVH. A number of antibiotic regimens are advocated for use after PPSROM. The following two regimens may be used (the two regimens were used in the largest PPSROM randomized controlled trials that showed a decrease in both maternal and neonatal morbidity): (1) Ampicillin 2 g IV every 6 hours and erythromycin 250 mg IV every 6 hours for 48 hours followed by amoxicillin 250 mg orally every 8 hours and erythromycin 333 mg orally every 8 hours for 5 days. (2) Erythromycin 250 mg orally every 6 hours for 10 days.²⁸

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The use of corticosteroids to accelerate lung maturity should be considered in all patients with PPSROM with risk of infant prematurity at gestational age 34 weeks or less. Corticosteroids reduce neonatal morbidity and mortality. The rates of RDS, NEC, and IVH were all lower when either 12 mg of betamethasone IM was given twice in a 24-hours interval or dexamethasone 12 mg / 12 hours was given for 2 doses.²⁹⁻³² The use of tocolysis, unlike corticosteroids and antibiotics should be considered only when clear clinical benefits exist such as in transport of patient to a tertiary institution with NICU, and to delay the delivery for 48 hours to administering the corticosteroids, and should not be used routinely.³³⁻⁴⁰

Material and methods:

Two hundred pregnant patients admitted to the obstetric department in Tripoli Medical Center from December-1-2009 to December-31-2010 with PPSROM were included in the study. The patients were divided in two groups, the study group (n=100) was received erythromycin 250mg orally every 6 hours for 7 days, whereas the control group (n=100) received placebo. Dexamethasone 12mg /12hours 2 doses was given to both groups if gestational age between 28 and 34 weeks. Non-randomized, special form was used. The data

including; age, parity, address, occupation, gestational age at onset of leakage, gestational age at delivery, mode of delivery, latency period, and fetal outcome were collected. After complete history was taken, speculum examination was performed for all patients. PPSROM was diagnosed if there was watery discharge coming from cervix. High vaginal swab for culture sensitivity was taken from every Patient. Baseline investigations especially leucocytes count were done and repeated twice weekly, ultrasound scan, cardiotocography, were performed to assess the fetal condition. Vital signs of patients (temperature, pulse rate) were performed every 6 hours. The data was analyzed using SPSS by chi-square test and was considered as statistically significant if ($p < 0.05$) and we used T student test for independent samples.

Results:

Our study included 200 pregnant patients with PPSROM. The participants divided into two groups; the study group (n= 100) received erythromycin and the control group (n= 100) received placebo.

In our study, the patients were aged between 18 and 42 years with mean age of the patients 28.4 ± 5.4 years. 61% were aged between 21 and 30 years, whereas 6% of the patients were less than 20 years (figure1).

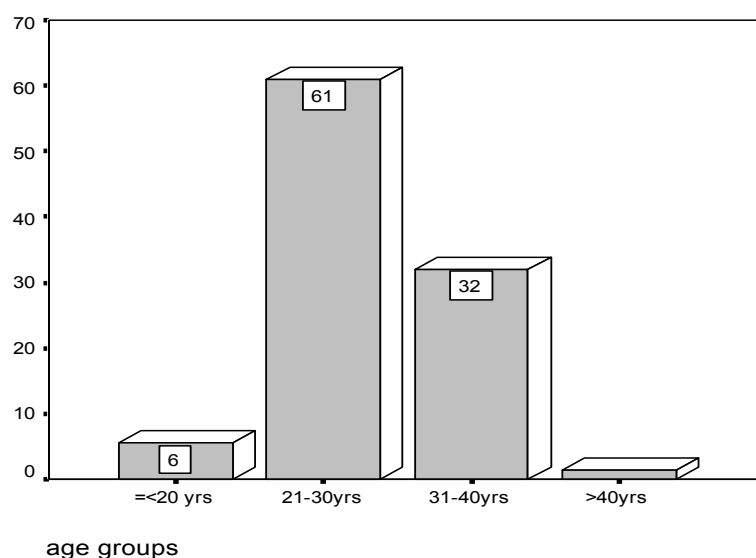


Figure 1: age distribution of patients with PPSROM

Regarding place of residence, 56% of our patients were from Tripoli, whereas 44% were

from periphery towns (figure 2).

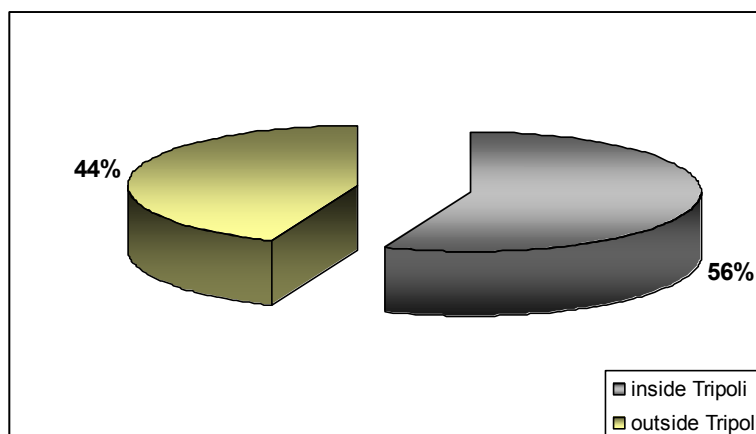


Figure 2: distribution of place residence of patients with PPSROM

Regarding number of pregnancies, we found that 25% of patients were primigravida and

75% were multigravida, the mean gravity was 3 ± 1.9 (table 1), (figure 3).

Table1: parity distribution of patient with PPSROM

Statistics

gravity		
N	Valid	200
	Missing	0
Mean		3.01
Std. Deviation		1.886
Minimum		1
Maximum		10

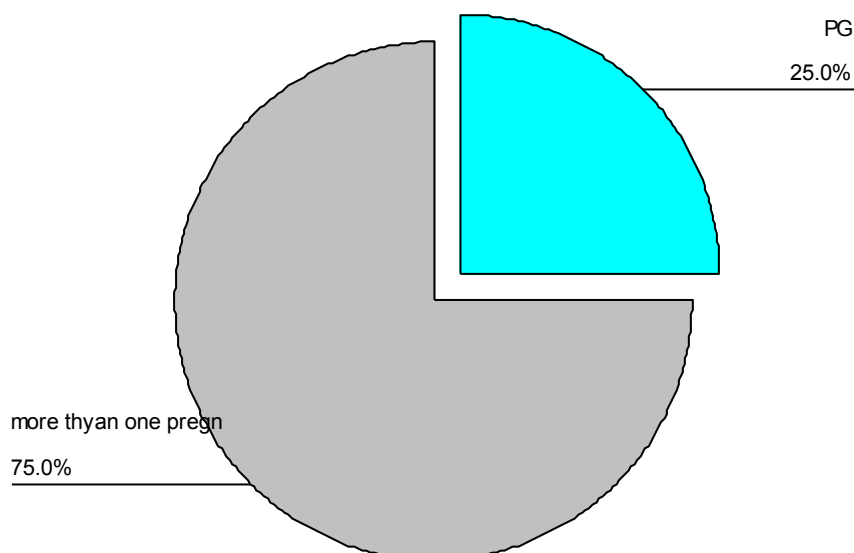


Figure 3: parity distribution of patient with PPSROM.

Our results showed that 22.5% of patients were delivered by emergency caesarean section,

while 77.5% were delivered by normal vaginal delivery (figure 4).

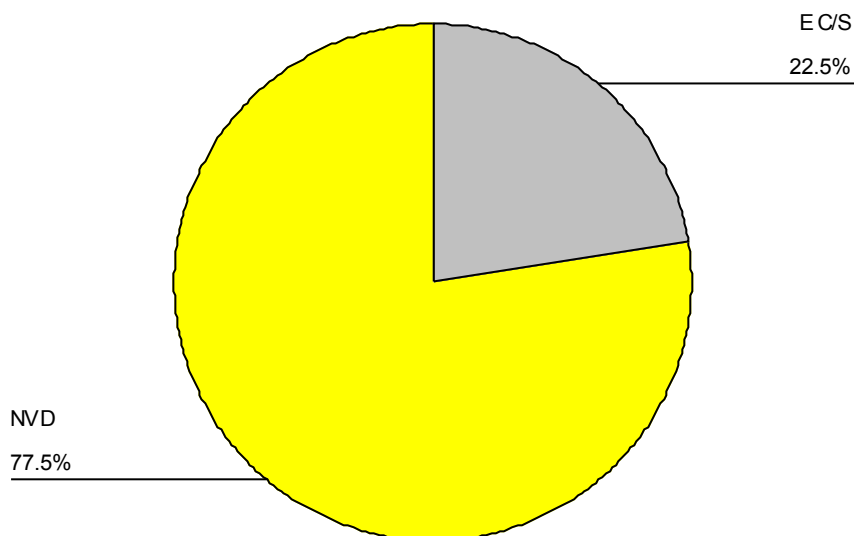


Figure 4: The mode of delivery of patient with PPSROM.

The mean latency period of patients who received erythromycin (study group) was 21.7 ± 11 days, whereas the mean latency period of patients who did not receive

erythromycin (control group) was 5.7 ± 5 days. We found that the difference between these two means were statistically significant ($p=0.001$) (tables 2,3, and 4), (figure 5).

Table 2: statistical difference of latency period between study and control groups.

Group Statistics

group of study		N	Mean	Std. Deviation	Std. Error Mean
latency period	study group	100	21.70	11.101	1.110
	control group	100	5.67	4.944	.494

Table 3: the latency period of study group.

latency period^a

	Frequency	Percent
Valid 7	14	14.0
14	31	31.0
21	18	18.0
28	17	17.0
35	10	10.0
42	9	9.0
56	1	1.0
Total	100	100.0

a. group of study = study group

Table 4: the latency period of control group

latency period^a

	Frequency	Percent
Valid 0	34	34.0
7	53	53.0
14	11	11.0
21	2	2.0
Total	100	100.0

a. group of study = control group

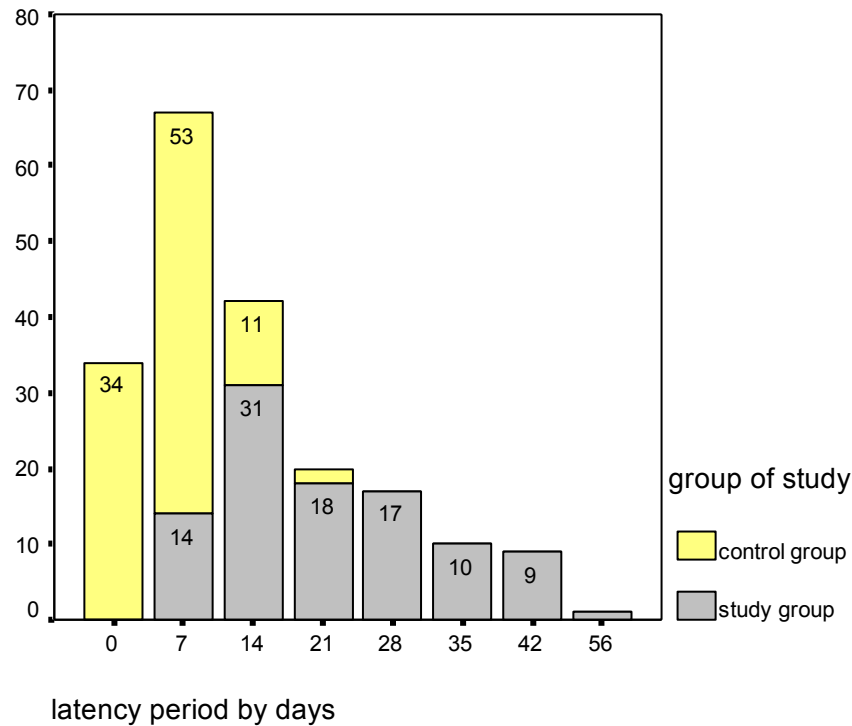


Figure 5: the difference of latency period between study group and control group.

This study showed that 59 babies were given to the mothers, whereas 44 babies of the control group were given to the mothers (59% vs. 44%). Regarding admission to NICU, 31 babies of the study group and 36 babies of the

control group were admitted to NICU (31% vs. 36%). 10 babies of study group and 20 babies of the control group were died (10% vs. 20%), (table 5, figure 6).

Table 5: The difference in fetal outcome between study and control groups.

fetal out come * group of study Crosstabulation

	group of study		Total
	study group	control group	
baby with mother	59	44	103
	59.0%	44.0%	51.5%
admitted to NICU, discharge	31	36	67
	31.0%	36.0%	33.5%
died	10	20	30
	10.0%	20.0%	15.0%
Total	100	100	200
	100.0%	100.0%	100.0%

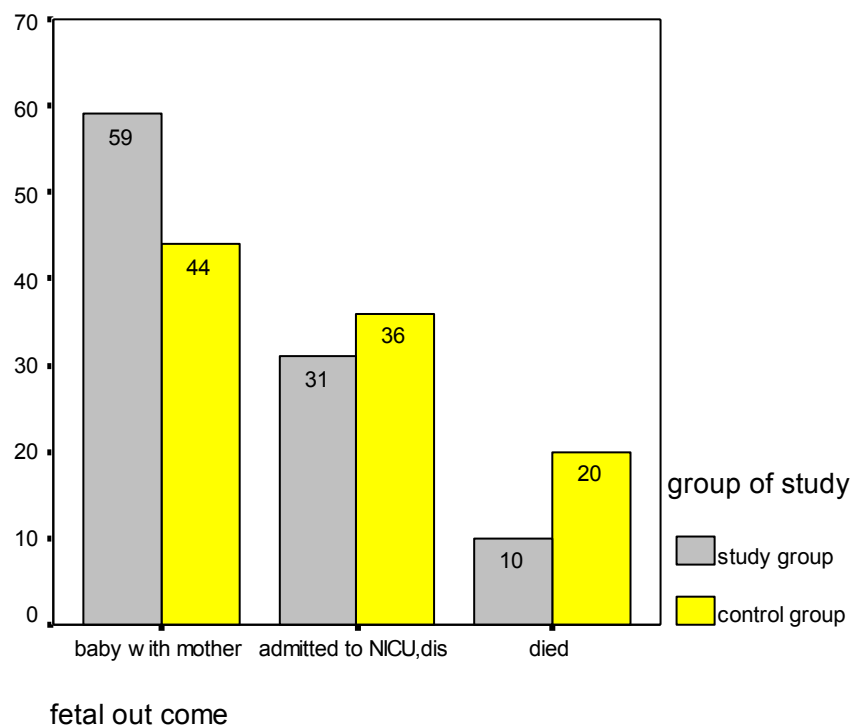


Figure 6: the fetal outcome in study and control groups.

Discussion:

Because of the strong correlation between infection and PPSROM, many authors were focused on the use of antibiotics following PPSROM to find weather the therapy decrease the complications associated with infection. Antibiotic treatment may improve outcome in two ways. First antibiotic therapy may reduce maternal and fetal/neonatal morbidity. Second, treatment or prevention of ascending infection by antibiotics may prolong pregnancy and delay delivery.⁴¹⁻⁴⁴ Our studies showed that routine antibiotic therapy to patients with PPSROM reduce maternal and neonatal morbidity. Regarding prolongation of pregnancy, our study found that, the latency period following erythromycin therapy was (21.7 ± 11 days vs. 5.7 ± 5 days) when compared with placebo ($p=0.001$). Our results were similar to the National Institute of Child Health and Human Development-Maternal Fetal Medicine Units (NICHD-MFMU) trial in which 614 patient with PPSROM from 24 to 32 weeks gestation were enrolled.⁴⁵ In this study patients were randomized either to receive antibiotics or placebo for 7 days. The regimen used was ampicillin 2g IV every 6 hours and erythromycin 250 mg IV every 6 hours for 48 hours then changed to amoxicillin

250 mg orally every 8 hours and erythromycin 333 mg orally every 8 hours. The authors found prolongation of pregnancy with a two – fold likelihood that patients would not deliver following 7 days of antibiotics treatment. In addition this study found a significant reduction in neonatal morbidity ($p<0.05$) which was in correlation with our result. Another large randomized controlled trial was published to assess the effect of antibiotics treatment after PPSROM, this study was the ORACLE trial in which 4826 women with PPSROM <37 weeks gestation were enrolled and randomized into four groups, group one received erythromycin + placebo, group two received co-amoxiclav + placebo, group three received erythromycin + co-amoxiclav, and group four received erythromycin only.⁴⁶⁻⁴⁷ The study found 48 hours prolongation of pregnancy when erythromycin alone was compared with placebo (34.8% vs. 40.7% $p=0.004$) and for 7 days when erythromycin was compared with no erythromycin (57.7% vs. 60.5%, $p=0.08$). Also the study found a reduction in the neonatal morbidity in the study group received erythromycin but oral co-amoxiclav was associated with a significant increase in NEC ($p=0.001$) although duration

of pregnancy was prolonged significantly ($p=0.001$).⁴⁸

In summary, this study concluded that erythromycin administration to women with PPSROM was associated with neonatal health benefit, and a significant delay in delivery following PPSROM which was similar to our result.

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Conclusion:

Antibiotics treatment following PPSROM is associated with a statistical significant delay in women giving birth and reduction in major markers of neonatal morbidity. This delay in delivery would allow sufficient time for prophylactic prenatal corticosteroids to take effect. On the basis of the available evidence erythromycin appears the choice of antibiotics.

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