Azithromycin versus Erythromycin in Preterm Premature Rupture of Membranes: Mansoura Experience

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Abstract

Background: Fetal membrane rupture prior to the 37th week of gestation is a condition termed preterm premature rupture of membranes (PPROM). Many institutions now recommend azithromycin over erythromycin in management of PPROM Due to national erythromycin shortages, azithromycin's better side effect profile, and ease of administration.

Aim of work: Assess effectiveness, side effects, and cost of azithromycin versus erythromycin in management of PPROM.

Patients and methods: this research involved women with PPROM who were distributed into two groups; group A (Azithromycin treated group) and group B (Erythromycin treated group). All cases underwent full history taking, clinical examination, laboratory analysis and obstetric ultrasound (including AFI and FHR). Different outcomes were determined including the duration of latency, chorioamnionitis, neonatal death, neonatal respiratory distress, drug prices and effects.

Results: Differences between groups have been shown to be statistically significant as regard incidence of nausea, vomiting and diarrhea. Higher incidence of side effects was detected among erythromycin than Azithromycin group. The cost of azithromycin was higher compared to the erythromycin regimen.

Conclusion: Azithromycin can be used in place of erythromycin for the expectant management of **PPROM**. Azithromycin only benefits from its availability and reduced gastrointestinal side effects..

Keywords: PROM, PPROM, Azithromycin, Erythromycin

INTRODUCTION

Preterm premature rupture of membranes (PPROM) is A term used to describe the occurrence of membrane rupture prior to the onset of labor in pregnancies that are less than 37 weeks along. About 30% of all births are premature because of this issue, and it affects 1-3% of all pregnancies. [1].

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It may cause devastating maternal, foetal, and neonatal outcomes. Chorioamnionitis, cord compression, abruptio placenta, neonatal sepsis, respiratory distress syndrome, intraventricular bleeding, and even neonatal death are some of the severe perinatal complications that can occur after PPROM. [2].

The infectious process seems to be one of the most important causes of PPROM and this seems to lead to an inflammatory reaction, which alters the tissue structure of the membrane, weakening it and, thus, allowing its rupture [3]. The main agents involved in this pathophysiology are Gardnerella vaginalis, Neisseria gonorrhoeae, Streptococcus agalactiae, Escherichia coli, and Bacteroides sp. [4]

There are many debates about the best course of medical action to take when a woman's ovular membranes rupture before 37 weeks of pregnancy, which is a common occurrence in obstetric practice.[5].

Disagreements include expectant management based on diagnosis, hospitalization, tocolysis, and corticosteroids. In addition, there are the methods used to diagnose infection, the ideal delivery time, and antibiotics usage both for prophylaxis of infection by Group B streptococcus, as well as to increase the period of latency [6].

The most common ACOG-approved PPROM regimen is intravenous erythromycin and ampicillin for two days, followed by oral erythromycin and amoxicillin for five days. This treatment plan reduced chorioamnionitis and other fetal/neonatal complications and prolonged latency delivery..[7].

Nowadays, azithromycin is used instead of erythromycin because it is simpler to administer, has fewer side effects, and is more readily available than erythromycin.[8].

PATIENTS AND METHODS

A prospective, randomized, and controlled clinical research was performed at the Obstetrics and Gynecology Department's inpatient and outpatient clinics at Mansoura University Hospitals in Mansoura, Egypt. The study was carried out from January 2021 to December 2021 over a period of a year.

This research included female cases with PPROM into two groups; Group A (that included 135 patients with were treated by azithromycin and group B (that included 134 patients who were treated with erythromycin)

We included the patients diagnosed with PPROM in the age between 18 and 38 years who are pregnant with gestational age before 37 weeks. We excluded patients with the following characters: PROM <24 or >37 weeks, patients in active labor, presence of any placental insufficiency or abnormality and signs of chorioamnionitis e.g. fetal tachycardia.

The study follows the 2013 Helsinki Standards.[9]. After receiving approval from Mansoura University's Faculty of Medicine's regional ethics committee and written or verbal informed consent from the included cases, the study was conducted.

The cases had a full physical examination, history (including demographics, general medical history, and comorbidities), and menstrual history (to confirm the date and ensure she had an LMP) (General and abdominal examinations focused on uterine contractions).

To confirm gestational age, measure the amount of amniotic fluid (AFI and FHR), and document the viability of the pregnancy, obstetric ultrasound (trans-abdominal) was performed. Total leucocyte count and CRP titer were two laboratory tests that were performed..

Women who had PPROM before 37 weeks of pregnancy, who were not in active labour, who had no clinical signs of chorioamnionitis or placental abruption, and who were admitted for expectant management according to the departmental protocol; women were treated in accordance with this protocol as follows: Every 12 hours, four intramuscular injections of 6-mg dexamethasone are to be given. [10].

The cases were split into two categories.:

- Group A (azithromycin treated group): comprised 135 cases who were given 500 mg of azithromycin orally once every 12 hours for 5 days (Zithromax 500, Pfizer, USA).
- Group B (erythromycin treated group): included 134 patients who were given 500 mg of erythromycin orally every eight hours for five days (Erythromycin 500, Amirya, Egypt).

The outcome measures involved assessment of the latency period as the primary outcome. The latency period is the interval between the beginning of membrane rupture and delivery.

Neonatal respiratory distress requiring oxygen supplementation, neonatal death, and secondary outcomes of chorioamnionitis were also reviewed. Additionally, in a post-treatment patient survey, the cost of medications and their respective side-effect profiles were evaluated.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 26 for Windows® was used to code, process, and analyse the collected data (IBM, SPSS Inc, Chicago, IL, USA). Number (frequency) and percent-based qualitative data were displayed. The Chi-Square test (or Fisher's exact test) made the comparison between groups. The Kolmogorov-Smirnov test tested quantitative data for normality. Parametric data were shown as median ± SD while non-parametric data were expressed as median (range).

Using independent samples (student's) t-test, two groups with normally distributed quantitative variables were compared, Additionally, the Mann-Whitney U-test was applied if the data had an abnormal distribution.For all tests, P values <0.05 are considered significant.

RESULTS

The current research initially included 278 female patients who were assessed for eligibility. Among them 6 females were excluded. The remaining 272 cases were randomly allocated into two groups using randomly generated computer tables; group A and group B .

One female only lost follow up in group A while two females lost follow up in group B. So, the final analyzed number was 135 cases in group A and 134 cases in group B.

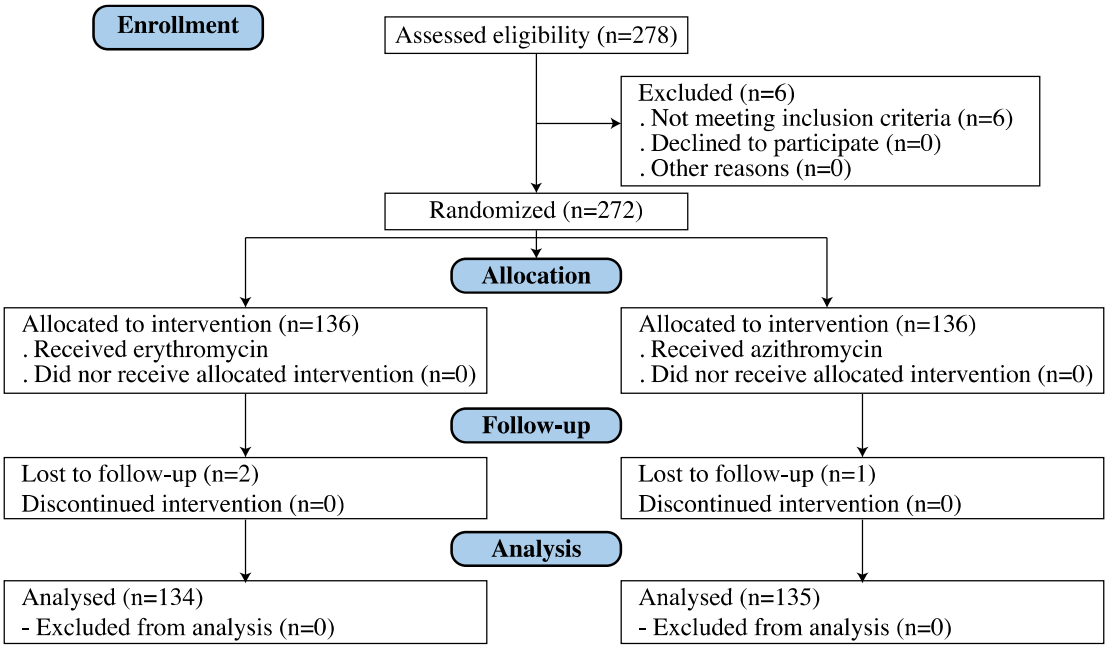

Figure (1): CONSORT Flow chart showing study design

Table (1): shows that there is no statistically significant difference between studied groups as regard age of the cases, gestational age, body mass index ,parity and number of CS .Mean age of erythromycin group is 25.81 years and 25.22 years for azithromycin group .Mean gestational age is 31.07 weeks versus 30.99 weeks for Erythromycin & Azithromycin group , respectively. For erythromycin group; 39.6% ≥2nd para, 32.1% primi-para and 28.4% nullipara and for Azithromycin group; 41.5% ≥2nd para, 30.4% primi-para and 28.1% nullipara.

Table (1): Comparison of sociodemographic data between the studied groups

	Erythromycin group N=134	**Azithromycin group N=135**	**test of significance**
Age in years mean±SD	25.81±5.31	25.22±4.75	t=0.938 p=0.349
Gestational age in weeks mean±SD	31.07±1.87	30.99±1.91	t=0.388 p=0.698
Body mass index (kg/m^2) mean±SD	29.0±1.97	28.85±2.01	t=0.395 p=0.693
Parity n(%) **Nullipara** **Primi para** **≥2nd para**	38(28.4%) 43(32.1%) 53(39.6%)	38(28.1%) 41(30.4%) 56(41.5%)	χ^2=0.126 P=0.939
Number of CS n(%) **NO** **1-2** **>2**	56(41.8%) 66(49.3%) 12(9.0%)	61(45.2%) 60(44.4%) 14(10.4%)	χ^2=0.650 P=0.723

Table (2): Mean temperature among erythromycin group is 37.3 versus 37.28 for azithromycin group without statistically significant difference between them .Mean heart rate illustrates non statistically significant difference between groups with mean heart rate among erythromycin group is 90.68 versus 90.32 for Azithromycin group.

Table (2): comparison of general examination between the studied groups

	Erythromycin group N=134	**Azithromycin group N=135**	**test of significance**
Temperature (°C) mean±SD	37.30±0.59	37.28±0.57	t=0.273 p=0.785
Heart rate (bpm) mean±SD	90.68±8.89	90.32±8.59	t=0.345 p=0.730

Table (3): A non-statistically significant difference between groups is detected for CRP , total leukocytic count , AFI & fetal heart rate .Mean CRP is 7.43 versus 6.96 ,mean total leukocytic count is 9.09 versus 8.23 , mean AFI is 4.62 versus 4.79 , mean fetal heart rate is 145.39 versus 144.19 , for Erythromycin & Azithromycin groups , respectively.

Table (3): comparison of laboratory and ultrasound examination between the studied groups

	Erythromycin group N=134	Azithromycin group N=135	test of significance
CRP mean±SD	7.43±4.07	6.96±4.57	t=0.88 p=0.379
Total leucocytic count mean±SD	9.09±4.26	8.23±3.03	t=1.90 p=0.06
AFI mean±SD	4.62±1.45	4.79±0.89	t=1.17 p=0.245
Fetal heart rate (bpm) mean±SD	145.39±14.11	144.19±14.99	t=0.682 p=0.496

Table (4) : A non-statistically significant difference is detected between studied groups as regard latency , mode of delivery , chorioamnionitis and maternal sepsis. Mean latency is higher among azithromycin than erythromycin group (11.48 versus 10.95) , 55.2% and 52.6% of erythromycin versus azithromycin groups , 9% & 7.4% of the erythromycin versus azithromycin groups, 6%&6.7% of erythromycin versus azithromycin groups have maternal sepsis.

Table (4): comparison of maternal outcome between the studied groups.

Maternal outcome	Erythromycin group N=134	Azithromycin group N=135	test of significance
Latency (days) mean±SD	10.95±5.18	11.48±4.56	t=0.921 p=0.358
Mode of delivery n(%)			
Vaginal	60(44.8%)	64(47.4%)	χ^2=0.187
CS	74(55.2%)	71(52.6%)	p=0.665
Chorioamnionitis n(%)			
-ve	122(91%)	125(92.6%)	χ^2=0.215
+ve	12(9%)	10(7.4%)	p=0.643
Maternal sepsis n(%)			
-ve	126(94%)	126(93.3%)	χ^2=0.055
+ve	8(6%)	9(6.7%)	p=1.0

Table (5) : A non-statistically significant difference is detected between studied groups as regard gestational age , birth weight , APGAR score , respiratory distress , neonatal sepsis & death . Mean gestational age is 32.7 versus 32.65 weeks for Erythromycin and azithromycin groups, respectively. Mean APGAR score is 6.41 and 6.31 for azithromycin and Erythromycin groups, respectively. Mean birth weight is 1809.37 and 1797.63 for Erythromycin and azithromycin groups, respectively. Respiratory distress was detected among 23.9%, 13.4% versus 31.9%&9.6% for azithromycin & Erythromycin groups and neonatal death was the same for both groups (3%).

Table (5): comparison of fetal outcome between the studied groups

fetal outcome	Erythromycin group N=134	Azithromycin group N=135	test of significance
Gestational age at birth in weeks mean±SD	32.70±1.42	32.65±1.49	t=0.280 p=0.780
Birth Weight in gram mean±SD	1809.37±313.93	1797.63±330.45	t=0.299 p=0.765
APGAR score mean±SD	6.31±0.87	6.41±0.97	t=0.831 p=0.407
Respiratory distress n(%)	32(23.9%)	43(31.9%)	χ^2=2.13 p=0.145
Neonatal sepsis n(%)	18(13.4%)	13(9.6%)	χ^2=0.954 p=0.329
Neonatal death n(%)	4(3.0%)	4(3.0%)	FET=0.0 P=1.0

Table (6) shows that there is statistically significant difference between studied groups as regard incidence of nausea , vomiting and diarrhea. Higher incidence of side effects were detected among erythromycin than Azithromycin group. of the studied cases ; 23.1% versus 10.4%, 18.7%versus 6.7% &11.2% versus 2.2% have nausea , vomiting and diarrhea ,respectively for Erythromycin & Azithromycin groups.

Table (6): comparison of drug side effects between the studied groups.

Drug side effects	Erythromycin group N=134	Azithromycin group N=135	test of significance
Nausea n(%)	31(23.1%)	14(10.4%)	χ^2=7.87 P=0.005*
Vomiting n(%)	25(18.7%)	9(6.7%)	χ^2=8.76 P=0.003*
Diarrhea n(%)	15(11.2%)	3(2.2%)	χ^2=8.67 P=0.003*

Table (7) demonstrates that dose of erythromycin treatment is 1*3*5 with total course is 15 tablets with 500 mg concentration and net cost is 13 LE. Dose of Azithromycin treatment is 1*2*5 with total course is 10 Caps with 500 mg concentration and net cost is 283 LE.

Table (5): comparison of fetal outcome between the studied groups

	Erythromycin group N=134	Azithromycin group N=135
Dose:	1x3x5	1x2x5
Total	15 tab.	10 caps.
Concentration:	500 mg	500 mg
Net Cost/ patient: (LE)	13	283

Table (8) shows that alternative treatment companies for Zithrokan , Zisrocin, Azithromycin are Hikma pharma ,EGYpharm & AUG pharma with course cost are 108, 108 & 90 LE, respectively.

Table (8): Lower-cost alternatives for ZITHROMAX® | Pfizer :

	Company	Price	Course cost
Zithrokan	Hikma pharma	32.5	108
Zisrocin	EGYpharm	32.5	108
Azithromycin	AUG pharma	27	90

This study compared azithromycin and erythromycin's cost, side effects, and efficacy in treating PPROM. All females were randomly divided into two groups: group A, which had 135 cases and received 500 mg of azithromycin orally every 12 hours for five days; and group B, which had 134 cases and received 500 mg of erythromycin orally every eight hours for five days.

Cases' age, gestational age, body mass index, parity, and number of CS are not statistically different between the study groups.

This was supported by Musavi et al. (2022), who included 194 pregnant women with PPROM and randomly .

DISCUSSION

assigned them to group A (the azithromycin group) or group B (the placebo group) (Erythromycin group). The two groups' demographic and environmental traits (age, body mass index, gravidity, parity, abortion, live birth) were not statistically different) [11].

Mohamed et al. found similar results in 162 singleton pregnant women aged 18–40 with PPROM between 24 and 32 weeks of gestation. Patients were randomly assigned to Group A or Group B. The findings revealed that differences in gestational age, parity, and the number of prior caesarean sections between the two studied groups were not statistically significant [12].

For CRP, total leucocytic count, AFI, and foetal heart rate, non-statistically significant differences between groups were found in the current study. Additionally, this was mentioned in the study by Musavi et al (2022).

The current findings supported Gelber et al.'s that included women with PPROM at 24-34 weeks who were given azithromycin (n = 29) or erythromycin (n = 67) had no difference in AFI, CRP, or total leucocytic count [13].

This was also in line with the findings of Mohamed et al. who demonstrated that there was no statistically significant difference in the parameters of temperature, heart rate, total leucocytic count, C-reactive protein concentration, foetal heart rate, and amniotic fluid index between the erythromycin and azithromycin groups [12].

In the current study, there was no statistically significant difference between the two study groups regarding latency, mode of delivery, chorioamnionitis and maternal sepsis.

Musavi and colleagues found that erythromycin and azithromycin did not significantly differ in chorioamnionitis or delivery method.

Additionally, a meta-analysis by Seaman et al. recently found a total of 5 studies with 1289 women. Both patients receiving erythromycin and those receiving azithromycin experienced similar mean latency times in women with PPROM. Clinical chorioamnionitis was 25% (95 percent confidence interval, 12-32) in women treated with erythromycin and 14% in those treated with azithromycin (95 percent confidence interval, 9-24) [8].

Navathe et al. found no statistically significant difference in latency to delivery, as did the current study. Azithromycin 1 day group, azithromycin 5 day group, azithromycin 7 day group, and erythromycin group all had unadjusted median times from PPROM to delivery of 5.0 days, 4.4 days, 4.7 days, and

4.7 days, respectively (P = 0.98) [14].

Martingano et al. noted that there was no difference in pregnancy latency and significant differences in the rates of clinical chorioamnionitis, but not histologic chorioamnionitis, about the primary outcomes. Azithromycin had a median latency difference of 5 days, with an interquartile range (IQR) of 6–11 days, and erythromycin had 4.5 days, with an IQR of 6–10.8 days [15].

Mohamed et al. found no statistically significant difference in the latency period for erythromycin patients (1-35 days) and azithromycin patients (2-28 days). They also found no significant differences in maternal outcomes like chorioamnionitis and postpartum haemorrhage between the two study groups [12].

Additionally, the current findings supported those of Gelber et al., who found no differences in latency or maternal outcomes between PPROM-positive women at 24-34 weeks who received either azithromycin (n = 29) or erythromycin (n = 67) as a treatment [13].

This was also consistent with Pierson et al. comparison's of 93 PPROM women treated with ampicillin and a single dose of azithromycin at 24-34 weeks to 75 comparable women treated with ampicillin and erythromycin. They discovered no variation in the latency from membrane rupture to delivery. The prevalence of chorioamnionitis was comparable [16].

With PPROM at 23-33 6/7 weeks, Finneran et al. compared 78 women who received 1 g of azithromycin once orally to 84 women who received erythromycin for 7 days in 2017. The only differences in maternal and neonatal outcomes were higher incidences of caesarean delivery, which was also reflected in the median latency from PPROM to delivery [17].

Non-statistically significant differences in gestational age, birth weight, APGAR score, respiratory distress, neonatal sepsis, and death were found between the studied groups in the current study.

This was consistent with a study by Musavi et al. that found no statistically significant difference between the erythromycin and azithromycin groups for any neonatal outcomes, such as gestational age at delivery, APGAR score, birth weight, or neonatal death [11].

The current findings were consistent with those of Finneran et al., who reported that the only difference in neonatal outcomes between the erythromycin and azithromycin groups that was statistically significant was the positive neonatal blood cultures in the erythromycin group [17].

Mohamed et al. reported similar findings, finding no statistically significant difference in neonatal outcomes, including foetal outcome measures such as birth weight, Apgar score, neonatal respiratory distress syndrome, neonatal sepsis, and neonatal death [12].

Additionally, the current findings supported those of Gelber et al., who found no differences in neonatal outcomes between women with PPROM at 24-34 weeks who received either azithromycin (n = 29) or erythromycin (n = 67) as treatment [13].

Additionally, the current findings were consistent with those of Pierson et al., who contrasted 93 PPROM patients at 24-34 weeks who received ampicillin and a single dose of azithromycin with 75 patients of a similar age who received ampicillin and erythromycin. Both groups had similar neonatal complications, Apgar scores, and birthweight [16].

Although the pharmacokinetic properties of azithromycin and erythromycin are different, both antibiotics cover a similar range of microorganisms. As opposed to erythromycin, which has a half-life of about 1.6 days, azithromycin has a half-life that can be as long as more than 70 hours in the myometrium [18-20].

Additionally, it has been demonstrated that azithromycin's gastrointestinal side effect profile is better [21]. Additionally, many institutions have promoted the use of azithromycin rather than erythromycin due to widespread shortages of the latter [22].

There is a statistically significant difference in the incidence of nausea, vomiting, and diarrhea between the studied groups when it comes to the side effects of the study drugs. The Erythromycin group had a higher incidence of side effects than the Azithromycin group.

This was in line with the findings of Mohamed et al., who discovered a statistically significant difference between the two studied groups in regards to gastrointestinal side effects, specifically in the areas of nausea (19:9), vomiting (15:6), and diarrhea (9:2) in the erythromycin group compared to the azithromycin group [12].

Azithromycin was compared to erythromycin and amoxicillin for treating C. trachomatis infection in pregnant women by Pitsouni et al. The study included 587 expectant women who had C. trachomatis infections that were verified microbiologically. Regarding the success of the treatment in patients who were being evaluated clinically or with an intention to treat, there was no difference between azithromycin and erythromycin. Azithromycin also had fewer gastrointestinal adverse events, overall adverse events, withdrawals, and adherence than erythromycin. Azithromycin is just as effective but safer for treating C. trachomatis infection in pregnant women [23].

In the current study, dose of erythromycin treatment is 1*3*5 with total course is 15 tablets with 500 mg concentration and net cost is 13 LE. Dose of Azithromycin treatment is 1*2*5 with total course is 10 Caps with 500 mg concentration and net cost is 283 LE.

Similar findings were presented by Mohamed et al. (2015), who demonstrated that azithromycin is more expensive than erythromycin in terms of the cost of treatment for the two groups.

Finneran et al. estimated a 95% cost savings for azithromycin over erythromycin; however, current results were in disagreement with their findings [22]. The difference could be mostly due to different geographic locations and different companies that subsequently could affect the price of the drugs.

CONCLUSION

Premature preterm membrane rupture (PPROM) is a common problem for pregnant women. Azithromycin and erythromycin had similar effects on mothers and newborns. If erythromycin is unavailable or not recommended, azithromycin may be used instead to treat PPROM in pregnant women. Apart from its accessibility and absence of gastrointestinal side effects, azithromycin does not appear to have any additional advantages.

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