Different Azithromycin protocols for management of preterm prelabour rupture of membranes: A randomized clinical trial

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Research article

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Abstract

1 Background: The American College of Obstetricians and Gynecologists recommends broad-spectrum antibiotics in cases of preterm prelabor rupture of membranes because the infection is polymicrobial**.** Many antibiotic regimens have been evaluated to prolong the latency to delivery. Nowadays, azithromycin is used instead of erythromycin due to erythromycin shortages, its ease of administration, decreased cost, and better side effect profile.

From the above evidence, there is a need for evaluation of the effect of different protocols of azithromycin in the management of preterm prelabor rupture of membranes.

2 Objective: To evaluate the efficacy of different azithromycin protocols for the conservative management of preterm prelabor rupture of membranes.

3 Study Design: It was a single-blinded randomized clinical trial including pregnant women at $24–36^{+6}$ weeks with viable singleton pregnancies and confirmed preterm prelabor rupture of membranes who attended the Aswan University Hospital from January 01, 2020, to June 01, 2021. The participants were randomized into two groups as follows: Group I was made of women that received Azithromycin 1000 mg PO once and Group II of women that received Azithromycin 500 mg PO once, followed by Azithromycin 250 mg PO daily for four days. The main study outcome was the length of the latency period from the diagnosis of preterm prelabor rupture of membranes to delivery (days). The outcome data were analyzed using the independent samples t-test. The collected data were coded, processed, and analyzed using SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc., Chicago, IL, USA). Data were tested for normality of distribution using the ShapiroWilk test. Qualitative data were represented as frequencies and percentages. The chi-square ($\chi 2$) test was used to calculate differences between two or more groups of qualitative variables. Quantitative data were expressed as the mean ± SD (Standard deviation). The independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). Comparisons between quantitative variables were performed using the one-way analysis of variance to test the difference between the means of several subgroups of a variable. P-values of < 0.05 were considered statistically significant.

4 Results: The latency period in Group I was significantly higher than that in Group II (5.80 ± 5.44 days vs. 2.88 ± 2.37; respectively, $p = 0.000$). The mean gestational age at the time of delivery was significantly higher in Group I ($p = 0.000$). However; the rates of postpartum endometritis and respiratory distress syndrome (RDS) were significantly higher in Group II ($p = 0.003$ and $p = 0.000$, respectively).

5 Conclusion: Antibiotic regimens such as ampicillin (ampicillin 2 gm IV every 6 hrs for 2 days) and azithromycin (azithromycin 1000 mg PO once) are effective in prolonging the latency period, decreasing the incidence of chorioamnionitis, and improving improve neonatal outcomes in women with preterm prelabor rupture of membranes .

Trial registration

First Posted: December 17, 2019

Date of registration: January 01, 2020

Date of initial participant enrollment: January 30, 2020

Clinical trial identification number:

Clinical trial.gov: NCT04202380.

URL of the registration site: https://www.clinicaltrials.gov/ct2/show/NCT04202380

Data sharing information: Individual participant data available, other documents available (e.g., study protocol, statistical analysis plan, etc.)

Why Was This Study Conducted?

1. **Condensation :** A randomized clinical trial designed to evaluate two different azithromycin protocols for management of PPROM and resulted in the effectiveness of single day protocol.
2. **Why was this study conducted?**

To evaluate the effective azithromycin protocol that lead to prolongation of latency period during conservative treatment of patients with PPROM.

Key findings

Ampicillin 2 gm IV every 6 hrs for 2 days) and azithromycin (Azithromycin 1000 mg PO once) is effective to prolong latency period, decrease incidence of chorioamnionitis and improve neonatal outcomes in women with PPROM between 24 – 36+6 weeks.

What does this add to what is known?

This work is basically a comparative effectiveness research comparing two interventional therapies in women complaining from preterm prelabor rupture of membranes and consider the first registered clinical trial comparing two different azithromycin protocols , and the most of studies compare azithromycin with erythromycin protocols are retrospective

1. Introduction

PPROM is defined as the spontaneous rupture of fetal membranes before 37 completed weeks of gestation. PPROM complicates approximately 3% of pregnancies and is associated with 30–40% of preterm births.[1,2]

ROM is diagnosed via the patient's history followed by a sterile speculum examination. If no amniotic fluid is observed, insulin-like growth factor-binding protein-1 (IGFBP-1) or placental alpha microglobulin-1 (PAMG-1) tests are carried out to confirm the diagnosis.[3]

PPROM is associated with an ascending infection that leads to chorioamnionitis and fetal and neonatal infections.[4] .

Microorganisms are present in approximately 30% of PPROM cases.[5] The frequency of infection increases over the latency period; so, when a patient with PPROM goes into active labor, microorganisms are detected in 75% of cases.[6].

The management between 24 weeks and 37 weeks includes hospital admission, fetal monitoring, assessment of infection, and courses of corticosteroids and antibiotics to prolong the latency period between PPROM and delivery.[3]

The American College of Obstetricians and Gynecologists (ACOG) recommends broad-spectrum antibiotics in cases of PPROM because the infection is polymicrobial. Many antibiotic regimens have been found to prolong the latency period.[5]

Intravenous erythromycin and ampicillin for two days followed by oral erythromycin and amoxicillin for five days is the most common regimen used in PPROM that is supported by the ACOG. This regimen was associated with prolonged latency to delivery and a decrease in the incidence of chorioamnionitis and fetal/neonatal complications.[6]

Nowadays, azithromycin is used instead of erythromycin due to its ease of administration, decreased cost, better side effect profile, and erythromycin shortages.[7,8]

From the above evidence, there is a need to evaluate the effect of the different azithromycin protocols.

2. Materials And Methods

The study was a single-center, single-blinded, randomized, parallel, and registered clinical trial (Clinical trial.gov- NCT04202380) carried out from January 01, 2020, to June 01, 2021. Pregnant women with gestational ages of 24–36^{+6} weeks who had PPROM and attended the Aswan University Hospital, Aswan, Egypt, were included in the study. Institutional Scientific and Research Ethical Committee approval (IRB: asw/433/1/20). Ethical approval was obtained before the start of the study and informed consent was obtained from all participants.

2.1 Eligible participants

We included womenwithviable singleton pregnancies atgestational ages of 24–36^{+6} weeks who had confirmed PPROM diagnosed via maternal history and sterile speculum examination demonstrating

liquor.

However, we excluded pregnant women with gestational ages of $\leq 23^{+6}$ weeks or ≥ 37 weeks, unconfirmed gestational ages, multiple pregnancy, macrolide allergy, women who received macrolide therapy within a week before recruitment, lethal fetal anomalies, and contraindications to the expectant management of PPROM at the time of diagnosis such as concurrent preterm labor, placental abruption, chorioamnionitis, or non-reassuring fetal testing.[9]

2.2 Randomization

Eligible women who gave their informed consent were randomized to either: the group taking azithromycin 1000 mg PO once (Group I) or that taking azithromycin 500 mg PO once, followed by azithromycin 250 mg PO daily for 4 days (Group II). Randomization was conducted using a computer-generated table of random numbers with allocation concealment. Blinding of the participant was done. Allocation concealment was done using serially-numbered closed opaque envelopes. Written informed consent was obtained from each of the eligible women.

2.3 Study intervention

After obtaining informed consent, women who met the eligibility criteria had their detailed history taken and underwent systemic examination, including general examination and abdominal examination. Then, the participants underwent ultrasonography to assess fetal biometry, amniotic fluid volume, biophysical profiles,and to exclude any fetal gross anomalies. Complete blood counts, urine analysis, and C-reactive protein measurements were performed as baseline investigations.

Two hundred and ten (210) women consented to participate and were divided randomly into two equal groups, withboth groups receiving ampicillin 2 gm IV every 6 hrs for two days (Unasyn 1.5 gm, Pfizer, Egypt).The participant in Group I received azithromycin 1000 mg PO once (Xithrone 500 mg, Amoun, Egypt), and those in Group II receivedazithromycin 500 mg PO once, followed by azithromycin 250 mg PO daily for four days (Xithrone 500 mg, Amoun, Egypt).

2.4 Follow-up schedule

The participants were admitted to our hospital. We followed up the cases to detect any maternal and fetal complications (preclinical chorioamnionitis or fetal compromise) till either the onset of spontaneous labor or the attainment of maturity by maternal pulse and temperature charts to detect early signs of chorioamnionitis, serial CRP measurements to detect rising titers twice weekly, CBC twice weekly to detect new-onset leukocytosis, the detection of labor pains, and the detection of the development of vaginal bleeding suggesting placental separation . Clinical chorioamnionitis was diagnosed when the temperature was elevated to 38°C and two or more of the following criteria were present: uterine tenderness, malodorous vaginal discharges, maternal leukocytosis, maternal tachycardia, and fetal

tachycardia in the absence of other sources of infection. Presence of established labor, moderate-to-severe bleeding, fetal distress, or intrauterine infection, termination of pregnancy is considered.

2.5 Study outcomes

The primary outcome was thelength of the latency period from the diagnosis of PPROM to delivery (days) and the secondary outcomes were the delivery mode, rate of chorioamnionitis, rate of NICU admission, length of stay in the NICU (LOS), number of stillbirths, number of babies with RDS, number of neonatal deaths, and the rate of postpartum endometritis.

2.6 Sample size

The sample size was calculated according to the following formula:

$$n = \frac{\left(\sigma_1^2 + \sigma_2^2\right)\left(z_{\frac{\alpha}{2}} + z_\beta\right)^2}{\left(\log(m_1) - \log(m_2)\right)^2}$$
$$= \frac{\left[\log\left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\phi_1^2}{m_1^2}}\right) + \log\left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\phi_2^2}{m_2^2}}\right)\right]\left(z_{\frac{\alpha}{2}} + z_\beta\right)^2}{(\log(m_1) - \log(m_2))^2}.$$

(Aidan G. O'Keeffe et al., 2017)18

Z α = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail).

Zβ = 0.84 (The critical value that separates the lower 20% of the Z distribution from the upper 80%).

m1: median of Group 1, according to a previous study by ***Reshama Navathe et al., 2019*** *19*(m1 = 4.9).

m2: median of Group 2, according to a previous study of ***Reshama Navathe et al., 2019*** *20*(m2 = 5).

σ2: the variance of the log-transformed primary outcome for the group.

φ2: The variance of the untransformed outcome for the group.

The sample size (n) = 210

The sample was divided into two groups:

Group 1 = 105 cases

Group 2 = 105 cases

Sample size correlation

The total sample size required to determine whether a correlation coefficient differs from zero.

Sample size correlation was done using the following formula:

Total sample size (N) = $[(Z\alpha + Z\beta)/C]^2 + 3 = 194$ ***(Hulley SB et al.; 2013).***

The standard normal deviation for $\alpha = Z_\alpha = 1.9600$

The standard normal deviation for $\beta = Z_\beta = 0.8416$

$C = 0.5 * [(1 + r)/(1 - r)] = 0.2027$

Where r = 0.2

The minimum sample size suitable for Pearson correlation at an expected correlation coefficient (r) ≥ 0.2 is 194; so, our sample size (210) was suitable to determine this correlation.

4.7 Statistical analysis

The collected data were coded, processed, and analyzed using SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc., Chicago, IL, USA). Data were tested for normality of distribution using the ShapiroWilk test. Qualitative data were represented as frequencies and percentages. The chi-square ($\chi 2$) test was used to calculate differences between two or more groups of qualitative variables. Quantitative data were expressed as the mean ± SD (Standard deviation). The independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). Comparisons between quantitative variables were performed using the one-way analysis of variance to test the difference between the means of several subgroups of a variable. P-values of < 0.05 were considered statistically significant.

3. Results

Initially, there were 234 potential participants; however, 24 of the women did not meet the selection criteria (seven women had multiple pregnancies four had lethal fetal anomalies, and 13 declined to participate). Two hundred and ten women consented to participate and were divided into two groups. Group I included 105 women and Group II included 105 women. All participants completed their follow-up visits till the end of the study **(**Fig. 1, **the study flow chart).**

There was no significant difference in baseline socio-demographic characteristics and obstetric data between the two groups. **(**Table 1 **and** Table 2**).**

Table 1
Personal data of the participants in the study groups

Personal data	**Group I** (n = 105)	**Group II** (n = 105)	**P-value**
Age (years)			
Mean ± SD	28.61 ± 5.33	28.86 ± 5.51	0.741
Range	19.0–42.0	18.0–43.0	
Residence, n (%)			
Urban	28 (26.7%)	20 (19.0%)	0.189
Rural	77 (73.3%)	85 (81.0%)	
Educational level, n (%)			
Illiterate	26 (24.8%)	29 (27.6%)	
Basic education	54(51.4%)	53(50.5%)	0.880
Secondary or more	25 (23.8%)	23(21.9%)	
Work, n (%)			
Working	23 (21.9%)	21 (20.0%)	0.735
Not working	82 (78.1%)	84 (80.0%)	
BMI(Kg/m^2)			
Mean ± SD	33.39 ± 4.21	32.84 ± 4.21	0.350
Range	25.3–40.6	25.3–40.6	

BMI body mass index, **kg/m^2** kilogram per square meter, **n (%)** number and percentage, **SD** standard deviation

Table 2
Obstetric data of women in our RCT

Obstetric data	**Group I (n = 105)**	**Group II (n = 105)**	**P-value**
Parity			
Mean ± SD	1.70 ± 1.70	1.64 ± 1.59	0.847
Median (Range)	1.0 (0.0–8.0)	1.0 (0.0–6.0)	
No. of NVD			
Mean ± SD	1.01 ± 1.47	0.81 ± 1.47	0.253
Median (Range)	0.0 (0.0–6.0)	0.0 (0.0–6.0)	
No. of CS			
Mean ± SD	0.70 ± 1.15	0.85 ± 1.22	0.404
Median (Range)	0.0 (0.0–5.0)	0.0 (0.0–5.0)	
No. of living children			
Mean ± SD	1.62 ± 1.49	1.57 ± 1.48	0.825
Median (Range)	1.0 (0.0–5.0)	1.0 (0.0–6.0)	
History of abortion, n (%)			
Yes	36 (34.3%)	38 (36.2%)	0.773
No	69 (65.7%)	67 (63.8%)	
Duration from last delivery (months)			
Mean ± SD	24.72 ± 3.43	23.95 ± 3.50	0.175
Range	18.0–30.0	18.0–29.0	
Gestational age (weeks)			
Mean ± SD	32.49 ± 2.96	31.95 ± 3.74	0.252
Range	25.0–36.9	24.3–36.9	

CS caesarian section, NVD normal vaginal delivery, **n (%)** number and percentage, **SD** standard deviation

More than 35% of the women had a history of vaginitis and approximately 45% of them had a previous history of UTIs. Moreover, 21.5% of them had a history of PROM during previous pregnancies. Collectively, no statistically significant differences were found between the two groups in the rates of vaginitis, UTI, and PROM (Table 3).

Table 3
History of the vaginitis, UTI, and PROM in women who participated in the RCT

Past history	Group I (n = 105)		Group II (n = 105)		P-value
	No.	%	No.	%	
History of vaginitis in current pregnancy					
Yes	40	38.1%	38	36.2%	0.775
No	65	61.9%	67	63.8%	
History of UTI in current pregnancy					
Yes	48	45.7%	45	42.9%	0.677
No	57	54.3%	60	57.1%	
History of PROM in previous pregnancy					
Yes	23	21.9%	20	19.0%	0.608
No	82	78.1%	85	81.0%	

PROM preterm rupture of membrane, **n (%)** number and percentage, **UTI** urinary tract infection

The mean latency period in Group I (5.80 ± 5.44 days) was significantly higher than that in group II (2.88 ± 2.37, p = 0.000). Again, the mean gestational age at the time of delivery was higher in Group I than in group II (35.12 ± 2.86 vs. 32.61 ± 3.86; p = 0.000, respectively). The rate of postpartum endometritis was significantly higher in Group II (p = 0.003). However, no statistically significant differences were found between the two groups in the rate of chorioamnionitis (p = 0.347) and the mode of delivery (p = 0.155) (Table 4).

Table 4
Maternal outcomes

Maternal outcomes	**Group I** (n = 105)	**Group II** (n = 105)	**P-value**
Latency period (days)			
Mean ± SD	5.80 ± 5.44	2.88 ± 2.37	0.000*
Median (Range)	4.0 (1.8–29.0)	2.5 (1.5–19.0)	
Chorioamnionitis, n (%)			
Yes	8 (7.6%)	12 (11.4%)	0.347
No	97 (92.4%)	93 (88.6%)	
Mode of delivery, n (%)			
NVD	35 (33.3%)	45 (42.9%)	0.155
CS	70 (66.7%)	60 (57.1%)	
Gestational age at time of delivery (weeks)			
Mean ± SD	35.12 ± 2.86	32.61 ± 3.86	0.000*
Range	25.0–37.0	25.0–37.0	
Postpartum endometritis, n (%)			
Yes	3 (2.9%)	15 (14.3%)	0.003*
No	102 (97.1%)	90 (85.7%)	
* Statistically significant difference (P < 0.05)			
CS caesarian section, NVD normal vaginal delivery, **n (%)** number and percentage, **SD** standard deviation			

Table 5 shows the neonatal outcomes of the study. The mean birth weight was significantly higher in Group I than in Group II (2476.71 ± 650.76 m vs. 1918.21 ± 773.55; p = 0.000). Moreover; Group I had a better Apgar score at 5 minutes than Group II (p = 0.000). The rate of NICU admission and length of stay at the NICU were lower in Group I than in Group II (p = 0.000, 0.001; respectively). The rate of RDS was significantly higher in group II than in Group I (p = 0.000) and better neonatal viability was observed in Group I than in group II (p = 0.041).

Table 5
Neonatal outcome.

	Group I (n = 105)	**Group II** (n = 105)	**P-value**
Birth weight (grams)			
Mean ± SD	2476.71 ± 650.76	1918.21 ± 773.55	0.000*
Range	600.0–3100.0	600.0–3050.0	
APGAR score at 5 minutes, n (%)			
< 7	36 (34.3%)	76 (72.4%)	0.000*
≥ 7	69 (65.7%)	29 (27.6%)	
NICU, n (%)			
Yes	27 (25.7%)	58 (55.2%)	0.000*
No	78 (74.3%)	47 (44.8%)	
Length of stay in the NICU (days)			
Mean ± SD	4.67 ± 2.97	7.21 ± 2.84	0.001*
Median (Range)	3.0 (1.0–11.0)	7.0 (1.0–12.0)	
RDS, n (%)			
Yes	25 (23.8%)	55 (52.4%)	0.000*
No	80 (76.2%)	50 (47.6%)	
Neonatal viability, n (%)			
Alive	96 (91.4%)	84 (80.0%)	
IUFD	6 (5.7%)	10 (9.5%)	0.041*
Neonatal death	3 (2.9%)	11 (10.5%)	

*Statistically significant difference (P < 0.05) **CS caesarian section, IUFD** intrauterine fetal death, **NICU** neonatal intensive care unit, **NVD** normal vaginal delivery, **n (%)** number and percentage, **RDS** respiratory distress syndrome, **SD** standard deviation

4. Comment

4.1 Principal findings

Regarding the primary outcomes, the latency period in **Group I** was significantly higher than that in **Group II**. Again, the mean gestational age at the time of delivery was higher in **Group I** than in Group II. However, regarding the secondary outcomes, the rate of postpartum endometritis was higher in **Group II** than in Group I. No statistically significant differences in the rate of chorioamnionitis and mode of delivery were noted between the two groups.

According to the neonatal outcomes of the study, the mean birth weight was significantly higher in **Group I** than in Group II. Moreover, **Group I** had a better Apgar score at 5 minutes than **Group II**. The rate of NICU admission and length of stay at the NICU were lower in **Group I** than in Group II. The rate of RDS was significantly higher in **Group II** than in Group I, and better neonatal viability was observed in **Group I** than in Group II.

To the best of our knowledge, most previous studies on the different dosing regimens on azithromycin in the management of PPROM were retrospective.

4.2 Comparison with existing literature

Gelber et al. [10] reported no significant difference in latency or maternal and neonatal outcomes between women with PPROM at 24–34 weeks of gestation who were given either azithromycin (n = 29) or erythromycin (n = 67) (doses and treatment durations were not specified).

Pierson et al. [7] compared 93 women with PPROM at 24–34 weeks of gestation who received ampicillin and single-dose azithromycin (doses were not specified) with 75 matched women who received ampicillin and erythromycin. They found no significant difference in the latency period from rupture of membranes to delivery. No statistically difference in chorioamnionitis, birth weight, Apgar scores, and neonatal complications between the two groups. They determined that with equivalent outcomes between the two groups, azithromycin may be a favorable substitution for the original seven-day erythromycin.

In contrast to our study, the previous two were retrospective studies that compared two different drugs in the management of PPROM (azithromycin vs. Erythromycin), which are different from our study that compared two dosing regimens of azithromycin in the management of PROM. However, it supported our study in the reliance on azithromycin as a powerful and effective alternative in the management of PPROM.

Finneran et al. [8] compared 78 women who received azithromycin 1 g once orally with 84 women who received erythromycin for seven days, all with PPROM at 23–33^{+6} weeks of gestation. The median latency from PPROM to delivery was also similar, with the only differences in maternal and neonatal outcomes being the higher rates of cesarean delivery and positive neonatal blood cultures in the erythromycin group.

Unlike our study, this study was a retrospective cohort study comparing two different drugs in the management of PPROM (azithromycin vs. Erythromycin). However, they used azithromycin in a dosing regimen that was similar to ours in the one-day azithromycin group. Comparisons of the results of the

azithromycin group of this study with those of our one-day azithromycin group revealed that the range of the latency period in our study was 1.8–29 days vs. 3.1–12.1 days for this study. We had a higher rate of CS deliveries (66.7% vs. 29.5% for this study), lower rate of chorioamnionitis (7.6% vs. 24.2% for this study), lower rate of neonatal RDS (23.8% vs. 64.5% for this study), and lower rate of neonatal death (2.9% vs. 4% for this study).

Navathe et al. [11] conducted a multicenter, retrospective cohort study that compared different dosing regimens of azithromycin with erythromycin in the management of PPROM. A total of 453 women with singleton pregnancies and confirmed PPROM at $23–33^{+6}$ weeks of gestation were included in the study. Seventy-eight women received azithromycin for one day, 191 women received azithromycin for five days, 52 women received azithromycin for seven days, and 132 women received erythromycin. They demonstrated that there was no significant difference in either latency to delivery, gestational age at the time of delivery, or the incidence of chorioamnionitis. According to neonatal outcomes, RDS was more common in the five-day azithromycin group. The five-day azithromycin group showed a lower proportion of neonates with five-minute Apgar scores of < 7 and a shorter length of stay in the NICU compared with other groups.

This study differed from ours in that it was retrospective study comparing three different dosing regimens of azithromycin with one regimen of erythromycin. Unlike the findings of our study, there was no difference in latency to delivery, the gestational age at the time of delivery, or the incidence of chorioamnionitis. According to neonatal outcomes, in line with our findings, RDS was more common in the five-day azithromycin group. However, in contrast to our results, the five-day azithromycin group showed a lower proportion of neonates with five-minute Apgar scores of < 7 and a shorter length of stay in the NICU compared with other groups.

Martingano et al. [12] conducted a prospective cohort study comparing 142 women with PPROM at 24–34 weeks of gestation who received the azithromycin regimen (azithromycin 1 g PO once and ampicillin 2 g every 6 hrs IV for 48 hrs followed by five days of amoxicillin 250 mg every 8 hrs PO for five days) and 168 matched women who received the erythromycin regimen (erythromycin 250 mg and ampicillin 2 g every 6 hrs IV for 48 hrs followed by amoxicillin 250 mg and erythromycin 500 mg every 8 hrs PO for 5 days). They found no significant difference in the latency period from rupture of membranes to delivery. However, they found a decreased risk for the development of clinical chorioamnionitis, neonatal sepsis, and postpartum endometritis in the azithromycin group.

Unlike in our study, this study was a prospective cohort study comparing two different drugs in the management of PPROM (azithromycin vs. Erythromycin). However, they used azithromycin in dosing regimens similar to ours in the one-day azithromycin group. Comparisons of the results of the azithromycin group of this study with those of our one-day azithromycin group showed that the range of the latency period in our study was 1.8–29 days vs. 6–11 days for this study. We had a higher rate of CS deliveries (66.7% for ours vs. 50.7% for this study), lower rate of chorioamnionitis (7.6% for ours vs. 13.4% for this study), and lower rate of postpartum endometritis (2.9% for ours vs. 14.8% for this study).

Sinrat et al. [13] conducted a retrospective, descriptive study on 88 women with PPROM at 24–33^{+6} weeks who received antibiotic regimens of ampicillin plus azithromycin to prolong the latency period (ampicillin 2 g intravenously every 6 hrs for 48 hrs, amoxicillin 500 mg orally thrice a day, and azithromycin 500 mg orally for 1 day, then 250 mg orally once daily for 6 days). They found that 86.4% of the women reached more than 48 hrs of latency, and 8% of them had chorioamnionitis as a complication. Regarding neonatal outcomes, 33% of the neonates had RDS as a complication, 54.5% had neonatal sepsis, and 3.4% experienced neonatal death.

Unlike our study, this study was a retrospective, descriptive study using the seven-day regimen of azithromycin in the management of PPROM. Comparisons of the results of this regimen with ours showed that the range of the latency period was 2.5–8 days vs. 1.8–29 days in our one-day azithromycin group vs. 1.5–19 days in our five-day azithromycin group. The rate of chorioamnionitis in this study was slightly higher than that in our one-day group but lower than that in our five-day group. Regarding neonatal outcomes, the rates of NICU admission, neonatal RDS, and neonatal deaths in this study were higher than those in our one-day group but lower than those in our five-day group. However, the median length of stay in the NICU in this study was higher than those in our two groups.

Kole-White et al. [14] conducted a retrospective study comparing two antibiotic regimens in the management of PPROM at 23–34 weeks' gestation. Seventy-nine women received the standard regimen (2 gm IV ampicillin/6 hrs and 500 mg IV azithromycin/24 hrs for two days followed by amoxicillin 500 mg PO/8 hrs and azithromycin 250 mg PO/24 hrs for five days). Thirty-seven women received a modified regimen (amoxicillin 500 mg PO/8 hrs for seven days and azithromycin 500 mg/24 hrs for two days followed by 250 mg PO/24 hrs for five days). They found no significant differences in the latency period, the rate of maternal infection, or neonatal outcomes between the two groups.

Unlike our study, this one was a retrospective study comparing two dose regimens of azithromycin in the management of PPROM: the standard regimen (two days of intravenous treatment followed by five days of oral azithromycin) and the modified regimen (seven days oral azithromycin). They had a longer mean latency period than ours. Their modified regimen group had a lower rate of chorioamnionitis and endometritis than our two groups. However, on the other hand, the rate of NICU admission in our study was significantly lower than theirs.

4.3 Clinical implications

The most common regimen used in the United States is that from the National Institute of Child Health and Human Development (NICHD) trial, which used an initial 48 hrs of intravenous therapy with ampicillin and erythromycin, followed by five days of oral therapy with either amoxicillin or an enteric-coated erythromycin base.

While the RCOG recommends erythromycin (250 mg orally six-hourly) should be given for 10 days following the diagnosis of PPROM. (Grade A Recommendations GTG NO 44).

Many institutions have advocated for the use of azithromycin instead of erythromycin. This is secondary to national erythromycin shortages and the ease of administration, better side effect profile, and decreased cost of azithromycin.[7,8,10]

The use of oral amoxicillin-clavulanic acid is, perhaps, best avoided because of the increased risk of necrotizing Enterocolitis (NEC) documented in one study; however, it should be noted that the NICHD trial that used ampicillin and erythromycin found a decreased risk of NEC.[17]

This study directly addresses the paucity of prospective data on the conservative management of PPROM. There is limited information regarding the most effective azithromycin protocol. These study findings highlight the need for the use of ampicillin and azithromycin 1000 once PO as it is effective in prolonging the latency period.

4.4 Strengths and limitations

Our study is the first registered clinical trial focused on the effect of the use of two different regimens of azithromycin with a large number of patients (210) over 17 months.

Better results could be obtained if future clinical trials including more cases and of a multicentric nature are carried out to compare different dosing regimens of azithromycin in the expectant management of PPROM.

4.5. Conclusions

Antibiotic regimens including ampicillin and azithromycin were effective in prolonging the latency period, decreasing the incidence of chorioamnionitis, and improving neonatal outcomes in women with PPROM at 24–36^{+6} weeks of gestation.The one-day azithromycin regimen was more effective than the five-day.

Declarations

Ethics approval and consent to participate : Ethical approval for this study was obtained from Aswan faculty of medicin ethical committee number IRB: asw/433/1/20 Written informed consent was obtained from all subjects before the study.

Consent for publication : We certify our authorship of the manuscript submitted forpublication

Availability of data and materials : Individual participant data available, other documents available (e.g., study protocol, statistical analysis plan, etc.)

Competing interests : There are no conflicts of interest between authors

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4.6. Recommendations

• The use of the single-day azithromycin regimen (2 gm ampicillin IV every 6 hrs for two days plus azithromycin 1000 mg PO once) in the expectant management of PPROM is very effective in prolonging the latency period, decreasing incidence of postpartum endometritis, and improving neonatal outcomes.

References

1. ACOG Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 80. premature rupture of membranes. Clinical management guidelines for obstetrician gynecologists. Obstet Gynecol 2007;109:1007-19.
2. Mercer BM. Preterm premature rupture of the membranes. Obstet Gynecol 2003;101:178-93.
3. Thomson AJ. On behalf of the Royal College of Obstetricians and Gynaecologists. Care of women presenting with suspected preterm prelabour rupture of membranes from 24+0 weeks of gestation. BJOG 2019;126:e152-66.
4. National Institute of Health and Care Excellence (NICE) pathways Diagnosing and managing preterm prelabour rupture of membranes. 2017:2-4.
5. Kenyon SL, Boulvain M, Neilson J. Antibiotic treatment in premature rupture of membranes: a systematic review. Obstet Gynecol 2004;104:1051-7.
6. Mercer BM. Preterm premature rupture of the membranes: current approaches to evaluation and management. Obstet Gynecol Clin North Am 2005;32:411-28.
7. Pierson RC, Gordon SS, Haas DM. Retrospective comparison of antibiotic regimens for preterm premature rupture of membranes. Obstet Gynecol 2014;124:515-9.
8. Finneran MM, Appiagyei A, Templin M, Mertz H. Comparison of azithromycin versus erythromycin for prolongation of latency in pregnancies complicated by preterm premature rupture of membranes. Am J Perinatol 2017;34:1102-7.
9. Bond DM, Middleton P, Levett KM, et al. Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. Cochrane Database of Syst Rev 2017;17:CD004735.
10. Gelber S, Brent E, Varrey A, Fridman B, Sapra K, Frayer W. Equivalence of erythromycin and azithromycin for treatment of PPROM. Am J Obstet Gynecol 2013;208:291.
11. Navathe R, Schoen CN, Heidari P, et al. Azithromycin vs erythromycin for the management of preterm premature rupture of membranes. Am J Obstet Gynecol 2019;221:1-8.
12. Martingano D, Singh S, Mitrofanova A . Azithromycin in the treatment of preterm prelabor rupture of membranes demonstrates a lower risk of chorioamnionitis and postpartum endometritis with an

equivalent latency oeriod compared with erythromycin antibiotic regimens. Infect Dis Obstet Gynecol 2020;2020:2093530.

13. Sinrat N. The outcomes of ampicillin plus azithromycin to prolong latency period in preterm premature rupture of membranes between 24 and 33^{+6} weeks of gestation at King Chulalongkorn Memorial Hospital. Thai J Obstet Gynaecol 2020;28:175-82.
14. Kole-White MB, Nelson LA, Lord M, et al. Pregnancy latency after preterm premature rupture of membranes: oral versus intravenous antibiotics. Am J Obstet Gynecol MFM 2021;3100333.
15. Combs CA, Gravett M, Garite TJ, et al. Amniotic fluid infection, inflammation, and colonization in preterm labor with intact membranes. Am J Obstet Gynecol 2014;210:125.e1-15.
16. Romero R, Quintero R, Oyarzun E, et al. Intraamniotic infectionand the onset of labor in preterm premature rupture of the membranes. Am J Obstet Gynecol 1988;159:661-6.
17. Caughey AB, Robinson JN and Norwitz ER .Contemporary diagnosis and management of preterm premature rupture of membranes. Rev Obstet Gynecol 2008;1:11-22.
18. Aidan G. O'Keeffe , Gareth Ambler and Julie A. Barber (2017): Sample size calculations based on a difference in medians fopositively skewed outcomes in health care studies. O'Keeffe et al. BMC Medical Research Methodology (2017) 17:157. DOI 10.1186/s12874-017-0426-1
19. Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB (2013). Designing clinical research : an epidemiologic approach. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; Appendix 6C, page 79.
20. Reshama Navathe, Corina N. Schoen, Paniz Heidari et al., (2019). Azithromycin vs erythromycin for the management of preterm premature rupture of membranes. Am J Obstet Gynecol;221:144.e1-8.

Figures

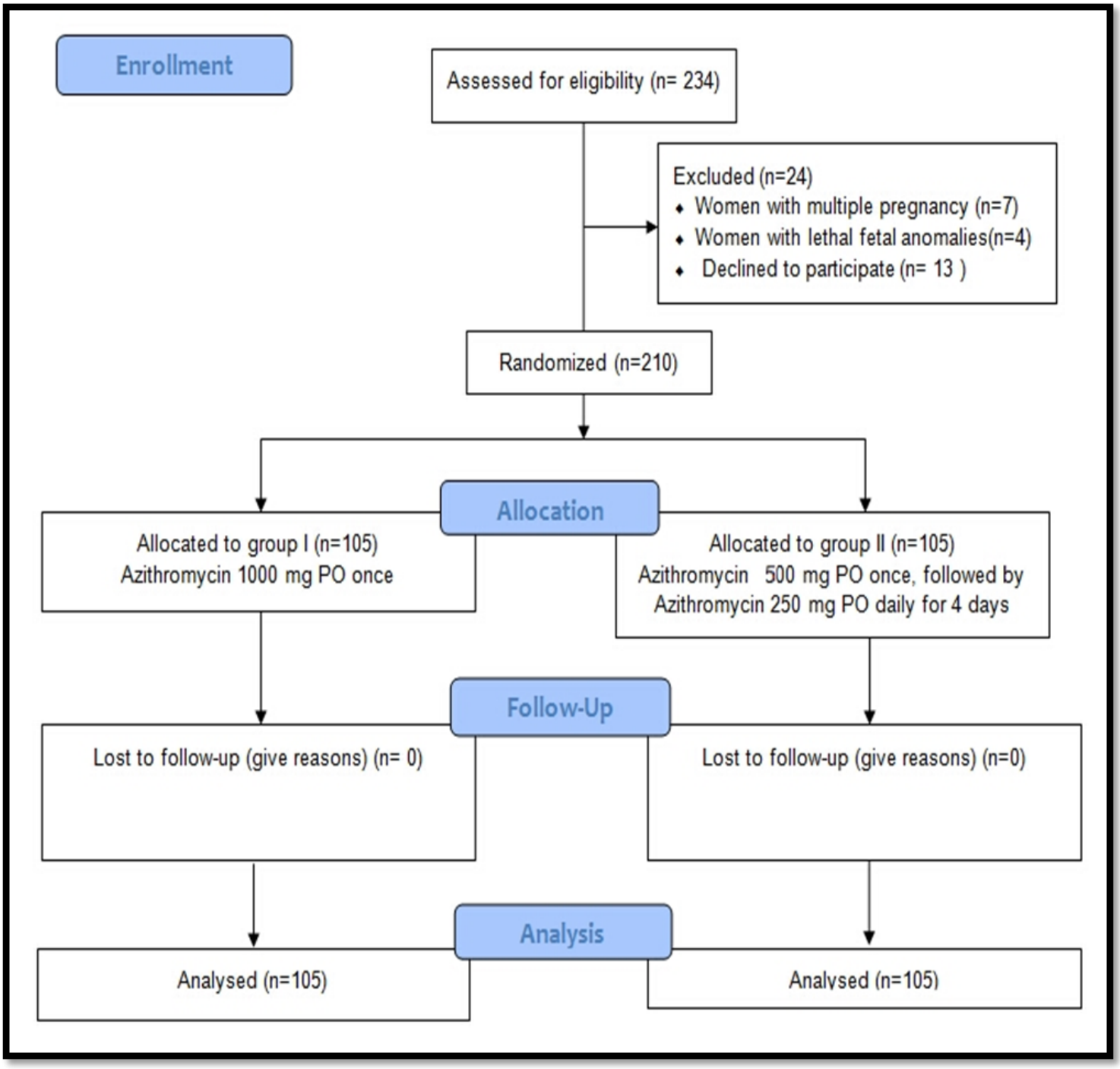

Figure 1

The study flow chart

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