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Alaa El-Din El-Sayed Sedeek
Department of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt

Ramy Mohamed El-Naggar
Department of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt

Raghda Ahmed El-Dakhakhni
Department of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt

Ayman Abdel_Aziz Eldorf
Department of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt

Manal Mostafa Abd Allah
Department of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt

Corresponding Author:
Alaa El-Din El-Sayed Sedeek
Department of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt

Evaluation of the role of azithromycin on pregnancy prolongation in patients at high risk for preterm labor

Alaa El-Din El-Sayed Sedeek, Ramy Mohamed El-Naggar, Raghda Ahmed El-Dakhakhni, Ayman Abdel_Aziz Eldorf and Manal Mostafa Abd Allah

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Abstract
Background: A significant contributor to newborn mortality and morbidity is preterm birth (PTB). The purpose of this study was to assess the advantages of extending pregnancy in high-risk preterm labor cases in women with intact membranes by combining azithromycin with standard therapies.
Methods: This randomised clinical trial work was performed on 130 women at high risk of preterm labor with singleton pregnancy of gestational age before the 20th weeks participants were split into two equal groups: Group I (cases group): high risk for preterm labor and who received azithromycin and were followed till delivery. Group II (control group): high risk for preterm labor who did not receive azithromycin and followed till delivery.
Results: Incidence of preterm was lower in azithromycin group but without statistically substantial variation a substantial variation was existed among the groups as regard cervical length, GA, birth weight, amniotic sludge and fetal biometry no substantial variation was existed among the groups in terms of neonatal intensive care unit admission, severe jaundice, respiratory distress, age, BMI, parity, and gravidity. Azithromycin and progesterone administration and absence of preterm labor history and amniotic sludge were found to be significant indictors of pregnancy prolongation.
Conclusions: Azithromycin usage significantly prolongs the pregnancy, while it has no significant effect on the rate of preterm labour and in terms of neonatal complications.

Keywords: Azithromycin, pregnancy prolongation, preterm labor

Introduction

One of the major indicators of risk for prenatal mortality and morbidity is preterm birth. Several epidemiological studies have estimated the frequency of preterm birth at 5–18% [1].
The projected preterm rate worldwide is rising, from 9.8% in 2000 to 10.6% in 2014, as reported by Chawanpaiboon *et al*. The predicted regional rates of PB varied from 8.7% in Europe to 13.4% in North Africa. Despite the fact that Asia and Sub-Saharan Africa accounted for 81% of all PB, information gathered from several high-income and high-middle-income nations suggests that those countries' PB rates are also rising. Moderate or late preterm newborns (84.7%) had the highest prevalence, subsequently surpassed by very preterm (11.3%) and extremely premature babies (4.1%), according to research involving 67 nations [2].
PTB also raises the likelihood of unfavorable short- and long-term health effects. It is the second-leading cause of under-five mortality and the primary cause of newborn death in short-term periods. Worldwide, prematurity is thought to be the primary cause of one million newborn deaths each year and a major contributor to morbidities that persist into adulthood [3]. Preterm babies often have severe and lasting health issues, such as lung conditions, loss of vision, and neurodevelopmental problems [4]. Preterm delivery is a condition that is well recognized to be brought on by a number of pathological processes, including vascular, infection, and decidual abnormalities, over-distension of the uterus, an impairment in maternal-fetal tolerance, a drop in progesterone activity, and cervical illness. A widely recognized indication of risk for recurrent spontaneous preterm births (SPB) is having had a prior preterm birth. The general probability of recurrent SPB was recently revealed by a meta-analysis [5].

Among the risk factors for preterm contractions, according to several types of pathogenic processes, is inflammation [1].
Antimicrobials, particularly macrolides, have been utilized to eliminate the colonizers of the vaginal flora (*Ureaplasma urealyticum*, *Mycoplasma hominis*) in an effort to minimize the risk of premature labor by preventing infections of the amniotic fluid and resulting inflammatory cascade [6].
Additionally, a lot of organizations have promoted the usage of azithromycin rather than erythromycin. This is due to widespread erythromycin shortages, azithromycin's ease of utilization, superior adverse effect profile, and lower cost when compared to erythromycin [7].
The purpose of this study was to assess if combining azithromycin with other therapies may help women at high risk for preterm labor who still had membranes that were intact to continue pregnancy.

Patients and Methods

This randomised clinical trial work was performed on 130 women at high risk of preterm labor with singleton pregnancy of gestational age before the 20th weeks (based on menstrual history and early ultrasonographic assessment before the 20th weeks). From May 2020 to December 2021, the research was carried out with the Ethical Committee Tanta University Hospitals, Egypt's consent. The patients provided signed permission after being fully briefed.
Criteria of exclusion were preterm pre-labour rupture of membranes (PPROM), overdistended uterus due to any cause for example: multiple pregnancy, polyhydramnios, or fetal macrosomia, required fetal extraction before 37 weeks, cervical incompetence, short cervix, metabolic diseases including diabetes.

Participants were split into two groups of equal numbers
Group I (cases group): high risk for preterm labor and who received azithromycin and were followed till delivery.
Group II (Control group): high risk for preterm labor who did not receive azithromycin and followed till delivery.
Each participant had a taking of history, general, abdominal, and local clinical examinations [inspection, palpation during pregnancy: fundal height (level), Fundal grip, lateral or umbilical grip Pelvic grip: 1st pelvic grip (Pawlik's grip): was carried out to determine the engagement of the presenting part, which is felt mobile if it is not engaged, 2nd pelvic grip: was carried on if the fetus was in a breech presentation it was performed only in cephalic presentation to determine whether the head is flexed. Utilizing a fetal stethoscope, the foetus's heart sound was auscultated].
Choosing where to place the presenting section. The posterior fontanelle, or occiput, serves as the point for reference in a vertex presentation. The chin, or mentum, serves as the point for reference in a facial presentation. The sacrum of the fetus serves as the point for reference in a breech presentation.

Sonographic Methods used for Determining Gestational Age

Abdominal ultrasonographic examinations was performed by one investigator using a 3.5-5-MHz transabdominal probe or assessment of Dating of the 1st Trimester: A sonographic examination was performed during the initial 13 weeks and 6 days of pregnancy.
The measurement most correlated with gestational age is the crown-rump length (CRL). CRL was calculated by determining a straight line from the outside edge of the cephalic pole towards the embryo' rump utilizing the ultrasound machine's calipers and taking the mean of the 3 measurements. This measurement may be used in a variety of tested calculations and tables that closely correspond to gestational age.

Dating of the 2nd Trimester: If the gestational age could not be established during the first trimester, further sonographic methods were used to make an estimate.

Biparietal Diameter (BPD): It was advised to use this biometric measure as a reliable technique for dating. By placing the curvilinear transducer or the phased array perpendicular to the parietal bones of the fetus, the procedure uses a transabdominal technique. The calvarium ought to appearance as a smooth, symmetrical hyperechoic (bright white) structure. The 3rd ventricle and the thalami are intersected on a plane where the BPD is calculated. The outside the proximal skull' edge and the distal skull' inner edge are marked with cursors utilizing the caliper feature. The biparietal diameter will be shown by this value.
According to certain research, the head circumference (HC), a biometric measurement, is a better predictor of gestational age than the biparietal diameter. The clinical evaluation of growth problems may also benefit from using this measure. Here, a sonographic method comparable to the BPD is used. The ultrasonography need to feature an elliptical measuring device that can calculate the calvarium's perimeter.

Femur Length (FL): Because of its density and size on ultrasound, it was visible as early as 10 weeks gestation. Align a curvilinear transducer or phased array along the nearest femur's long axis. Visualize the head of the femoral bone or the greater trochanter proximally, and the femoral condyle distally. Measure the distance between the bone and cartilage where the diaphysis is, utilizing the calipers, being careful not to incorporate the greater trochanter, femoral head, or femoral condyle.

Abdominal Circumference (AC): It is less accurate in predicting gestational age and was more challenging to calculate.

Dating of the 3rd Trimester: Several factors are connected with estimated age and maturity of the fetus in the 3rd trimester if gestational age is still not established.
The transducer was in the sagittal plane when the transabdominal cervical measure was taken. There was a bladder filling. At the moment of TAS, the bladder's largest vertical urine pocket was determined. This was carried out to calculate how much urine was still present in the bladder. The probe was positioned to show the cervical canal length and for bringing the shape of the cervical corpus into view when the cervix was seen transabdominally. The callipers were positioned at the farthest locations where the cervical canal walls were juxtaposed in order to determine the cervical length.
For TVS, a 5 MHz vaginal transducer was utilized. If required, the participant evacuated her bladder before the scan. To provide convenient access to the perineum and simple probe manipulation without inflicting pain on the individual, the patient was positioned in the Lloyd-Davies posture. The transvaginal (TV) probe was gently introduced

until the cervix was apparent in the sagittal plane and the canal was lined with echogenic endocervical mucosa. The probe was then carefully removed until the picture became hazy, and then carefully reinserted, being careful to avoid applying too much pressure. In order to distinguish the internal os from the lower segment endometrium and to clearly identify the echogenic endocervical mucosa, the picture was appropriately enlarged. Only the portion of the cervical length that was surrounded by endocervical mucosa was included in the measurement of the cervical length, which was obtained from the internal os to the external os.

Medication: The study group was given azithromycin (500 mg orally one tab/day for 3 days every month beginning during the period from the20th week till the 34th weeks of gestation) and was followed up till delivery and compared with the control group who did not receive azithromycin.

Statistical analysis

Utilizing SPSS v20.0 (SPSS Inc., Chicago, IL, USA), statistical analysis was carried out. Utilizing the Shapiro Walk test, the distribution of the data was examined for normality. The Independent T and Mann Whitney tests were used for comparing quantitative data that were provided as mean and standard deviation (SD). The difference between qualitative parameters was determined using the Chi square test (2) and Fisher exact, and qualitative parameters were provided as frequency and percentage (%). The possible indicators of pregnancy extension were identified utilizing multivariate logistic regression analysis utilizing the stepwise approach. An assessment of the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of diagnosing performance. The correlation was performed using Spearman's or Pearson's correlation. Significant results were defined as two tailed P values < 0.05.

Results

No substantial variation was existed among the groups as regard maternal age, BMI, parity, gravidity and in term of treatment. Table 1

Table 1: Demographic characteristics, clinical data, history and risk factors and treatment distribution among the groups under the study.

	Azithromycin (n=65)	Control (n=65)	test	p
Age (years)	30.11±4.33	29.56±4.82	T=.684	.495
BMI (kg/m^2)	27.3±2.55	26.8±2.39	T=1.15	.251
Parity	1.82±1.04	1.55±1.02	T=1.49	.138
Gravidity	2.61±1.44	2.43±1.32	T=.743	.459
Preterm labor history	23 (35.4%)	20 (30.8%)	χ2=.313	.576
Interval ≤ 18 months	21 (32.3%)	18 (27.7%)	χ2=.329	.566
Amniotic sludge	15 (23.1%)	4 (6.2%)	χ2=.7.46	.006
Chorioamnionitis	8 (12.3%)	2 (3.1%)	χ2=.2.93	.087
HTN	5 (7.7%)	7 (10.8%)	χ2=.367	.544
Smoking	2 (3.1%)	1 (1.5%)	χ2=.341	.559
Cerclage	22 (33.8%)	15 (23.1%)	χ2=1.85	.174
Progesterone	24 (36.9%)	18 (27.7%)	χ2=1.27	.261
Administration of tocolytics	25 (38.5%)	24 (36.9%)	χ2=.033	.856
Administration of betamethasone	34 (52.3%)	32 (49.2%)	χ2=.123	.726
Other antibiotics	19 (29.2%)	10 (15.4%)	χ2=3.59	.058

Data are presented as mean ±SD or frequency (%), HTN: hypertension, BMI: body mass index. *P*<0.05 is significant

A substantial variation was existed among the groups regarding cervical length. no substantial variation was existed among the three groups under the study as regard fetal biometry. Table 2

Table 2: US findings, fetal biometry of the two groups under the study

	Azithromycin (n=65)	Control (n=65)	t	P
Cervical length (mm)	25.38±3.29	23.96±4.66	2.01	.047
Fundal thickness (mm)	6.07±0.652	5.84±0.718	1.91	.058
Biparietal diameter	77.15±3.86	75.77±5.36	1.68	.095
Abdominal circumference	26.11±3.82	24.78±4.21	1.89	.062
Femur length	56.19±3.49	55.8±3.98	.594	.554

Data are presented as mean ±SD. *P*<0.05 is significant.

A substantial variation was existed among the groups as regard GA, and birth weight. Table 3

Table 3: Neonatal characteristics and clinical data the two studied groups

		Azithromycin (n=65)	Control (n=65)	t/ χ2	p
GA (weeks)		37.8±0.929	37.41±1.13	2.15	.033
Birth weight (kg)		2.98±0.314	2.83±0.438	2.24	.027
Neonatal gender	Male	37 (56.9%)	30 (46.2%)	1.51	.219
	Female	28 (43.1%)	35 (53.8%)		
Apgar at 1 min		7.29±1.27	7±1.54	1.09	.278
Apgar at 5 min		9.75±0.532	9.51±0.857	1.92	.057

Data are presented as mean ±SD or frequency (%), GA: gastetional age. *P*<0.05 is significant

Incidence of preterm was lower in azithromycin group contrasted to control group but without statistically substantial variation no substantial variation was existed among the groups in term of NICU admission, severe jaundice and respiratory distress. Table 4

Table 4: Preterm delivery outcome Neonatal complications and outcome of the two studied groups

	Azithromycin (n=65)	Control (n=65)	$\chi 2$	P
Preterm	13 (20%)	22 (33.8%)	3.17	.075
Term	52 (80%)	44 (66.2%)		
Admitted to NICU	6 (9.23%)	10 (15.4%)	1.14	.287
Severe jaundice	10 (15.4%)	13 (20%)	.475	.491
Respiratory distress	2 (3.1%)	4 (6.2%)	.699	.403

Data are presented as frequency (%), GA: gastetional age. $P<0.05$ is significant.

Azithromycin and progesterone administration and absence of preterm labor history and amniotic sludge were found to be substantial indictors of pregnancy prolongation. Table 5

Table 5: Multivariate logistic regression analysis to determine the possible indictors of pregnancy prolongation.

	OR	S.E.	Sig.	95% Confidence Interval
Age	.242	.215	.663	.160 -.550
BMI	.148	.156	.095	.116 -.541
Parity	1.537	.382	.103	.737 - 2.338
Gravidity	.163	.107	.176	.075 -.378
Azithromycin administration	.747	.034	.039*	.216 - 1.655
Preterm labor history	.788	.011	.041*	.044 - 1.789
Progesterone administration	.862	.024	.027*	.070 -.932
Amniotic sludge	.985	.029	.015*	.142 - 1.598
Chorioamnionitis	3.725	.055	.091	.117 - 8.321

BMI: body mass index $P<0.05$ is significant.

Discussion

Around 2-3% of pregnancies are complicated by Preterm birth, which is also responsible for 30% of infant mortality and morbidity in early gestations. Although inherent preterm and impending delivery account for a large portion of the morbidity, intrauterine inflammation and infection certainly play a role [8].

According to the study's findings, there was no variation among the groups in terms of BMI, maternal age, parity, gravidity and in term of treatment including (Cerclage Progesterone, Administration of tocolytics, Administration of betamethasone and other antibiotics). Also, that a substantial variation was existed among the groups in term of amniotic sludge, while non-substantial variation was existed among the groups in term of other risk factors including (Preterm labor history, Interval ≤ 18 months, Chorioamnionitis, HTN and Smoking)

A study by Finneran *et al*., [9] demonstrated that no substantial variation was existed among the groups as regard BMI, maternal age, parity, and gravidity. Also reported that no substantial variation was existed among the groups as regard risk factors including (Preterm labor history, Hypertensive disorder, DM, and Smoking) and that a statistically substantial variation was existed among the groups in term of treatment by tocolytics, while no substantial variation was existed among the groups in term of treatment including (Magnesium, Betamethasone).

Also, the study by Martingano *et al*., [10] stated that no substantial variation was existed among the groups regarding risk factors including (Pregestational diabetes, Hypertensive disorder, and Group β-streptococcus positive).

In addition, the study by Goyer *et al*., [11] reported that no substantial variation was existed among the groups as regard treatment by tocolytics and betamethasone while a substantial variation was existed among the groups in term of treatment by other antibiotics during hospitalization.

Regarding US findings of the current study, it was found that a substantial variation was existed among the groups regarding cervical length, while no substantial variation was existed among the groups as regard Fundal thickness, fetal biometry, neonatal gender, Apgar at 1 min and Apgar at 5 min. And regarding Neonatal characteristics and clinical data, the results revealed that a substantial variation was existed among the groups as regard GA, and birth weight.

The study by Finneran *et al*., [9] reported that no substantial variation was existed among the groups regarding GA, Apgar at 1 min and Apgar at 5 min, which partially agree with our results.

In agreement with the present results the study by Navathe *et al*., [12] reported that a substantial variation was existed among the groups as regard GA and birth weight, while in contrast with these results a substantial variation was existed among the groups as regard Apgar at 5 min.

In line with our findings the study by Schreiber *et al*., [13] reported that no substantial variation was existed among the groups regarding GA, Apgar at 1 min and Apgar at 5 min, while in contrast with our results no substantial variation was existed among the groups regarding birth weight.

This study results demonstrated that incidence of preterm was lower in azithromycin group contrasted to control group but without statistically substantial variation. Also that no substantial variation was existed among the groups in term of NICU admission, severe jaundice and respiratory distress.

In agreement with our results, the study by Goyer *et al*., [11] reported that no substantial variation was existed among the groups regarding incidence of preterm labour.

Furthermore, several studies [10, 11, 13] used the Latency interval to measure that primary outcome of the use azithromycin, the majority of them [9, 10, 14] found that no substantial variation was existed among the groups regarding Latency, while the study by Schreiber *et al*., [13] revealed that a substantial variation was existed among the groups regarding Latency.

In line with our results the study by Finneran *et al*., [9] who stated that no signifi substantial variation was existed among the groups regarding NICU admission, neonatal death and respiratory distress.

Our results were supported by the study by Navathe *et al*., [12] who reported that no substantial variation was existed among the groups as redard neonatal death and respiratory distress syndrome. Also revealed that azithromycin and progesterone administration and absent of preterm labor history and amniotic sludge were found to be significant indictors of pregnancy prolongation.

Our findings were further supported by the study by Pierson *et al*. [14], who reported that no substantial variation was existed among the groups regarding respiratory distress syndrome, neonatal death, and Neonatal sepsis.

The study by Schreiber *et al*., [13] found that a substantial variation was existed among the groups regarding Latency give the superiority for Azithromycin which mean that the Azithromycin usage significantly prolongs that pregnancy that is in consistency with our results.

While Martingano *et al*., [10] reported that no variations was existed in pregnancy latency when using different antibiotic regimens that was line with the prior studies by Finneran *et al*., [8], Pierson *et al*., [14] and Navathe *et al*. [12]. Martingano *et al*., [10] Results from the three trials are different in that they reported considerably lower rates for azithromycin than erythromycin regimens in terms of rates and risk of clinical chorioamnionitis.

Further research on a broad geographic scale and with a bigger sample size was advised in order to underline our findings. It was suggested that the effects of azithromycin exposure on neonates in terms of bacterial infections, colonization, and bacterial resistance be assessed. To meet the requirements of the global WHO action plan on antimicrobial resistance, obstetrics and other medical specialties should use antimicrobials as efficiently as possible. Additionally, new drugs with good anti-Ureaplasma activity should continue to be identified and researched in order to create efficient therapies for intra-amniotic infection with *Ureaplasma spp*.

Conclusions

Azithromycin usage significantly prolong the pregnancy, while it has no significant effect on the rate of preterm labour and in terms of neonatal complications.

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