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Antenatal azithromycin to prevent preterm birth in pregnant women with vaginal cerclage: A randomized clinical trial

Vajinal serklajlı gebelerde preterm doğumu önlemek için antenatal azitromisin: Randomize bir klinik çalışma

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Abstract

Objective: To assess whether antenatal azithromycin given to pregnant women with vaginal cerclage can reduce preterm birth or not.

Materials and Methods: We randomized 50 pregnant ladies who underwent cerclage at Ain Shams University Maternity Hospital in group A (receiving 500 mg Azithromycin oral tablets (Zithrokan®, Hikma, Egypt) one tablet orally twice daily for three days in 3 courses at 14th, 24th and 32nd week, plus usual antenatal care) and an identical group B (receiving usual antenatal care). Our primary outcome was gestational age at delivery, and secondary outcomes were birthweight, mode of delivery, and maternal, and perinatal complications. This study was registered on ClinicalTrials.gov with number: NCT04278937.

Results: Pregnancy was more prolonged in the Azithromycin group (delivery at 36.8 weeks vs 34.1 weeks; p=0.017). Also, a higher birthweight was observed in the Azithromycin group (2932.6 gm vs 2401.8 gm; p=0.006). No significant difference was found between the two groups as regards to other outcomes (miscarriage, stillbirth, neonatal intensive care unit admission, antepartum hemorrhage, postpartum pyrexia, need for blood transfusion).

Conclusion: Adding antenatal azithromycin to women undergoing cerclage prolongs pregnancy and reduces the risk of preterm birth, with a slight increase in birthweight.

Keywords: Azithromycin, birth weight, cerclage, cervical, premature birth

Öz

Amaç: Bu çalışmanın amacı vajinal serklaj uygulanan gebelere antenatal azitromisinin erken doğumu azaltıp azaltamayacağını değerlendirmektir.

Gereç ve Yöntemler: Ain Shams Üniversitesi Doğum Hastanesi'nde serklaj yapılan 50 hamile kadını grup A'ya [500 mg Azitromisin oral tablet (Zithrokan®, Hikma, Mısır) günde iki kez üç gün boyunca 14., 24. ve 32. haftalarda rutin doğum öncesi bakım ile birlikte uygulandı] ve serklaj yapılan 50 hamile kadın rutin doğum öncesi bakımın uygulandığı grup B'ye randomize edildi. Birincil sonlanım doğumdaki gebelik yaşı idi ve ikincil sonlanımlar doğum ağırlığı, doğum şekli, maternal ve perinatal komplikasyonlardı. Bu çalışma ClinicalTrials.gov'da NCT04278937 numarasıyla kayıtlıdır.

Bulgular: Azitromisin grubunda gebelik süresi daha uzundu (36,8 haftaya karşılık 34,1 hafta; p=0,017). Ayrıca Azitromisin grubunda daha yüksek doğum ağırlığı gözlendi (2932,6 g'ye karşılık 2401,8 g; p=0,006). Diğer sonlanımlar (düşük, ölü doğum, yenidoğanın yoğun bakıma yatış, antepartum kanama, postpartum pireksi, kan transfüzyonu ihtiyacı) açısından iki grup arasında anlamlı fark bulunmadı.

Sonuç: Serklaj uygulanan kadınlara antenatal azitromisin eklenmesi gebeliği uzatır, doğum ağırlığında hafif bir artış sağlar ve erken doğum riskini azaltır.

Anahtar Kelimeler: Azitromisin, doğum ağırlığı, serklaj, servikal, erken doğum

PRECIS: We concluded that adding azithromycin as antenatal prophylaxis in women undergoing vaginal cerclage prolongs pregnancy, with slight increase in birth weight.

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Introduction

Preterm birth (PTB) is defined as any birth occurring before completed 37 weeks gestation[1]. It represents an estimate of 10.6% of livebirths worldwide; of which, more than 80% were born in South Asia and Sub-Saharan Africa[2]. Complications of PTB are the main cause of mortality in children under 5 years of age, responsible for approximately 1 million deaths in 2015; most of which could be prevented with current, cost-effective interventions[3]. These interventions include cervical cerclage, tocolytic, progestational agents, and infection treatment or prophylaxis[4].

It's now been established that cervical cerclage reduces PTB in women at a high risk of PTB[5]. National Institute for Health and Care Excellence (NICE) guidelines recommend choosing either vaginal progesterone or cervical cerclage as prophylaxis for women at risk of PTB with a transvaginal ultrasound performed between 16 and 24 weeks of pregnancy revealing a cervical length of less than 25 mm[6].

Amniocentesis-proved intra-amniotic infection was observed in 8-52% of patients with cervical insufficiency, and these patients have poor pregnancy outcomes even if cerclage was done[7]. Furthermore, cervical insufficiency is associated with intra-amniotic inflammation, sometimes with no identifiable microorganisms, caused by alarming signals that elicit an intra-amniotic inflammatory response leading to early preterm delivery, neonatal complications, and maternal morbidity[7]. Antimicrobials, mainly macrolides, may be used against vaginal flora colonizers (Ureaplasma species, Chlamydia trachomatis, and Mycoplasma hominis) to prevent amniotic fluid infection and subsequent inflammation cascade, thereby lowering the risk of preterm labor[8]. Also, macrolides have immunomodulatory properties, suppressing intra-amniotic inflammation by downregulating the expression of proinflammatory transcription factors that induce the production of proinflammatory cytokines[7].

This study aimed to explore the value of adding azithromycin as an antibiotic prophylaxis in preventing PTB in pregnant women who underwent vaginal cerclage at Ain Shams University Maternity Hospital (ASUMH).

Materials and Methods

This randomized clinical trial was conducted in ASUMH, Cairo, Egypt over the period of one year (April 2019-April 2020). The study protocol was approved by the ethical committee, the Faculty of Medicine, Ain Shams University (FMASU 1304/2019). The study was conducted in accordance with the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT04278937). Informed consent was obtained from all participants before recruitment in the study. All data were collected confidentially.

We included 20-35-year-old pregnant ladies who had vaginal cerclage (history- or ultrasound-based) performed at ASUMH. We excluded patients with multiple pregnancy, current or past medical disorders, structural fetal anomalies, allergy to azithromycin, and bacterial vaginal infection, as detected by high vaginal swab, before cerclage. McDonald cerclage was the procedure adopted at our institution. Under general anesthesia, with the patient in the Trendelenburg position, a reinforcing purse-string suture was placed around the proximal cervix, using the Mersilene suture. After tightening leaving the cervical canal open 3-5 mm, the knot was tied posteriorly. The patients were usually discharged on the same day, with instructions to avoid excess physical effort.

We randomized eligible women using a computer-generated sequence 1:1 using MedCalc© version 13 either to Azithromycin group (group A) or non-Azithromycin group (group B). Allocation and concealment were performed using sealed opaque envelopes. Every woman was requested to pull out an envelope, and with the letter within she was allocated to either: Group A: Women received azithromycin 500 mg (Zithrokan®, Hikma, Egypt) one tablet orally twice daily for three days in 3 courses at 14th, 24th and 32nd week, in addition to routine antenatal care; group B: women received usual antenatal care without antibiotic prophylaxis after cerclage. Follow-up through antenatal care was done at 4 weeks-interval till 28 weeks of gestation, and then fortnightly till delivery. Women were subjected to: History taking (with special comment on pain, bleeding, or offensive vaginal discharge); examination (with special comment on signs of infection as fever and tachycardia, and investigations as routine labs (complete blood count and urinalysis) and ultrasound. Although the Society of Maternal and Fetal Medicine recommends giving 17-alpha-hydroxy-progesterone caproate 250 mg intramuscularly weekly to women with short cervical length and history of PTB in addition to cerclage; in our study, we adopted the NICE guidelines, which recommend choosing either vaginal progesterone or cervical cerclage as prophylaxis to those cases[6]. In this study, we selected women undergoing cerclage.

Our primary outcome was gestational age at delivery; whereas the secondary outcomes included birthweight, neonatal intensive care unit (NICU) admission, stillbirth, miscarriage, hospital-stay, antepartum hemorrhage, postpartum pyrexia, need for blood transfusion, and maternal intensive care unit admission.

To decrease the risk of bias, the observer collecting the data was blinded as regards whether the patients were the Azithromycin group or non-Azithromycin group.

Sample Size Justification

Sample size was calculated using STATA® program, setting alpha error at 5%, power at 80% and drop-out rate at 10%. Previous results, from the study by Illia et al.[9], showed that only 5.7% of the women in the azithromycin group had low and very low birthweight newborns, as compared to 45.6% of the non-azithromycin group. Hence, the required total sample size was calculated to be 50 women.

Statistical Analysis

The collected data were revised, coded, tabulated, and introduced to a PC using (SPSS 20.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Quantitative variables were expressed as mean and standard deviation, or median and interquartile range according to the distribution of data. Qualitative variables were expressed as frequencies and percentages. Student t-test and the Mann-Whitney test were used to compare a continuous variable between the two groups. The chi-square test and Fishers' exact test was used to examine the relationship between categorical variables. A p-value <0.05 was considered statistically significant. Intention-to-treat analysis was employed.

Results

Eighty-four pregnant women who underwent vaginal cerclage at ASUMH were recruited and assessed for eligibility; of which, 50 women were enrolled and randomized into two groups: Azithromycin group (n=25) and non-azithromycin group (n=25). The process of recruitment and follow-up of the study population are shown in the CONSORT diagram (Figure 1).

A summary of the baseline demographic characteristics, and obstetric history of the two groups being studied is shown in Table 1. The two groups were comparable regarding the baseline characteristics: age, body mass index, parity, and obstetric history.

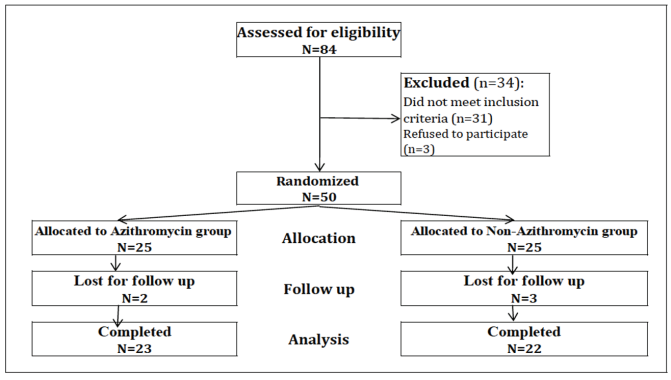

Figure 1. CONSORT flowchart

At enrollment, both groups had a mean gestational age of 13 weeks; however, upon follow-up, pregnancy was more prolonged in the Azithromycin group (delivery at 36.8 weeks vs 34.1 weeks; p=0.017), with significant prolongation of pregnancy in the Azithromycin group (23.7 weeks vs 21.1 weeks; p=0.005) (Table 2).

Regarding birthweight, it was significantly higher in the Azithromycin group (2932.6 gm vs 2401.8 gm; p=0.006). Although there were fewer babies with low birthweight (<2.500 gm) in the Azithromycin group (3 vs. 7 babies in non-azithromycin group), this difference was not statistically significant (p=0.157), as in Table 3.

There was no significant difference between the two groups as regards to mode of delivery. Ten women in the Azithromycin group were delivered by cesarean section, as compared to 12 women in the non-azithromycin group (p=0.569).

Two pregnancies (8%) in non-azithromycin group ended in miscarriage, and two (8%) ended with a stillbirth, whereas there were no miscarriages or stillbirths in the Azithromycin group. Also, there was no significant difference between the two groups as regards to NICU admission and duration of NICU stay; however, we should consider that 4 cases in the non-azithromycin group was not NICU admitted as they were losses (2 miscarriages and 2 stillbirths) (Table 4).

Maternal complications (antepartum hemorrhage, blood transfusion, intensive care unit admission, and postpartum pyrexia) did not differ significantly between the two groups, as shown in Table 5. Postoperative hospital-stay (in days) was significantly shorter among the Azithromycin group (1.2±0.9 vs. 1.9±1.0; p=0.009).

Discussion

This randomized clinical trial evaluated the efficacy of antenatal Azithromycin given prophylactically to reduce PTB in pregnant women who underwent vaginal cerclage in ASUMH. Our results demonstrated that adding azithromycin prolonged pregnancy and reduced the risk of PTB compared to the non-azithromycin group. Additionally, birthweight was significantly higher in the azithromycin group.

Table 1. Demographic characteristics and obstetric history among the study groups

Items		Azithromycin (n=25)	Non-azithromycin (n=25)	p-value
Age (years), mean ± SD		30.0±4.8	29.7±3.9	0.824[a]
BMI (kg/m²)		27.8±1.5	27.4±2.2	0.444[a]
Obstetric history				
Parity, (n, %)	Primiparous	3 (12.0%)	4 (16.0%)	1.000[b]
	Multiparous	22 (88.0%)	21 (84.0%)	
Previous preterm birth		7 (28.0%)	4 (16.0%)	0.306[b]
Previous miscarriage		15 (60.0%)	16 (64.0%)	0.771[b]

[a]: Independent t-test, [b]: Fisher's Exact test, BMI: Body mass index, SD: Standard deviation

Table 2. Gestational age at enrolment and at delivery (weeks) among the study groups

Time	Measures	Azithromycin	Non-azithromycin	p-value
GA at enrolment	**Total**	**25**	**25**	0.626[a]
	Mean ± SD	13.0±0.6	13.0±0.5	
GA at delivery	**Total**	**23**	**22**	**0.017**[a]
	Mean ± SD	36.8±0.9	34.1±4.8	
Prolongation	**Total**	**23**	**22**	**0.005**[a]
	Mean ± SD	23.7±1.0	21.1±4.8	

[a]: Independent t-test, GA: Gestational age, SD: Standard deviation

Table 3. Birthweight (gm) and percentage of low birthweight (<2.500 gms) among the study groups

Measures	Azithromycin (n=23)	Non-azithromycin (n=22)	p-value
Birthweight mean ± SD	2932.6±246.6	2401.8±851.5	**0.006**[a]
	Azithromycin (n=25)	**Non-azithromycin (n=25)**	**p-value**
Low birthweight (n, %)	3 (12.0%)	7 (28.0%)	0.157[b]

[a]: Independent t test, [b]: Chi-square test, SD: Standard deviation

Table 4. Pregnancy fate and neonatal outcomes among the study groups

Fate	Azithromycin (n=25)	Non-azithromycin (n=25)	p-value
Miscarriage	0 (0.0%)	2 (8.0%)	0.490[a]
Stillbirth	0 (0.0%)	2 (8.0%)	0.490[a]
NICU admission	1 (4.0%)	5 (20.0%)	0.189[a]
Duration of NICU stay			
One week	1 (100.0%)	4 (80.0%)	1.000[a]
Two weeks	0 (0.0%)	1 (20.0%)	

[a]: Fisher's Exact test, NICU: Neonatal Intensive Care Unit

Table 5. Maternal complications among the study groups

Complications	Azithromycin (n=25)	Non-azithromycin (n=25)	p-value
Antepartum hemorrhage	0 (0.0%)	4 (16.0%)	0.110[a]
Blood transfusion	0 (0.0%)	1 (4.0%)	1.000[a]
Postpartum pyrexia	1 (4.0%)	2 (8.0%)	--
ICU admission	0 (0.0%)	0 (0.0%)	--

[a]: Fisher's Exact test, ICU: Intensive care unit

Prolonged antibiotic therapy with azithromycin has been previously evaluated in a study by Illia et al.[9]; a prospective study that analyzed pregnancy outcomes in women who had previous perinatal losses due to amnionitis. Pregnant women were treated with prolonged antibiotic therapy (azithromycin 500 mg/day for 3 days; repeated every 10 days and continued till the 34th week of gestation) in a group with cervical cerclage and another group without cerclage. In the group of 35 patients with cerclag, prematurity was decreased from 65.7% to 5.7% (p<0.001)[9].

Also, other studies have used different antibiotic prophylaxis and adjunct therapies with cerclage. A randomized clinical trial evaluated whether indomethacin and antibiotics (cefazolin or clindamycin) given at the time of examination-indicated cerclage resulted in prolonging pregnancy. More pregnancies were prolonged by at least 28 days in patients who received indomethacin and perioperative antibiotics [24 (92.3%) vs. 15 (62.5%), p=0.01]; But there was no notable difference between the two groups in the gestational age at delivery and neonatal outcomes[10].

This contrasted a retrospective observational cohort study by Goyer et al.[11], who evaluated the role of adding azithromycin to the usual treatments (cerclage, tocolysis, rest, etc.) to prolong gestation in patients with intact membranes who were at risk of, or already in preterm labor. They concluded that the median gestational age in the control group was 36 weeks, but 32 weeks in the group receiving azithromycin[11]. However, we must consider that patients in the azithromycin group were more at risk for PTB, having conditions such as: Chorioamnionitis, short cervix, amniotic sludge, bulging membranes, cerclage, or polyhydramnios. However, once adjusted for most confounding factors, prolongation of pregnancy and gestational age at the

event did not differ between the groups, considering that chorioamnionitis could not be excluded or adjusted for. This might explain the earlier age at delivery in the azithromycin group. Also, azithromycin was given as one course, and not as a prophylactic repeated course[11].

Our results showed a higher birthweight among the Azithromycin group (2932.6 gm vs 2401.8 gm; p=0.006). Babies who had low birthweight (<2.500 gm) were non-significantly less frequent in the azithromycin group (3 cases vs. 7 cases; p=0.157). Also, in the study by Illia et al.[9], in the combination of the cerclage and azithromycin group, the number of newborns with low birthweight was non-significantly reduced from 11.4% to 5.7% (p=0.671). However, the percentage of newborns with very low birthweight was significantly reduced from 34.2% to 0 (p<0.001)[9]. An important point to consider when comparing our results with those concluded by Illia et al.[9], is the difference in methodology, and that they compared a group with cerclage to another group without cerclage; therefore, so they evaluated the combined effect of both azithromycin and cerclage.

Azithromycin is an antibiotic of the macrolide group, that inhibits bacterial protein synthesis. It's highly accumulated in cells, especially phagocytes, and thus, it reaches a high concentration at areas of infection and inflammation[12]. Itis a broad-spectrum antibiotic acting against various gram-positive and gram-negative bacteria, and especially obligate intracellular pathogens such as *Chlamydia* species. *Chlamydia* is one of the main causative organisms of cervicitis/urethritis in women, and may cause PTB, preterm rupture of membranes, fetal demise, or endometritis. Azithromycin is highly effective in the treatment of chlamydial cervicitis/urethritis, as well as other non-gonococcal urethritis caused by Ureaplasma urealyticum or *Mycoplasma genitalium*[12]. Another beneficial effect of azithromycin is its immunomodulatory action. Intra-amniotic inflammation has been noted in patients with short cervix and is related to PTB and adverse pregnancy and neonatal outcomes[7]. Late immunomodulatory effects of azithromycin comprise reduction in neutrophil oxidative responses, down-regulation of myeloperoxidase formation, enhanced neutrophil-programmed death, and reducing chemokine [interleukin (IL)-8]- and leukotriene (LT)B4-dependent and chemokine-independent neutrophil chemotactic effects; by inhibition of different transcription factors[12]. Azithromycin also decreases the prostaglandin E2 formation by reducing the expression of prostaglandin synthetic enzymes (COX-1 and COX-2) in leukocytes and monocytes. Azithromycin also decreases tumor necrosis factor-α and granulocyte-macrophage colony-stimulating factor synthesis in monocytes[12].

Other interventions have been investigated previously to reduce PTB; these include using prophylactic antibiotics only without cerclage. Different studies have showed conflicting results. A 2007 meta-analysis to evaluate macrolides (known to be effective against mycoplasma species) on the rate of PTB concluded that erythromycin was associated with a lower risk of premature delivery (odds ratio=0.72; confidence interval 95% 0.56-0.93)[13].

However, another study included 97 women; 51 women were given antibiotics orally (46 received azithromycin and 5 received moxifloxacin), and 46 were not given antibiotics. There was no difference in the median latency from diagnosis to delivery (p=0.47). Neither there was a difference in birthweight (p=0.99). NICU admission was not affected by antibiotic treatment (p=0.08). The average NICU stay did not differ between the treated and untreated groups[14]. These different contradicting results can be explained by different regimens of used antibiotics, different inclusion criteria, and these cases mostly did not have cerclage before starting antibiotic therapy.

In a Cochrane review to assess the benefit of prophylactic antibiotics on maternal and perinatal outcomes during second and third trimester pregnancies, the authors concluded that antibiotic prophylaxis did not decrease the risk of preterm prelabor rupture of membranes or PTB (apart from the subgroup of women with a previous PTB who had bacterial vaginosis); but it decreased the risk of postpartum endometritis, term prelabor rupture of membranes, and gonococcal infection when given routinely to all pregnant women[15].

This was affirmed in another Cochrane review to evaluate the effects of prophylactic antibiotics given to women with PTB and intact membranes, on maternal and neonatal outcomes[16]. That review did not demonstrate any benefit in important neonatal outcomes, although maternal infection may be reduced[16]. However, there were concerns about the short- and longer-term harm for children of mothers treated with antibiotics. The evidence supported not giving antibiotics routinely to women with PTB and intact membranes with no sure signs of infection[16].

More research is needed to evaluate the long-term neurodevelopmental effects of prophylactic antibiotics used during pregnancy. Also, we need more reliable readily available methods to assess subclinical maternal infection, which is still an important factor in the pathogenesis of PTB[16], as intra-amniotic infection is identified in 10% of patients who had PTB[7].

Intra-amniotic microbial invasion could be detected by amniocentesis and cultivation techniques as well as broad-range polymerase chain reaction (PCR) and mass spectrometry[17]. Previous studies have demonstrated microorganisms in the amniotic cavity in 8-52% of pregnant women with cervical insufficiency, and mostly initiate an inflammatory response that predisposes to preterm delivery and neonatal complications[7]. However, "sterile" intra-amniotic inflammation was also evident in patients with preterm labor, where no organism could be detected in the amniotic fluid either by culture or PCR, but analysis of the amniotic fluid showed high concentrations of IL-6. This was observed in the study by Romero et al.[17], where they found that sterile intra-amniotic inflammation was more frequently observed than microbial -associated intra-

amniotic inflammation, but with similar rates of acute placental inflammation and adverse neonatal outcome, and the patients delivered at comparable gestational ages as patients with microbial-associated intra-amniotic inflammation[17].

A study was performed to assess the benefit of antibiotics in treating intra-amniotic infection or intraamniotic inflammation in patients with preterm labor and intact membranes. Treatment of intra-amniotic inflammation or intra-amniotic infection was objectively proven by analysis of amniotic fluid after giving antibiotics in 75% of patients[7]. These findings offer new therapeutic options after personalized evaluation of patients to identify those who can benefit from this intervention[7].

Another potential biomarker of PTB is the amniotic fluid sludge. Evidence suggests that PTB, birth at earlier gestational age, and lower birthweight and NICU admission and neonatal death are increased in patients with amniotic fluid sludge[18]. In addition, another study found that the rates of histological chorioamnionitis with grades II and III were higher when amniotic fluid sludge was present[19]. This simple ultrasound sign might identify patients at risk of PTB who could benefit from adding antibiotics, as proposed in the study by Hatanaka et al.[20]. They concluded that giving antibiotics to high-risk patients with amniotic fluid sludge can effectively reduce the frequency of spontaneous PTB and can increase the birthweight[20].

Study Limitations

Our study has both strength and limitations. To the best of our knowledge, this is the first prospective randomized clinical trial to assess the additional effect of azithromycin in women who already underwent cervical cerclage, with comparable baseline characteristics in both groups. In addition, we reported different neonatal outcomes and maternal complications. However, our study was limited by the small sample size, which might not be large enough to explore whether there is a significant difference in the other outcomes. Also, we did not evaluate the patients' compliance to the drug and its possible side effects. Another important limitation is that we did not assess the presence/absence of intra-amniotic infection/inflammation at the time of delivery, as this was not feasible in the current study. Amniotic fluid culture and analyses of placental chorioamnionitis are not routinely available at our institution; thus definitive diagnosis of intra-amniotic infection/inflammation, or histologic chorioamnionitis couldnot be proved. This would have added more to prove the presumed benefit of using azithromycin.

Conclusion

Using azithromycin as antenatal prophylaxis in women undergoing vaginal cerclage prolongs pregnancy and reduces the risk of PTB, with a slight increase in birthweight. However, there was no clear effect on the incidence of low birthweight, or perinatal morbidity/mortality. Future research is needed to evaluate the long-term neurodevelopmental outcomes of prolonged antibiotic therapy. Also, we must identify a subset of women with subclinical infection who will benefit most out of this therapy.

Ethics

Ethics Committee Approval: The study protocol was approved by the ethical committee, the Faculty of Medicine, Ain Shams University (FMASU 1304/2019).

Informed Consent: Informed consent was obtained from all participants before recruitment in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.H.M.A., Concept: H.A.B, S.A.A., Data Collection or Processing: R.H.M.A., S.A.A., W.K.L.G., Analysis or Interpretation: R.H.M.A., S.A.A., Literature Search: R.H.M.A., Writing: R.H.M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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