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Interconceptional antibiotics to prevent spontaneous preterm birth: A randomized clinical trial

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Objective: We hypothesized that upper genital tract microbial infection associated with spontaneous preterm birth may precede conception. Our objective was to estimate if antibiotic administration during the interpregnancy interval in nonpregnant women with a previous preterm birth before 34 weeks' gestational age would reduce the rate of spontaneous preterm birth in the subsequent pregnancy.

Study design: Women with a spontaneous preterm birth <34 weeks' gestational age were randomized at 4 months' postpartum to receive oral azithromycin 1 g twice (4 days apart) plus sustained-release metronidazole 750 mg daily for 7 days, or identical-appearing placebos. This regimen was repeated every 4 months until the subsequent pregnancy.

Results: A total of 241 women were randomized; 124 conceived a subsequent pregnancy and were available for study, including 59 in the antibiotic group and 65 in the placebo group. In the antibiotic versus placebo group, neither subsequent spontaneous preterm birth (<37 weeks: 52% vs 46%, $P = .568$; <35 weeks: 40% vs 30%, $P = .276$; <32 weeks: 31% vs 23%, $P = .376$) nor miscarriage (<15 weeks: 12% vs 14%, $P = .742$) was significantly different. Although not statistically significant, mean delivery gestational age in the subsequent pregnancy was 2.4 weeks earlier in the antibiotic versus placebo group (32.0 $\pm$ 7.9 vs 34.4 $\pm$ 6.3 weeks, $P = .082$), and mean birth weight was lower in the antibiotic group (2046 $\pm$ 1209 vs 2464 $\pm$ 1067 g, $P = .060$).

Conclusion: Intermittent treatment with metronidazole plus azithromycin of nonpregnant women with a recent early spontaneous preterm birth does not significantly reduce subsequent preterm birth, and may be associated with a lower delivery gestational age and lower birth weight.

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The pathophysiology of a majority of very early spontaneous preterm births is thought to be a clinically silent upper genital tract bacterial infection and/or histologic chorioamnionitis.[1-5] A prevailing hypothesis is that microbial colonization of the chorioamnion and amniotic fluid results from ascending infection by bacteria initially localized in the cervix and vagina.[1-7] These

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bacteria may reside for some time in the upper genital tract, producing a clinically silent inflammatory response before ultimately resulting in a spontaneous preterm birth.[1]

The timing of the upper genital tract infection is not completely understood. However, available evidence indicates that bacterial ascension from the lower to the upper genital tract often occurs early in gestation and may occur before conception.[1] This is supported by evidence that there is an inverse relationship between upper genital tract infection or inflammation with both birth weight and gestational age at delivery among women with a spontaneous, but not indicated preterm delivery.[1,2,5,7] Additionally, reports indicate that an activated host immune response, as evidenced by elevated concentrations of interleukin-6 in amniotic fluid, can be demonstrated as early as the mid-trimester and, when present, is associated with an increased risk of early pregnancy loss and spontaneous preterm delivery.[8-10]

For well over a decade, numerous randomized clinical trials of antibiotic therapy to reduce preterm birth have been conducted in pregnant women selected based on varying risk factors for preterm birth.[1,2,11] The results of these trials have been mixed and generally disappointing. One explanation for the failure of many of these trials is the potential that antibiotic administration may have been given too late in gestation.

We, and others,[12,13] have reported that between the second trimester and term, the earlier the delivery occurs in an index pregnancy, the higher the risk of a preterm delivery in a subsequent pregnancy. Furthermore, very early preterm delivery is significantly associated not only with preterm delivery in the subsequent pregnancy, but also with delivery at earlier gestational ages.[12,13] The reason for the high rate of repeat preterm birth in these women remains uncertain. We have reported that both asymptomatic endometrial microbial colonization and plasma cell endometritis are common in nonpregnant parous women.[14] These data, along with studies linking spontaneous preterm birth to intrauterine inflammation that is present at least as early as the second trimester, have led us to speculate that microbial colonization of the endometrial cavity may actually precede conception. Such chronic interpregnancy interval microbial colonization or inflammation of the endometrium in nonpregnant women may partially explain the high incidence of repeat spontaneous preterm birth in women with a previous spontaneous preterm delivery. Thus, the objective of this study was to determine if antibiotic administration during the interpregnancy interval in nonpregnant women with a previous preterm birth before 34 weeks' gestational age would reduce the rate of spontaneous preterm birth in the subsequent pregnancy.

Material and methods

This was a double-masked randomized clinical trial conducted at the Center for Research in Women's Health, University of Alabama at Birmingham that enrolled women between January 1998 and August 2001. Follow-up was continued through March 2003. Women with singleton pregnancies who presented with spontaneous labor or preterm premature rupture of membranes that ultimately resulted in a preterm birth or pregnancy loss between 16 weeks, 0 days and 33 weeks, 6 days' gestation were prospectively recruited by research personnel while still in the hospital following their qualifying birth. Gestational age was based on the best obstetric estimate, including last menstrual period (LMP) and ultrasound examination. Following discharge from the hospital, these women received follow-up care at a clinic specifically dedicated to this study at the Center for Research in Women's Health. All subjects provided written informed consent before initiation of the study. The study was approved by the Institutional Review Board.

Exclusion criteria included multiple gestations in the index pregnancy, hysterectomy, tubal ligation, vasectomy in the partner, use of a progesterone silastic implant system for contraception (Norplant, Wyeth Laboratories, Philadelphia, PA), or use of an intrauterine device. Our experience in this pregnant population indicated that the rate of subsequent pregnancy was high even if reversible forms of contraception were used. Thus, these women were not excluded. Additional exclusion criteria included use of immunosuppressive medications, HIV-positive, insulin-dependent diabetes mellitus, history of or current ethanol abuse, impaired hepatic or renal function, seizure disorder on medication, positive pregnancy test, fetal anomaly in the qualifying pregnancy, and an unexplained intrauterine demise in the index pregnancy. None of the enrolled subjects had a pregnancy resulting from an assisted reproductive technology.

Subjects then received an initial evaluation at approximately 4 months' postpartum during a scheduled visit to the Center for Research in Women's Health. Presence of pregnancy was excluded before the initial evaluation by menstrual history, physical examination, and pregnancy test when necessary. The initial evaluation consisted of a history and physical examination, including a speculum examination. Endometrial specimens were obtained and cultures were performed for aerobic and anaerobic bacteria, as well as *Ureaplasma urealyticum*, Mycoplasma species, *Neisseria gonorrhoeae*, group B beta *Streptococcus*, *Trichomonas vaginalis*, and a ligase chain reaction test for *Chlamydia trachomatis*. Histopathology was also performed on the endometrial specimens. The methods for cultures, chlamydia ligase chain reaction, histology, and method of endometrial sampling have all been previously described.[14]