Asymptomatic maternal genital tract infection during pregnancy, particularly bacterial vaginosis, has been consistently associated with preterm birth. In response to this evidence, the Maternal-Fetal Medicine Units Network (MFMU) designed and conducted 2 large randomized, placebo-controlled clinical trials of metronidazole treatment of asymptomatic pregnant women with bacterial vaginosis or trichomoniasis in a general obstetrical population. These studies showed that treatment of women with bacterial vaginosis failed to prevent preterm birth, regardless of their history of prior preterm birth. Metronidazole treatment of women with trichomoniasis significantly increased the risk of preterm birth compared to placebo. These results formed the basis of the US Preventive Services Task Force recommendation that screening for bacterial vaginosis not be undertaken in low-risk pregnant women, and show that MFMU network studies can have a direct and immediate impact on obstetrical practice.

Preterm birth is a leading cause of neonatal morbidity and mortality. A large body of evidence suggests that asymptomatic infections are associated with and may cause preterm birth. Histologic chorioamnionitis is more common in the placentas of infants who deliver preterm. A variety of genital tract infections have been associated with preterm birth, and vaginal, cervical, and serum markers known to be associated with infection are also associated with preterm birth. However, clinical trials of treatment of Chlamydia, Ureaplasma, and group B streptococcus showed that treatment of these infections did not reduce the risk of preterm birth.

A meta-analysis of 19 studies concluded that there was a 60% increased risk of preterm birth in the presence of bacterial vaginosis (BV). Minkoff et al. found that women with trichomoniasis were significantly more likely to have preterm premature rupture of membranes. Hardy et al. reported that carriage of Trichomonas vaginalis was associated with low birth weight and preterm birth in adolescent women.

Other investigators have conducted randomized clinical trials to determine the effect of treatment of BV on adverse pregnancy outcomes. Morales et al. conducted a trial of metronidazole 250 mg 3 times a day compared to placebo in women with a prior preterm birth. Of 94 eligible women, 80 completed the trial; 44 were randomized to metronidazole and 36 to placebo. Preterm birth occurred in 18% of the metronidazole group and 39% of the placebo group (P < .05). McDonald et al. studied 879 women with BV by Gram-stain or culture for G vaginalis at 19 weeks of gestation and randomized them to either oral metronidazole 400 mg or placebo twice daily for 2 days at 24 weeks’ and at again at 29 weeks’ if the BV was persistent. Metronidazole was effective at eradicating BV. Preterm delivery occurred in 7.2% of those randomized to metronidazole and 7.5% of those...
randomized to placebo. Subgroup analysis of those who had BV diagnosed by Gram-stain also showed no effect of treatment on preterm birth (4.5% vs 6.3%). However, in women with a prior preterm birth, 2 of 22 (9.1%) randomized to metronidazole delivered preterm compared to 10 of 24 (41.7%) randomized to placebo.

Hauth et al\textsuperscript{11} studied 624 women at risk for preterm delivery because of a prior preterm birth or low prepregnancy weight. They randomized 433 to metronidazole and erythromycin treatment and 191 to placebo. Subgroup analysis of those who had BV diagnosed by Gram-stain using Nugent criteria, candidiasis diagnosed by 10% potassium hydroxide preparation, and \textit{Trichomonas vaginalis} (TV) diagnosed by wet mount of vaginal secretions. Evaluations were performed at 24 and 28 weeks’ gestation. The rates of detected infection at 24 and 28 weeks’, respectively, were 23.4% and 19.4% for BV, 3.3% and 2.7% for trichomoniasis, and 21.1% and 19.5% for Candida. The occurrence of bacterial vaginosis at 28 weeks’ was associated with an increased risk of spontaneous preterm birth with an odds ratio of 1.84 (95% confidence interval 1.15 to 2.95, \( P < .01 \)). Neither TV nor Candida detected by microscopy had a significant association with preterm birth.

Goldenberg et al\textsuperscript{19} reported on the association between bacterial vaginosis, fetal fibronectin and preterm birth in 2,899 women followed in the MFMU Network Preterm Prediction Study. Bacterial vaginosis was diagnosed by Gram-stain. Fetal fibronectin was present in 4.0% of cervical and/or vaginal samples at 23 to 24 weeks’ and was nearly twice as common in women with bacterial vaginosis as in those who did not have BV. After adjusting for the presence of BV, race, and parity, they found that women who were positive for fetal fibronectin were much more likely to have clinical chorioamnionitis, with an odds ratio of 16.4 and 95% confidence interval of 7.1-37.8, and neonatal sepsis (6.3; 95% confidence interval = 2.0-20.0, respectively), than those who were fetal fibronectin-negative. Women with a positive fetal fibronectin test who delivered before 32 weeks’ gestation all had evidence of histologic chorioamnionitis. They concluded that the presence of fetal fibronectin at 23 to 24 weeks’, upper genital tract infection and preterm birth were strongly linked.

Andrews et al\textsuperscript{20} reported on the association between \textit{Chlamydia trachomatis} infection at 24 weeks’ as measured by a urinary ligase chain reaction and subsequent preterm birth in 190 cases (delivered \(< 37 \) weeks) and 190 controls. Women with chlamydial infection were more likely to have bacterial vaginosis (57.1% vs 32.9%; \( P = \) .002) and a short cervical length (\( \leq 25 \text{ mm}; 33.0\% \) vs 17.9%; \( P = .02 \)) but not a positive fetal fibronectin test result (7.1% vs 9.5%; \( P = .62 \)). After adjustment for other risk factors for spontaneous preterm birth, women with \textit{Chlamydia trachomatis} infection at 24 weeks’ gestation were approxi-

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\textbf{The Preterm Prediction Study}

The Preterm Prediction Study was designed to determine clinical and laboratory findings that could be used to predict women at increased risk for a preterm birth. Meis et al\textsuperscript{18} reported on the association of preterm birth and BV diagnosed by Gram-stain using Nugent’s criteria, candidiasis diagnosed by 10% potassium hydroxide preparation, and \textit{Trichomonas vaginalis} (TV) diagnosed by wet mount of vaginal secretions. Evaluations were performed at 24 and 28 weeks’ gestation. The rates of detected infection at 24 and 28 weeks’, respectively, were 23.4% and 19.4% for BV, 3.3% and 2.7% for trichomoniasis, and 21.1% and 19.5% for Candida. The occurrence of bacterial vaginosis at 28 weeks’ was associated with an increased risk of spontaneous preterm birth with an odds ratio of 1.84 (95% confidence interval 1.15 to 2.95, \( P < .01 \)). Neither TV nor Candida detected by microscopy had a significant association with preterm birth.

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approximately 2 times as likely as uninfected women to have a spontaneous preterm birth at <37 weeks' gestation (odds ratio, 2.2; 95% confidence interval, 1.08-4.78) and 3 times as likely to have a spontaneous preterm birth at <35 weeks' gestation (odds ratio, 3.2; 95% confidence interval, 1.08-9.57).

Goldenberg et al reported on the association between granulocyte colony-stimulating factor and spontaneous preterm birth using a nested case-control study involving 194 women who had a singleton spontaneous preterm birth and 194 matched term control subjects. They reported that women who were delivered of their infants spontaneously at <28 weeks' gestation had increased mean granulocyte colony-stimulating factor values at 24 weeks' gestation (84.7 ± 38.4 vs 67.7 ± 28.6 pg/mL; P = .049), and women who were delivered of their infants at <32 weeks' gestation had increased mean plasma granulocyte colony-stimulating factor values at 28 weeks' gestation (80.4 ± 24.1 vs 55.9 ± 16.5 pg/mL; P = .001). When measured at 24 or 28 weeks' gestation, granulocyte colony-stimulating factor did not predict spontaneous preterm birth at 32 to 34 weeks' gestation or at 35 to 36 weeks' gestation.

Goepfert et al investigated the association between cervical interleukin 6 concentration at 22 to 24 weeks' and spontaneous preterm birth. They compared 125 cases delivered at 35 weeks' or less with 125 matched controls delivered at 37 weeks' or greater. The mean (±SD) interleukin 6 concentration was significantly higher in case than in control subjects (212 ± 339 vs 111 ± 186 pg/mL; P = .008). Elevated interleukin 6 concentration was not found to be significantly associated with BV, maternal body mass index <19.8 kg/m², or a short cervix (≤25 mm), but it was significantly associated with a positive cervical fetal fibronectin test result (90th percentile, odds ratio, 5.5; 95% confidence interval, 2.6-11.9; 95th percentile, odds ratio, 5.3, 95% confidence interval, 2.1-12.9). Cervical interleukin 6 levels were highest within 4 weeks of delivery, and the trend continued until term. In a regression analysis that adjusted for risk factors significantly associated with spontaneous preterm birth, elevated cervical interleukin-6 concentration was not independently associated with spontaneous preterm birth (odds ratio, 1.8; 95% confidence interval, 0.8-4.3).

The BV/TV Study

The BV and TV studies were designed to test the hypothesis that metronidazole therapy of asymptomatic women who had either bacterial vaginosis or TV would reduce the risk of preterm birth (delivery <37 weeks'). Women who had vaginal symptoms, significant obstetrical complications in the current pregnancy, or chronic medical conditions were excluded. The studies were designed as two nested clinical trials. Women who had TV were preferentially enrolled in the TV trial. Women with bacterial vaginosis who did not have Trichomonas were enrolled in the BV trial. Over 40,000 women were screened for enrollment in the 2 trials.

BV was diagnosed by Gram-stain and elevated pH. We randomly assigned 1,953 women with BV who were 16 to less than 24 weeks pregnant to receive two 2-gram doses of metronidazole or placebo. The diagnostic studies were repeated and a second treatment was administered to all women at 24 to less than 30 weeks' gestation. Metronidazole therapy was effective at resolving BV. BV resolved in 657 of 845 women who had follow-up Gram staining in the metronidazole group (77.8%) and 321 of 859 women in the placebo group (37.4%). Data on the time and characteristics of delivery were available for 953 women in the metronidazole group and 966 in the placebo group. Preterm delivery occurred in 116 women in the metronidazole group (12.2%) and 121 women in the placebo group (12.5%) (relative risk, 1.0; 95% confidence interval, 0.8 to 1.2). Treatment did not prevent preterm deliveries that resulted from spontaneous labor (5.1% in the metronidazole group vs 5.7% in the placebo group) or spontaneous rupture of the membranes (4.2% vs 3.7%), nor did it prevent delivery before 32 weeks' (2.3% vs 2.7%). Treatment with metronidazole did not reduce the occurrence of preterm labor, intraamniotic or postpartum infections, neonatal sepsis, or admission of the infant to the neonatal intensive care unit.

Women with TV were enrolled in an identical trial. TV was diagnosed by a culture using Diamond’s media. Cultures were obtained from 31,157 women. Of these, 2,377 were positive (7.6%). We randomly assigned 617 women with asymptomatic trichomoniasis who were 16 to 23 weeks pregnant to receive two 2-gram doses of
metronidazole (320 women) or placebo (297 women) 48 hours apart and treated women again with the same 2-dose regimen at 24 to 29 weeks of gestation. Trichomoniasis resolved in 249 of 269 women for whom follow-up cultures were available in the metronidazole group (92.6%) and 92 of 260 women with follow-up cultures in the placebo group (35.4%). Data on the time and characteristics of delivery were available for 315 women in the metronidazole group and 289 women in the placebo group. Delivery occurred before 37 weeks of gestation in 60 women in the metronidazole group (19.0%) and 31 women in the placebo group (10.7%) (relative risk, 1.8; 95% confidence interval, 1.2 to 2.7; \( P = .004 \)). The difference was attributable primarily to an increase in preterm delivery resulting from spontaneous preterm labor (10.2% vs 3.5%; relative risk, 3.0; 95% confidence interval, 1.5 to 5.9). Preterm delivery was more common in the metronidazole group whether BV was also present (26.1% vs 14.2%) or not (14.9% vs 8.7%). Metronidazole therapy did not reduce the occurrence of postpartum endometritis or intra-amniotic infection.

Goldenberg et al reported on fetal fibronectin values from 8 to 22 weeks of gestation in 13,360 women who were screened for the BV/TV study. Vaginal fetal fibronectin values at each gestational age ranged from unmeasurable to \( >1,000 \) ng/mL, with median values always being \( <10 \) ng/mL. Fetal fibronectin values declined progressively with increasing gestational age at sampling. BV and black race were associated with higher values, whereas nulliparity was associated with lower values. High values after 13 weeks’ gestation were associated with a 2- to 3-fold increased risk of subsequent spontaneous preterm birth overall and a 4-fold increased risk of very early preterm birth.

Discussion

Studies conducted by the MFMU network units have shown an association between infections and preterm birth, but the Network’s treatment trials have not shown a beneficial effect of treatment and in the case of treatment of TV, showed harm. These results are similar to those seen by some other investigators. The relationship between infections and preterm birth remains enigmatic. It is possible that some women have an underlying condition that causes both genital infections and preterm birth. Treatment of the infections might not treat the underlying cause. If this were true, however, we could not explain the increased rate of preterm birth seen in women with trichonomiasis treated with metronidazole, women with bacterial vaginosis treated with clindamycin cream, or in women without bacterial vaginosis who were treated with metronidazole and erythromycin. Nor could we explain the fact that some studies have reported reductions in preterm birth when high-risk women with BV received treatment. It seems more plausible that there is a yet unidentified infection, associated with Chlamydia, BV, and trichomonas, which causes asymptomatic chorioamnionitis and preterm birth. This infection might be in the form of chronic, asymptomatic endometritis. Whether the various antibiotic regimens used in these trials effectively treated this infection is unknown. Further research is needed to investigate the relationships between infection and preterm birth. However, based on our studies, we cannot recommend screening and treatment of either BV or trichomoniasis in either low or high-risk women.

The results of the MFMU Network studies were crucial in the development of the US Preventive Services Task Force’s recent recommendation against routinely screening average-risk pregnant women for bacterial vaginosis and their conclusion that evidence is insufficient to recommend for or against screening high-risk pregnant women for bacterial vaginosis. The rapid incorporation of MFMU Network study results into practice recommendations is a clear example of how Network research can have an immediate, clinically relevant impact.

References