Sexually Transmitted Infections and Preterm Birth—Attempting to Pin Down Targets for Intervention From Population-Level Observational Data

Emily H. Adhikari, MD; Scott Roberts, MD, MS

From 2016 through 2018, national surveillance data demonstrate that rates of chlamydia, gonorrhea, and syphilis in pregnancy rose significantly in the US, in parallel with the rise in sexually transmitted infections (STIs) in the general population. Simultaneously, the rate of preterm birth in the US increased from 9.9% to 10.0%. A question that persists is whether—and to what degree—these 2 trends may be related.

In the largest population-based study to date, Gao et al attempt to address this very question with rigorous methodology. Their analysis includes over 14 million US births (from 2016 to 2019) with recorded exposure to maternal infections present at the time of pregnancy diagnosis or during the pregnancy. The prevalence of STIs among US births for 2016 through 2019 (chlamydia, 1.9%; gonorrhea, 0.3%; and syphilis, 0.1%) is consistent with what has been reported in National Vital Statistics Reports for 2016 to 2018. The main outcome measured was preterm birth before 37 weeks of gestation, including spontaneous or iatrogenic. The investigators constructed 2 regression models adjusting for multiple factors associated with preterm birth (such as smoking, prepregnancy diabetes, and hypertension) and performed a sensitivity analysis to exclude women without prenatal care who may not have been screened for STIs. The adjusted odds ratio for the association of STIs with preterm birth were 1.03 (95% CI, 1.02-1.04) for chlamydia, 1.11 (95% CI, 1.08-1.15) for gonorrhea, and 1.17 (95% CI, 1.11-1.22) for mothers who had syphilis prior to or during pregnancy.

Findings from observational studies concerning chlamydia have been inconsistent: some, but not all, suggest that chlamydia is associated with increased risk of preterm birth. Good observational data, but not all, have shown that gonorrhea is associated with increased risk of preterm birth. We are not aware of any randomized controlled trials evaluating the effect of treatment or lack of treatment of chlamydia, gonorrhea, or syphilis infections on primary prevention of preterm birth. Other genital infections such as bacterial vaginosis have been studied with more rigor. Subtil and associates found no reduction of late miscarriage (ie, 16-21 weeks) or spontaneous preterm birth (22-32 weeks) in a randomized, placebo-controlled trial of early clindamycin treatment in low-risk women with bacterial vaginosis.

Other than screening trials, exposure or interventional trials involving reportable STIs would be difficult to justify and lack beneficence. And yet, with only observational studies to interpret, we are faced with a mountain of sometimes conflicting data. While the massive sample size of this study and point estimates with tight confidence intervals might suggest precision, they do not necessarily suggest validity. In this study, the effect sizes were larger for very preterm (28-31 weeks) compared with moderately (32-36 weeks) or extremely (<28 weeks) preterm birth. Why the outcome of interest occurred more commonly in a very specific gestational age window is somewhat perplexing. Does it make sense? We must still interpret the conclusions in light of the known limitations of observational studies. Most epidemiologists consider such modest effect sizes in cohort studies, as seen here, to generally represent noise, not signal, and they are considered noninformative.

Observational studies cannot control for individual behaviors and other unknown covariates (ie, residual confounding), which may, in fact, be responsible for the occurrence of preterm birth. The unknown variables in this data may be tied to risk of preterm birth, such as chronic stress, gestational age of diagnosis, or lack of access to treatment. Without a better understanding of which infections
were and were not treated, we have little to guide a search for targeted interventions to prevent preterm birth in a cohort with treatable infectious diseases.

To date, numerous medications have been studied to identify interventions that successfully prevent preterm birth, including β-mimetics, magnesium sulfate, calcium channel blockers, oxytocin inhibitors, and intramuscular and intravaginal progesterone. Even bed rest has been prescribed by physicians to prevent preterm birth. Although used with great abandon (even to the present day), none has been shown to primarily prevent this perinatal morbidity.

The Centers for Disease Control and Prevention (CDC) and US Preventive Services Taskforce (USPSTF) recommend screening for chlamydia and gonorrhea in young (ie, age <25 years) and high-risk pregnant women. The CDC recommends screening at the first prenatal visit and again in the third trimester in high-risk groups. The CDC and USPSTF recommend screening for syphilis in all pregnant women at the initiation of prenatal care, with additional screening recommended by the CDC in the third trimester among high-risk women. No one would suggest no screening, but has the case been made to screen (or treat) early in every pregnant woman to prevent preterm birth? While the benefits are many, screening for sexually transmitted infections also comes with costs, both monetary and social. When available therapeutic options are limited to address preterm birth as a persistent problem, it is tempting to promote methodologies or interventions that might work, particularly if the intervention (in this case, STI screening) is also beneficial to overall reproductive health. Hypothesis-generating work is important, but remains limited in strength. While Gao et al demonstrate in this high-quality, observational study that STIs and preterm birth are associated at a population level, we are still faced with the challenge of understanding the nature of this association: to what degree do STIs cause preterm birth, and how effective can STI treatment be in reducing preterm birth in the US?
