Maternal Titers After Adequate Syphilotherapy During Pregnancy

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(See the Editorial Commentary by Ramsey on pages 691–2.)

Background. We aimed to construct a timeline for nontreponemal titer decline specific to pregnancy and evaluate factors associated with inadequate decline by delivery.

Methods. This was a retrospective medical records review from September 1984 to June 2011 of women diagnosed with syphilis after 18 weeks of gestation. Women were treated according to stage of syphilis per Centers for Disease Control and Prevention guidelines. Patients with both pretreatment and delivery titers were included for data analysis. Demographics, stage of syphilis, maternal titers, delivery, and infant outcomes were recorded. Standard statistical analyses were performed for categorical and continuous data. The titer decline was analyzed using mixed-effects regression modeling.

Results. A total of 166 patients met inclusion criteria. Mean gestational age at treatment was 29.1 ± 5 weeks, and 93 (56%) women were diagnosed with early-stage syphilis. For all stages of syphilis, maternal titers declined after syphilotherapy. Pretreatment titers were higher and declined more rapidly in primary and secondary disease than in latent-stage disease and syphilis of unknown duration. Sixty-three (38%) patients achieved a 4-fold decline by delivery. Patients without a 4-fold decline by delivery were older (24.6 vs 21.5 years; \( P < .001 \)), treated later in pregnancy (30.3 vs 27.3 weeks; \( P < .001 \)), diagnosed with latent syphilis or syphilis of unknown duration, and had less time from treatment to delivery (7.8 vs 11.1 weeks; \( P < .001 \)).

Conclusions. Maternal serologic response during pregnancy after adequate syphilotherapy varied by stage of disease. Failure to achieve a 4-fold decline in titers by delivery is more a reflection of treatment timing than of treatment failure.

Keywords. maternal titers; syphilis; serologic response.

Despite the availability of penicillin for >70 years for the treatment of syphilis, questions still remain regarding adequate serologic response during pregnancy. A 4-fold decline in a nontreponemal titer is considered an adequate serologic response after syphilotherapy [1]. However, recommendations regarding time allotted to achieve an adequate decline in nontreponemal titers are based on observational and randomized controlled trials from nonpregnant populations [2–4]. Serologic response also depends on stage of syphilis, initial pretreatment titer, human immunodeficiency virus (HIV) status, and history of prior syphilitic infection. All studies used by the Centers for Disease Control and Prevention (CDC) when formulating the definition of “adequate serologic response” listed pregnancy as an exclusion criteria. It is unknown whether pregnant women have a similar nontreponemal titer response after treatment as that observed in nongravid populations.

For nonpregnant individuals, the CDC recommends that 6–12 months in early-stage disease (primary, secondary, and early latent syphilis) or 12–24 months in late-stage disease (late latent syphilis or syphilis of unknown duration) is required to gauge adequate
serologic response. In HIV-infected patients, a full 12 and 24 months is allotted for early-stage and late-stage disease, respectively, as a slower serologic response has previously been described in this population [1, 2–5]. Physiologic changes during pregnancy may alter the rate of maternal serologic response to treatment. In the only other study that evaluated maternal serologic response in pregnancy, Galan et al found that only 55% of the 49 women treated for syphilis during pregnancy achieved a 4-fold decline by 3 months after syphilotherapy, leading them to question treatment adequacy during pregnancy [6]. Knowledge of serologic response per stage of syphilis is important to develop guidelines specific to pregnancy and guide clinical management of both the mother and infant. The purpose of this study was to construct a timeline for nontreponemal titer decline specific to pregnancy and evaluate factors associated with and without a 4-fold decline in titer by delivery.

METHODS

This is a secondary analysis of a retrospective cohort of women diagnosed with syphilis after 18 weeks’ gestation from September 1981 to December 2011 at our institution. All women received targeted sonography prior to treatment to evaluate for fetal syphilis, which is standard of care at our institution. Patients were treated per the CDC treatment guidelines according to the stage of syphilis [1]. For the purpose of this study, we included only those patients with both pretreatment and delivery nontreponemal titers in an effort to establish trends in maternal serologic response after syphilotherapy. All patients in the cohort had a reactive nontreponemal serology that was subsequently confirmed by a positive treponemal antibody test. Nontreponemal serology was performed with either the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) test. During the study period, our institution replaced VDRL with RPR for both screening and posttreatment surveillance. However, all patients in the cohort had concordant nontreponemal tests before and after treatment performed at our institution alone.

Maternal demographic data, stage of syphilis at diagnosis, nontreponemal titers (pretreatment and at delivery), delivery and infant outcomes were recorded. Data were analyzed by comparing women with a 4-fold decline in nontreponemal titers by delivery to those who did not achieve a 4-fold decline. Time from treatment to delivery was also analyzed with regard to serologic response and measured from treatment initiation in women who required >1 penicillin injection. Congenital syphilis was diagnosed using CDC diagnostic criteria per the attending neonatologist [1].

Student t test was used to evaluate continuous variables, and χ² squared was used for frequencies. Logistic regression analysis was used to adjust for gestational age at treatment as a linear effect modifier. The absolute decrease in nontreponemal titer by stage as well as comparison of the rate of change by stage was performed using analysis of variance and mixed-effects regression model with unstructured variance/covariance. Pairwise comparisons between the stages were made using regression contrasts, with P values adjusted for multiple testing by the method of Tukey–Kramer. P < .05 was considered significant and all tests were 2-tailed. This study was approved by the

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<td>Congenital syphilis</td>
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<td>HIV-infected</td>
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Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation.
* One hundred forty-seven infant outcomes available.

Figure 1. Nontreponemal titer decline after treatment by stage of maternal syphilis.
institutional review board of the University of Texas Southwestern Medical Center.

**RESULTS**

Two hundred thirty-five women were included in the original cohort, and 166 (71%) had both pretreatment and delivery nontreponemal titers available for review. Table 1 details the characteristics of these 166 patients. Mean gestational age at treatment was 29.1 ± 4.6 weeks, and 93 (56%) patients were diagnosed with early-stage syphilis. Of the 147 infant outcomes available, 27 (18%) required treatment for congenital syphilis. Figure 1 depicts the maternal serologic response per stage of syphilis after appropriate syphilitotherapy. For all stages of syphilis, maternal nontreponemal titers declined by delivery. Secondary syphilis was associated with the highest titers at diagnosis followed by primary syphilis, syphilis of unknown duration, late latent syphilis, and early latent syphilis ($P < .001$). Titers from women with primary and secondary syphilis declined more rapidly after treatment than titers from women with latent-stage disease ($P < .001$). There was no significant difference in titers at delivery between all stages of syphilis ($P = .054$). Overall, 63 (38%) patients achieved a 4-fold decline by delivery.

Table 2 shows the characteristics of the cohort divided into those with and those without a 4-fold nontreponemal titer decline by delivery. No differences were noted in race or parity. Maternal age, stage of maternal syphilis, and timing of treatment differed significantly between the 2 groups. Maternal stage of syphilis remained significant after adjusting for treatment timing ($P = .003$). Patients with secondary syphilis were most likely to achieve a 4-fold titer decline by delivery ($P = .02$). Patients not achieving a 4-fold decline in titers by delivery tended to be older (24.6 ± 5.8 vs 21.5 ± 4.4 years; $P < .001$) and treated later in pregnancy (30.3 ± 4.6 vs 27.3 ± 4.2 weeks; $P < .001$), and were diagnosed with early and late latent-stage disease or syphilis of unknown duration (87 [84%] vs 35 [55%]; $P < .001$). Only 1 patient in the cohort was HIV-infected, and she achieved a 4-fold titer decline by delivery. There was no significant difference in gestational age at delivery between those women with and those without a 4-fold decline in titer (38.4 ± 2.9 vs 38.1 ± 2.6; respectively). However, women not achieving a 4-fold decline in titers by delivery had less time from treatment to delivery (7.8 ± 5 vs 11.1 ± 5.1 weeks; $P < .001$), with 22% delivering <4 weeks after treatment. Of the 147 available infant outcomes, the diagnosis of congenital syphilis was similar between patients with and those without a 4-fold titer decline (9 [16%] vs 18 [20%]; $P = .63$). No women in the cohort required retreatment with penicillin for a treatment failure (defined as an 4-fold increase in nontreponemal titer).

**DISCUSSION**

This study provides data on the serologic response rates per stage of syphilis in pregnancies diagnosed at or beyond 18 weeks of gestation. We found that syphilis titers were highest in primary and secondary syphilis and the rate of titer decline was greatest in these women. Overall, less than half of the women diagnosed with syphilis after 18 weeks of gestation achieved a 4-fold decline in nontreponemal titers by delivery. Whereas lack of a 4-fold titer decline by delivery was associated with older maternal age, latent syphilis, and less time from treatment to delivery, the risk of having an infant needing treatment for congenital syphilis did not correlate with the 4-fold titer decline by delivery.

There are several important considerations in the interpretation of maternal serologic response resulting from our data. First, serologic response is similar in the pregnant and nonpregnant populations. Romanowski et al reviewed 882 nonpregnant patients with syphilis <1 year of duration and found that titer decline was dependent on stage of syphilis. Patients with primary and secondary syphilis achieved a 4-fold titer decline sooner than those with early latent syphilis [2]. In our cohort, women treated for primary and secondary syphilis also had a more
rapid rate of decline irrespective of treatment timing, and these women were more likely to achieve a 4-fold titer decline by delivery. Older age has been demonstrated previously in nonpregnant patients to be associated with slower serologic response to syphilotherapy [7] and was a risk factor in our pregnant series. Immunosenescence has been suggested as a cause of slower serologic response in older patients [7]. There is also evidence that repeat infections affect the rate of titer decline in both nonpregnant and gravid populations [2, 6]. Although we did not collect information regarding multiple repeat infections, it is possible that older age could serve as a surrogate for the prior infection vs first episode phenomenon.

HIV status has been shown to influence the rate of titer decline in nonpregnant populations in both retrospective and prospective series [3, 4]. Patients with HIV coinfection have higher rates of serologic treatment failure compared with HIV-uninfected patients, although clinical treatment failures are similar [3, 4, 8]. Only 1 patient was coinfected with HIV in our cohort, limiting our ability to draw conclusions regarding the effect HIV has on the maternal serologic response. However, it is worth mentioning that she achieved a 4-fold titer decline by delivery.

It is clear from previous studies in nonpregnant populations that time from treatment is the most important variable in achieving an adequate serologic response. We found that less than half of women diagnosed and treated for syphilis after 18 weeks of gestation achieved a 4-fold titer decline by delivery. Because CDC recommendations regarding adequate serologic response state that treatment failure should not be considered until 6–12 months after therapy in early-stage disease or 12–24 months in late-stage disease [1], it appears that the normal length of human gestation is insufficient to achieve an “adequate” serologic response. In our cohort, the average gestational age at treatment was 29 weeks, limiting our ability to draw conclusions regarding treatment failures based on a 6- to 12-month timeframe. However, late prenatal care is a known problem in seropositive women [9–15], making the results of our cohort more clinically applicable to the majority of women who contract syphilis while pregnant.

Inadequate maternal serologic response is not necessarily indicative of inadequate treatment, however, as equal rates of congenital syphilis were seen in those women with and those without a 4-fold titer decline. In the only other study to evaluate the serologic response during pregnancy, Galan et al in 1997 found that only 47% of seropositive gravidas achieved a 4-fold titer decline 3 months after maternal treatment, which was considered an adequate amount of time to achieve a serologic response per CDC recommendations [6, 16]. As a result, they questioned whether syphilis was undertreated during pregnancy. However, infant outcomes were not reviewed, limiting their ability to correlate maternal serologic response to vertical transmission rates. Well-designed prospective studies have shown the recommended penicillin treatment regimens for syphilis [1] to be 98% efficacious for eradicating both maternal and fetal infection [17]. Our study provides additional data to suggest that the risk of congenital syphilis in the neonate is more dependent on the time interval from treatment until delivery, a known risk factor for presumed treatment failures [9], than on whether a 4-fold decline in titer by delivery was documented.

Several study limitations should be acknowledged. This study was retrospective and required review of medical records. However, all women were treated at a single institution using a standardized protocol. Infant outcomes were also incomplete. Among 166 pregnancies, we had available 147 infant outcomes for a follow-up rate of 89%. Additionally, because serologic response is measured in 3- to 6-month epochs, not including women before 18 weeks of gestation could have underestimated the number of women who achieved a 4-fold titer decline by delivery. However, late prenatal care, poor compliance, and inadequate follow-up are known problems in seropositive gravidas [10, 18, 19], making our results applicable to the majority of pregnancies afflicted with syphilis.

Despite these limitations, this is the largest cohort describing the serologic response to syphilotherapy during pregnancy. We have shown that decline in maternal titers during pregnancy after adequate syphilotherapy varied by stage of disease, with a more rapid rate of decline noted in women with primary and secondary syphilis. Of women diagnosed and treated for syphilis after 18 weeks, less than half will achieve a 4-fold decline in nontreponemal titer by delivery. That being said, the diagnosis of congenital syphilis did not correlate with maternal serologic response to syphilotherapy. The assumption of inadequate maternal treatment based solely on “adequate” titer decline at delivery will result in an excess of women being retreated and of infants being treated unnecessarily for syphilis. A prospective study across all stages of pregnancy would be prudent to complete the maternal serologic response to syphilotherapy and establish national guidelines.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References