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Syphilitic Reinfections During the Same Pregnancy — Florida, 2018

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Abstract

We reviewed all cases of syphilis reported among pregnant women in Florida during 2018 for syphilitic reinfection. Nineteen (7.3%) of 261 pregnant women with syphilis were reported as reinfected during the same pregnancy. Timely rescreening and treatment prevented six (31.6%) of nineteen reinfected women from delivering infants with congenital syphilis.

Short Summary:

Over 7% of pregnant women treated for syphilis had serologic evidence of reinfection during their pregnancy. Rescreening for syphilis at 28–32 weeks of gestation can prevent congenital syphilis.

Introduction

Reported cases of congenital syphilis increased during 2009–2018 in Florida (21 to 108; 414.3%) and in the United States (427 to 1,306; 205.9%).[1,2] At the same time, reported cases of infectious syphilis among women increased by 142.2% in Florida (147 to 356) and 123.8% in the United States (2,232 to 4,995). These increases prompted the Centers for Disease Control and Prevention's "Call to Action" to prevent the continued increase of syphilis in the United States.[3]

One of the best methods to prevent congenital syphilis is to screen for maternal infection early in pregnancy and again at 28–32 weeks of gestation and to provide timely treatment to all women diagnosed with syphilis.[4] Florida statutes require health care providers to screen pregnant women for syphilis at their first prenatal visit and again at 28–32 weeks' gestation.[5]

One challenge with preventing congenital syphilis is the possibility of multiple episodes of syphilis during the same pregnancy. Pregnant women with multiple episodes of syphilis

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during the same pregnancy are not commonly described in the literature. Three studies found between 8.4%–22.1% of congenital syphilis cases were due to maternal reinfection or treatment failure.[6–8] Two of these studies reported the total number of infected mothers with syphilis who were followed, allowing calculation of the percentage of pregnant women with syphilis who had repeat infections (1.8% and 2.6%).[6,8] However, as rates of syphilis among women and their partners increase, reinfections are likely to increase. We examined syphilis case reports among pregnant women in Florida from 2018 to determine how often reinfections occurred, the nature of these reinfections, if these infections occurred among a subset of women or all women, and whether reinfections resulted in congenital syphilis.

Materials and Methods

Syphilis case records for women reported as a case in Florida between January 1, 2018, and December, 31 2018 and reported as pregnant, were extracted from Florida's electronic STD surveillance information system. Case records were organized by woman and then by pregnancy for each woman, allowing us to calculate a total number of pregnancies with a syphilitic infection and allowing for a clear picture of the timing and number of infections within a single pregnancy. We reviewed test results, particularly non-treponemal titers, for each pregnancy with a reported infection to determine if the mother met the CSTE surveillance case definition of infection more than one time (reinfection) during the course of the pregnancy.[9] Each pregnancy was also reviewed to determine if the mother was susceptible to reinfection (defined as having started treatment for her initial infection ≥30 days prior to delivery and then completing the regimen as appropriate for her stage of disease).[4] The proportion of pregnancies with reinfection was determined after excluding those not susceptible to reinfection. Demographic characteristics of the reinfected women were compared to characteristics of women susceptible to reinfection using z-test for two proportions.

Pregnant women with reinfection were further examined to describe stage of syphilis at second diagnosis, non-treponemal test titer value changes over the pregnancy, treatment history, HIV status, illicit drug use, syphilis testing outcomes for partners named from partner services interviews, and variation in laboratory testing locations. Moreover, these pregnancies resulting in reinfection were reviewed to determine if the pregnancy resulted in a congenital syphilis case as defined by the CSTE surveillance case definition and to describe the clinical or laboratory findings among these infants. All data captured in this analysis are part of routine STD surveillance activities. The project was reviewed by the Florida Department of Health Institutional Review Board Office and classified as "exempt"; it was determined to be public health practice, not research involving human subjects.

Results

A total of 369 pregnancies were reported among women with syphilis in Florida during 2018. Mothers were deemed not susceptible for reinfection and excluded from this analysis if they met one of the following conditions: their initial infection was diagnosed at delivery (57), they were diagnosed but not treated for initial infection ≥ 30 days prior to delivery (15), their infection was diagnosed < 30 days prior to delivery (15), they miscarried in the

first trimester (11), they terminated the pregnancy (4), they left Florida during pregnancy and were lost to follow-up (4), or they were inadequately treated for initial infection (2) (Figure 1). After excluding these 108 (29.3%) pregnancies where the mother was not susceptible to reinfection, 261 (70.7%) susceptible pregnancies remained. These 261 pregnancies include mothers with at least one episode of syphilis diagnosed and who were treated ≥30 days before delivery. Among the 261 mothers at risk, 19 (7.3%) met CSTE case definition for reinfection during the same pregnancy (1 was reported with reinfection twice).

Reinfected women were classified as Hispanic (7; 36.8%), non-Hispanic black (6; 31.6%), non-Hispanic white (4; 21.1%) and non-Hispanic other race (2; 10.5%). Most reinfected women were aged 20–24 years (7; 36.8%) followed by 25–29 years (5; 26.3%) and ranged from 16–43 years of age. There were no statistically significant differences in the demographic characteristics of the susceptible women who were or were not reinfected.

At the time of the second diagnosis, the 19 reinfections were all staged as early non-primary, non-secondary syphilis, a stage of disease presenting with no signs or symptoms (Table 1). None was reported to be HIV-infected and only one reported drug use (6.7%) although four mothers were not asked about drug use. As required by the inclusion criteria for this analysis, all reinfected women received appropriate treatment for their initial infections, had a decrease in nontreponemal titer, then had a 4-fold or greater increase in nontreponemal test titer(on average 137 days later range 72–222 days). Sixteen of nineteen women also received treatment for their second infection, 11 received 1 dose of 2.4 million units of benzathine penicillin G and 5 received 3 doses of 2.4 million units of benzathine penicillin G at one-week intervals. The median non-treponemal titer at initial diagnosis was 1:32 (range: 1:4–1:128) and the median titer decrease was 8-fold (range: 2-fold–64-fold) following initial treatment. Eight (44%) of 19 women with ≥ 8-fold titer increase in non-treponemal titer at second diagnosis were retested 5–180 days after their second treatment: 1 had an increased titer, 4 had a sustained titer, and 3 had decreased titers. One of these 3 women was reinfected a second time so she had three infections during the same pregnancy. The other 11 had a 4-fold titer increase at second diagnosis. Nine of these 11 were tested again after their second treatment, with 5 tested 7–60 days later and 4 tested 100–191 days later. Among these nine who were retested after their second treatment, 3 had titers increase further, 4 had titers remain elevated at the 4-fold increase, and 2 had titers decrease. The other two women with 4-fold titer increases include a woman who was not retested and a woman who was not retreated when her titer increased. She was retested 62 days later and had a titer decrease; however, her infant had a reactive CSF-VDRL tests and elevated CSF protein levels).

Among the women with reinfections, 18 (95%) of 19 had a partner services interview. Infected partners were identified for 3 (17%) of these women following one of their infections, but not both. Twelve women had at least one partner tested but no linked infection identified, and three women had no partners located for testing. In total, these 18 women claimed 36 sex partners (mean 2; median 2) during the preceding 12 months.

Of the 19 reinfections, 17 (89.5%) had laboratory testing conducted by multiple laboratories, with day-of-delivery testing often occurring at a different laboratory than the preceding test.

However, susceptible mothers who were not reinfected were equally likely to have a result from multiple laboratories (221 of 242, 91.3%).

Of the 19 reinfections, 7 (36.8%) were diagnosed ≥ 30 days prior to delivery, including 3 that were identified in the second trimester and 4 that were identified during 28–32 weeks' gestational age portion of the third trimester. The remaining 12 were diagnosed at delivery (11; 57.9%) or within 30 days of delivery (1; 5.3%). Diagnosis at delivery or shortly before does not allow sufficient time for treatment to prevent congenital syphilis; however, 10 (83%) of these 12 women were tested for syphilis at 28–32 weeks' gestational age. One of the 7 mothers diagnosed in a timely fashion became infected a third time, with her final reinfection detected at delivery. Therefore, rescreening previously infected women, usually in the third trimester, coupled with timely and appropriate treatment, prevented 6 (31.6%) congenital syphilis cases. The remaining 13 (68.4%) pregnancies resulted in congenital syphilis cases meeting the national case definition. Only 7 of the 19 infants had a full clinical work-up reported, including cerebral spinal fluid (CSF) analysis, and 2 of 7 (28.6%) had laboratory findings indicative of congenital syphilis. One infant had a reactive CSF-VDRL test and elevated CSF protein levels (mother's initial diagnosis was secondary syphilis with a maximum non-treponemal titer of 1:32), and another had only a reactive CSF-VDRL test (mother's initial diagnosis was unknown or late duration syphilis with a maximum non-treponemal titer of 1:16). Of the 13 infants that met the case definition, 11 were treated for congenital syphilis, 6 with benzathine penicillin G 50,000 units/kg/dose intramuscular times 1 dose and 5 with aqueous crystalline penicillin G 200,000–300,000 units/kg/dose intravenous for 10 days. Four of the 6 infants whose mothers were treated sufficiently to prevent congenital syphilis were also treated 3 with benzathine penicillin G 50,000 units/kg/dose intramuscular in 1 dose and 1 with aqueous crystalline penicillin G 200,000–300,000 units/kg/dose intravenous for 10 days.

Discussion

This study found reinfection was common among pregnant women treated for syphilis in Florida in 2018. The risk of reinfection was nearly three to four times higher than what was observed in previous studies.[6,8] However, both previous studies were conducted at a time when the rate of syphilis among women was low.[2] Reinfection may be more likely now than in the past, given the high number of claimed sex partners in this study and the relatively low number of partners with documented intervention.[6,8] Our study excluded mothers not susceptible to reinfection but even if we included them our rates would have been more than double the rates in the aforementioned studies. Our data suggest that some pregnant women and their partners may benefit from active case management for their syphilis throughout the course of their pregnancy.

All reinfections were diagnosed because of increasing non-treponemal titers. Some women may have experienced titer fluctuations rather than true reinfections. Determining a mother's true probability of reinfection would be aided by a clearly defined history of exposure to infected partners, a clinical and sexual history for all partners, and—in some cases—potential retesting. Illicit drug use, HIV infection, pregnancy, and other comorbidities contributing to biological false positive non-treponemal test results have been associated

with fluctuating test non-treponemal test titers.[10–14] Only one of our reinfected women reported any drug use, and none was HIV infected. Intra-laboratory variation in non-treponemal testing is possible, but we found that the proportion of women with non-treponemal results reported from multiple laboratories occurred just as frequently among reinfected and non-reinfected mothers.[4] Differentiating treatment failure from reinfection is difficult because partner information was very incomplete. However, in all 19 cases of reinfection there was a decline in titer (17 [89.5%] were ≥4-fold decline suggesting positive response to therapy) followed by an increase in titer, and nearly two-thirds of the reinfections had a ≥8-fold increase in titers. Clinical guidelines recommend retreatment for women with these findings, and if the women are not retreated, the surveillance definition classifies their infants as cases of congenital syphilis.[4,9] When treatment is urgent at the end of pregnancy, waiting to see if titer changes are sustained may not be possible.

Although not the focus of this study, congenital syphilis elimination will continue to be a challenge when nearly 30% of maternal infections were not susceptible to reinfection primarily because they were identified at or near delivery or the mothers were not treated. A lack of prenatal care, infection acquired late in pregnancy, delays in treatment administration, and inadequate therapy for stage of syphilis have all been identified in previous studies as significant contributors to the congenital syphilis problem in the United States.[6,8,15,16]

The risk of acquiring syphilis continues throughout pregnancy and is particularly high among women who have been diagnosed with syphilis at least once already. Providers should closely monitor pregnant women diagnosed with syphilis during their pregnancy, and ensure that they are retested for syphilis at 28–32 weeks of gestation. Rescreening all pregnant women at 28–32 weeks in high-morbidity areas like Florida will also identify newly acquired infections among women whose initial test was negative.[17]

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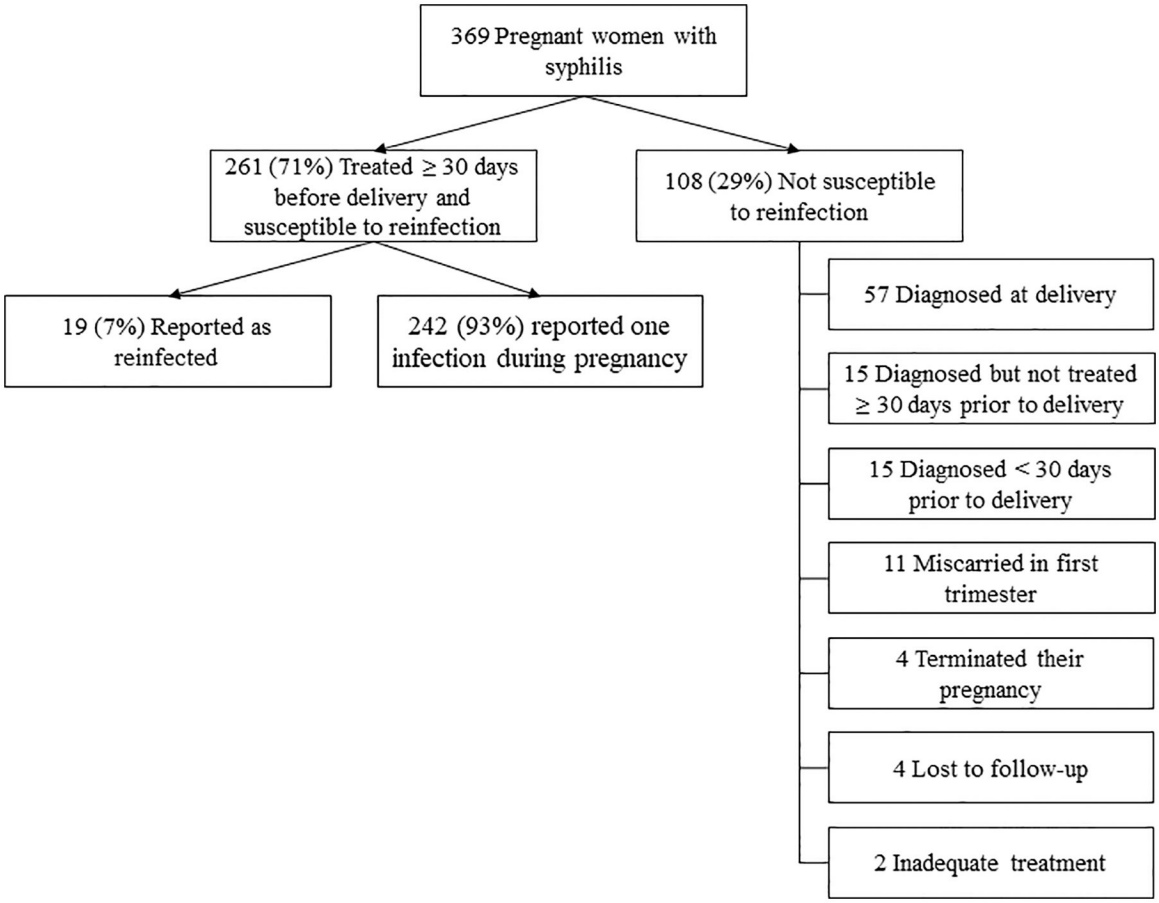

Figure 1.

Flow diagram of pregnant women diagnosed with syphilis in Florida, 2018. Diagram highlights the inclusion criteria of 'susceptibility to syphilitic reinfection' by depicting the number of women who are not susceptible to reinfection and the reasons for their exclusion.

Table 1.

Initial Syphilis Diagnosis and Non-Treponemal Titer History for Syphilitic Reinfections During Pregnancy in Florida, 2018

Case Number	Stage of Syphilis at First Diagnosis	Maximum Non-Treponemal Titer at Initial Diagnosis	Minimum Non-Treponemal Titer after Treatment	Maximum Non-Treponemal Titer at Subsequent Diagnosis	Days from Treatment for Initial Diagnosis to Subsequent Diagnosis
1	Unknown/Late	1:32	Non-Reactive	1:8	160
2[†]	Unknown/Late	1:16	1:4 / 1:4	1:128 / 1:16	88 / 87
3	Unknown/Late	1:64	1:4	1:16	222
4	Unknown/Late	1:64	1:2	1:128	140
5	Unknown/Late	1:8	1:4	1:16	140
6	Unknown/Late	1:64	1:4	1:16	182
7	Unknown/Late	1:8	1:2	1:8	158
8	Unknown/Late	1:16	1:2	1:8	168
9	ENPNS[*]	1:8	1:1	1:8	145
10	ENPNS[*]	1:32	1:8	1:64	82
11	Unknown/Late	1:16	1:2	1:8	99
12	Secondary	1:128	1:4	1:32	163
13	Unknown/Late	1:8	1:4	1:16	168
14	Unknown/Late	1:128	1:32	1:1024	72
15	Unknown/Late	1:64	1:8	1:32	173
16	Secondary	1:64	Non-Reactive	1:8	117
17	Primary	1:4	1:1	1:8	160
18	Secondary	1:32	1:1	1:4	137
19	ENPNS[*]	1:64	1:2	1:8	78

[*] ENPNS – Early non-primary, non-secondary syphilis is a stage of disease in which transmission can be epidemiologically determined to have likely occurred in the past 12 months but symptoms of primary or secondary syphilis are not present.

[†] Case had more than one reported reinfection during the same pregnancy.