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Retrospective Cohort Study of the Incidence and Outcomes of Jarisch-Herxheimer Reactions After Treatment of Infectious Syphilis in Late Pregnancy

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Abstract: Of 39 pregnant women at ≥20 weeks' gestation treated with benzathine penicillin G for infectious syphilis, we identified only 2 mild Jarisch-Herxheimer reactions. There were no immediate fetal sequelae. Data from our study do not support the recommendation for routine admission for the treatment of infectious syphilis in late pregnancy.

After falling precipitously with the availability of penicillin treatment in 1945, the incidence of syphilis is now rising globally. In Alberta, Canada, the incidence of infectious syphilis has climbed to 57 cases per 100,000 in 2020.[1] Most cases were concentrated in Edmonton, and women in their reproductive years were most affected, with an incidence of 119 per 100,000.[1] Pregnancies complicated by maternal syphilis are common, and the number of congenital syphilis cases has risen sharply from 1 in 2014 to 56 in 2020.[1]

Pooled estimates show that among untreated pregnant women with syphilis, fetal loss and stillbirth were 21% more common, neonatal deaths were 9.3% more frequent, and prematurity and low birth weight were 5.8% more frequent than among women without syphilis.[2] Signs and symptoms of syphilis were found in 15% of infants born to untreated women with syphilis.[2] Benzathine penicillin G is highly efficacious for both the mother and the fetus, but it can precipitate the Jarisch-Herxheimer (JH) reaction.[3] This phenomenon is attributed to spirochetolysis, lipopolysaccharide exposure, and inflammatory mediators and may result in fever, hypotension, headache, and rash.[3] Symptoms usually resolve within 24 hours.[3] Attributed adverse events in the second half of pregnancy include fetal heart rate abnormalities, preterm labor, and fetal death.[3] Jarisch-Herxheimer reactions are thought to occur in 10% to 45% of treated women, but clinically relevant reactions may be far less common.[3–6]

Expert opinion varies in the recommendations for maternal and fetal monitoring after the treatment of infectious syphilis in pregnancy.[3,7–9] Canadian guidelines acknowledge possible adverse reactions; however, they do not provide monitoring recommendations.[7] In Alberta, pregnant women at or beyond 20 weeks' gestation are admitted for 24 hours of maternal and fetal monitoring.[8] In contrast, the Centers for Disease Control and Prevention suggests that outpatient self-monitoring may be appropriate.[9]

The objective of our study was to determine the incidence and outcomes of JH reactions in monitored patients after the treatment of infectious syphilis in pregnancy.

METHODS

We conducted a retrospective review of a cohort of women admitted in the Edmonton zone at ≥20 weeks' gestation for the treatment of infectious syphilis from January 1, 2015, to October 30, 2020. A list of eligible women was obtained from the provincial Communicable Disease and Outbreak Management database, which houses all cases of syphilis. Extracted data included maternal demographics, clinical, and behavioral characteristics and were supplemented with a review of maternal and neonatal records. Maternal and fetal outcomes collected included stillbirth, preterm birth (<37 weeks), neonatal intensive care unit (NICU) admission, and a diagnosis of congenital syphilis. Cases were excluded if the women were not staged as infectious syphilis (primary, secondary, and early latent) or if hospital records were not available.

All pregnant women who access prenatal care are screened for syphilis using a reverse sequence algorithm. Screening is recommended in the first trimester and again at the time of delivery. In women at high risk of acquisition or reinfection with sexually transmitted infection/syphilis in their current pregnancy, more frequent screening is recommended.[8] The sample is first tested with a treponemal-specific enzyme immunoassay (EIA; Architect Syphilis TP Microparticles; Abbott Laboratories, Abbott Park, IL). If the EIA is positive, it is followed by a quantitative rapid plasma reagin (RPR) titer (Macro-Vue RPR kit; Becton Dickinson Microbiology Systems, Ontario, Canada). The first time the EIA is positive, it is followed by a second treponemal test, the *Treponema pallidum* particle agglutination (SERODIA-TP-PA; Fujirebio Europe, Gent, Belgium). Syphilis staging for pregnant women and infants is done by 3 designated consultants using provincial case criteria.[10,11] Most infectious cases in pregnancy are treated with benzathine penicillin G 2.4 million units by intramuscular injection weekly for 2 doses; women at ≥20 weeks' gestation with fetal ultrasounds suggestive of congenital syphilis are sometimes treated with 10 to 14 days of intravenous penicillin G. Affected women at ≥20 weeks' gestation are routinely admitted to hospital for 24 hours after the first dose of penicillin. Continuous fetal monitoring is performed for 4 hours after treatment and then reflexively if the patient reports fever, contractions, or reduced fetal movement.

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No validated scoring system exists for the assessment of JH reactions. We defined a reaction as at least one of the following within 24 hours of penicillin administration: fever (≥38.0°C), hypotension (systolic blood pressure ≤100 mm Hg), tachycardia (≥110 beats/min), new rash, or patient-reported headache, myalgia, or contractions.

Because of the small sample size and low outcome frequency, descriptive analysis was used for categorical variables, whereas medians were calculated for continuous variables using Excel (Microsoft Corporation, 2018). Comparison of medians was completed using the Mann-Whitney test. Ethics approval was obtained from the University of Alberta Health Research Ethics Board (protocol number: Pro 00105917).

RESULTS

There were 39 cases of infectious syphilis treated at ≥20 weeks' gestation; 37 were treated with benzathine penicillin and 2 cases with fetal ultrasound findings suggestive of congenital syphilis (Table 1) were treated with 10 to 14 days of intravenous penicillin G. All were HIV negative. The median gestational age at treatment was 27 weeks (interquartile range [IQR], 23–30 weeks), and the median time to treatment from a positive test result was 4 days (IQR, 2.8–7.3 days).

There were 41 births because of 2 twin pregnancies; 4 neonatal records could not be located. Of the 37 with neonatal records (Table 1), 2 were stillborn. One occurred in a patient with a JH reaction (details hereinafter). The second occurred after feticidal intracardiac injection due to significant fetal anomalies; a polymerase chain reaction from fetal tissue was positive for syphilis, and the stillbirth was therefore presumed to be related to syphilis. Six live preterm births occurred at a median gestational age of 34 weeks (IQR, 31–36 weeks). In one case, preterm labor started before administration of benzathine penicillin, so treatment and delivery occurred 1 day apart. All other preterm births occurred 8 to 39 days after the first dose of penicillin. The other 29 births (including both twin pregnancies) occurred at term.

Eleven cases of congenital syphilis were identified; the median duration between the first dose of penicillin and delivery was 3 weeks (IQR, 2–5 weeks) compared with 13 weeks (IQR, 12–16 weeks; $P < 0.001$) for uninfected neonates. Twenty-one neonates required NICU admission for suspected congenital syphilis (n = 9), term respiratory distress (n = 4), prematurity (n = 4), or another/unstated indication (n = 4).

There were 2 JH reactions, both with normal fetal ultrasounds. The first occurred in a patient with secondary syphilis (RPR reactive at 1:256 dilutions), treated at 30 weeks' gestation. Fever (38.2°C) and headache developed within 8 hours of treatment. External fetal heart rate monitoring was normal, and no contractions were reported. Acetaminophen 650 mg was administered once. No additional intervention or escalation of monitoring was required. The outcome of this pregnancy was a term neonate with no evidence of congenital syphilis. The second JH reaction occurred in a patient with early latent syphilis (RPR reactive at 1:128 dilutions), treated at 28 weeks' gestation. Fever (38.4°C), tachycardia (117 beats/min), and uterine contractions occurred within 4 hours of penicillin administration. External fetal monitoring was normal. The patient declined supportive measures, and no additional intervention was required. This pregnancy was complicated by preeclampsia and ended with an unattended out-of-hospital stillbirth at 37 weeks' gestation. We were unable to determine if the death was related to congenital syphilis.

TABLE 1. Maternal (n = 39) and Neonatal (n = 37) Characteristics of Infectious Syphilis Cases Treated at ≥20 Weeks' Gestation

Maternal Characteristic (n = 39)	n (%) or Median (IQR)
Median age at treatment, y	27 (21–30)
Median gestational age at treatment, wk	27 (23–30)
Ethnicity	
First Nation	23 (59.0)
Metis	5 (12.8)
White	5 (12.8)
Other	6 (15.4)
Substance use	
No	17 (43.6)
Stimulant	10 (25.6)
Opiates	1 (2.6)
Both	11 (28.2)
Syphilis stage	
Primary	10 (25.6)
Secondary	4 (10.3)
Early latent	25 (64.1)
Perinatal ultrasound findings	
Normal	34 (87%)
Suggestive of congenital syphilis*	2 (5.1%)
Abnormal; not syphilis related†	3 (7.7%)
RPR at case identification, dilutions	
≤8	9 (24)
16	5 (14)
32	6 (16)
64	12 (32)
128	3 (8)
256	2 (5)

Neonatal Characteristic (n = 37)	n (%) or Median (IQR)
Birth outcome	
Stillbirth	2 (5.4)
Live birth	35 (94.6)
Median gestational age, wk	38 (37–39)
Median birth weight, g	3110 (2573–3515)
Neonatal syphilis diagnosis	
Congenital syphilis	11 (29.7)
Noncase	26 (70.2)
NICU admission	
No	15 (40.5)
Yes	22 (59.5)
Median length of stay, d	10 (10–14)

*Case 1: hepatosplenomegaly and suspect fetal anemia, ascites. Case 2: oligohydramnios, ascites, splenomegaly, and fetal anemia.

†Oligohydramnios with normal fetal anatomy, echogenic focus in left ventricle, and partial bladder outlet obstruction.

DISCUSSION

Adolf Jarisch first described the JH reaction in 1895, and despite the passage of more than 125 years, JH reactions in pregnancy remain poorly characterized.[12] In our study of 39 pregnant women with infectious syphilis treated after 20 weeks' gestation, we identified 2 mild JH reactions. Adverse neonatal outcomes including preterm delivery (n = 6) and stillbirth (n = 2) were otherwise explained or occurred more than 7 days after the first dose of penicillin, so they were presumably unrelated to the treatment itself. It is noteworthy that, although all the women were treated shortly after their positive test results (median of 4 days, IQR of 2.8–7.3 days), all the women accessed prenatal care late in their pregnancy (median gestation age at treatment of 27 weeks (IQR, 23–30 weeks).

This low incidence of JH reactions contrasts with a 1990 study from Texas where JH reactions occurred in 15 of 33 pregnant

women (46%), including all 3 with primary and 12 of 20 with secondary syphilis.[4] The most frequent reaction was transient fever, sometimes associated with changes in uterine activity and decreased fetal movement; tocolysis was never required.[4] Adverse neonatal outcomes potentially related to the JH reaction included (i) death 26 hours after treatment and (ii) preterm delivery 1 week after treatment.[4] Similarly, a 1998 Chicago study reported that 40% (20 of 50) of pregnant women developed JH reactions.[5] However, a recent Canadian study reported only 1 JH reaction in 58 pregnant women but acknowledged that women did not remain in hospital after treatment, so mild reactions could have been missed.[6] The reasons for discrepancies in the incidence of JH reactions are unclear but may include differences in mean GA at treatment (e.g., in the Chicago study, average GA was 30.8 weeks compared with 27.2 weeks in our study), or JH definitions. It is unclear if other differences in the studied populations such as ethnicity or substance use may account for the differences between the US and Canadian studies. The location (Edmonton) of our study and of Dhaliwal et al.[6] (Winnipeg) have the second and largest urban Indigenous populations in Canada, respectively.[13] Although the Dhaliwal study did not report ethnicity, 71.8% of women in our study self-identified as Indigenous and 59.5% had a history substance use.[6] In the studies by Myles et al.[5] and Klein et al.,[4] 94% and 30% of the women were Black, and in the study by Myles et al., 32% reported "drug abuse."

Limitations of our study include the small sample size precluding the analysis of factors that may increase the risk of JH reaction. Another limitation is the retrospective design, leaving the possibility that not all JH reactions were recognized or recorded in the patient record. We were also unable to determine the neonatal outcomes of 4 exposed infants because of our inability to locate their birth records, and we were unable to determine if one stillbirth was related to syphilis.

Our findings combined with the previous literature suggest that severe adverse outcomes immediately after the treatment of infectious syphilis are uncommon and are not sufficiently severe to warrant routine observation in hospital. None of the published studies to date required an intervention (e.g., tocolysis) in the 24 hours after treatment. In addition, the adverse neonatal outcomes typically occurred after discharge from hospital, suggesting that the admission itself did not prevent later adverse outcomes. We do acknowledge, however, that there may be a subset of women who are at higher risk of adverse outcomes and encourage further prospective study to identify the characteristics of pregnant women who could potentially benefit from admission for treatment of syphilis in pregnancy. Finally, given the high prevalence of comorbidities such as substance use and the frequent occurrence of adverse pregnancy and neonatal outcomes after the treatment of infectious syphilis during pregnancy despite the low incidence and mild manifestations of the JH reactions, close follow-up is recommended for all women diagnosed with infectious syphilis during pregnancy.

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