Ineffective penicillin treatment and absence of partner treatment may drive the congenital syphilis epidemic in Brazil

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BACKGROUND: Reducing congenital syphilis has been the focus of Brazilian health programs for decades, yet the cases continue to increase. Although health interventions have targeted HIV screening and treatment, syphilis management continues to be challenging. Syphilis during pregnancy may enhance the HIV maternal seroconversion risk. The potential factors fueling the syphilis epidemic were evaluated in south Brazil, an area of high HIV or syphilis endemicity.

OBJECTIVE: We hypothesized that ineffective treatment because of a lack of partner treatment, late presentation to care, and reinfection of previously treated mothers were potential drivers of syphilis mother-to-child transmission.

STUDY DESIGN: Data on women diagnosed with syphilis during pregnancy between January 1, 2008 and December 31, 2018 were obtained from a large urban hospital in Porto Alegre, Brazil. The patients were stratified into effective vs ineffective treatment groups according to the World Health Organization guidelines. Crude and adjusted risk ratios for the prediction of congenital syphilis and adverse fetal or neonatal outcomes were computed using Poisson regression.

RESULTS: Nearly 56,000 pregnant women delivered over the 11-year period; 1541 (2.8%) had confirmed syphilis during pregnancy, with 934 (61%) receiving ineffective syphilis treatment because of late presentation and diagnosis, delayed treatment initiation, and loss to follow-up with no treatment recorded. Ineffective treatment was associated with maternal education, prenatal care, timing of syphilis diagnosis, venereal diseases research laboratory titers, and maternal HIV coinfection. On multivariate regression analysis, ineffective treatment (adjusted risk ratio, 4.52; 95% confidence interval, 2.35–8.69), absence of prenatal care (adjusted risk ratio, 9.31; 95% confidence interval, 3.77–23.0), syphilis diagnosis at delivery (adjusted risk ratio, 3.08; 95% confidence interval, 2.07–4.58), and maternal nontreponemal titers ≥1:64 (1.09–1.93) were associated with an increased risk of fetal loss. Ineffective treatment (adjusted risk ratio, 1.71; 95% confidence interval, 1.59–1.84), year of diagnosis 2014 to 2016 (adjusted risk ratio, 1.07; 95% confidence interval, 1.02–1.13), absence of prenatal care (adjusted risk ratio, 1.44; 95% confidence interval, 1.17–1.76), and maternal nontreponemal titers >1:4 were associated with an increased risk of congenital syphilis. Although partner treatment reduced the congenital syphilis risk (adjusted risk ratio, 0.60; 95% confidence interval, 0.55–0.66), only 31.8% of partners received treatment. Maternal HIV coinfection was not associated with an increased risk of fetal loss, low birthweight, preterm birth, congenital syphilis, or symptomatic neonatal infection.

CONCLUSION: Public health initiatives promoting effective syphilis treatment in pregnancy, increased access to high-quality prenatal care, and partner treatment should be considered to reduce congenital syphilis.

Key words: Brazil, HIV, ineffective treatment, mother-to-child transmission, partner treatment, pregnancy, prenatal care, public health, syphilis

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Why was this study conducted?

To identify the parameters associated with the mother-to-child transmission (MTCT) of syphilis in pregnant women at a large medical network in Porto Alegre, Brazil.

Key findings

61% of women diagnosed with maternal syphilis between 2008 and 2018 received ineffective syphilis treatment. Ineffective treatment (adjusted risk ratio [ARR], 1.71; 95% confidence interval [CI], 1.59−1.84) and absence of prenatal care (ARR, 1.44; 95% CI, 1.17−1.76) were associated with an increased risk of congenital syphilis. Partner treatment reduced the risk of congenital syphilis (ARR, 0.60; 95% CI, 0.55−0.66).

What does this add to what is known?

A significant proportion of pregnant mothers with syphilis do not receive effective treatment, placing them at an increased risk of syphilis MTCT in the future.

Introduction

Attempts to control the mother-to-child transmission (MTCT) syphilis epidemic in Brazil has been fraught with challenges. The rates of maternal syphilis increased 5-fold in the country in the past decade despite clear testing guidelines in place and treatment availability.[1] The incidence of congenital syphilis in 10 Brazilian states surpassed the national rate in 2019 at 8.2 per 1000 live births.[1−3] Porto Alegre, the capital of the state of Rio Grande do Sul, stands out as a high-prevalence region for syphilis and HIV.[1] In our previous work, we found an increase in cumulative maternal syphilis diagnoses in Brazil from 2010 to 2018[4]; 8704 cases of maternal syphilis were identified in 2010 compared with 46,340 cases in 2018.[4] Furthermore, yearly increases in syphilis among pregnant women occurred despite high rates of engagement in prenatal care, whereas 8.7% of maternal syphilis cases diagnosed from 2010 to 2018 in Brazil were not treated appropriately with penicillin.[4]

The growing syphilis epidemic in Brazil poses a threat to the control of the spread of HIV infection. Members of high-risk populations with syphilis exposure demonstrated a 2-fold increase in HIV incidence than those without syphilis.[5] Although the care of persons living with HIV has been an area of enhanced focus in Brazil, aims to successfully reduce syphilis have not gained the same traction.[6] The discrepancy between syphilis monitoring and HIV monitoring has also been observed in the prenatal care of pregnant women. Healthcare professionals in São Paulo, Brazil reported that the standard routines for screening and treating HIV-infected pregnant women and infants are better-established and more utilized than those for patients infected with syphilis.[7] Further, patient follow-up was significantly higher for pregnant women with HIV than for those with syphilis.[7] Women diagnosed with syphilis during pregnancy represent a subset of the population that is vulnerable to HIV seroconversion in the future.[8,9]

Current Brazilian Ministry of Health guidelines for syphilis management during pregnancy recommend routine screening at the initiation of prenatal care, week 28, and delivery.[10,11] Complete maternal syphilis treatment is defined as penicillin therapy more than 30 days before delivery.[11] The treatment is highly effective at reducing MTCT of syphilis, and safety to the fetus is well-established.[2] Maternal syphilis can lead to fetal death, preterm birth, low birthweight infants, and higher risks of maternal HIV seroconversion and HIV transmission to the infant. It remains unclear why the maternal and congenital syphilis epidemic persists in Brazil when there are testing guidelines in place and accessible treatment.[12]

We hypothesized that ineffective treatment because of a lack of partner treatment, late presentation to care, and reinfection of previously treated mothers were potential drivers of syphilis MTCT transmission.

Materials and Methods

Study population and data sources

This was a retrospective cohort study of women diagnosed with syphilis during pregnancy. All the participants reached a pregnancy endpoint (delivery or miscarriage) at the Conceição Hospital in Porto Alegre, Brazil, between January 1, 2008 and December 31, 2018. The Conceição Hospital is part of the Grupo Hospitalar Conceição—a public tertiary medical care network including 4 hospitals and a group of ambulatory clinics in Brazil—in the same city. Anonymous syphilis pregnancy surveillance data reported to the Brazilian "Sistema de Informação de Agravos de Notificação" (SINAN) by the Conceição Hospital Network was evaluated.

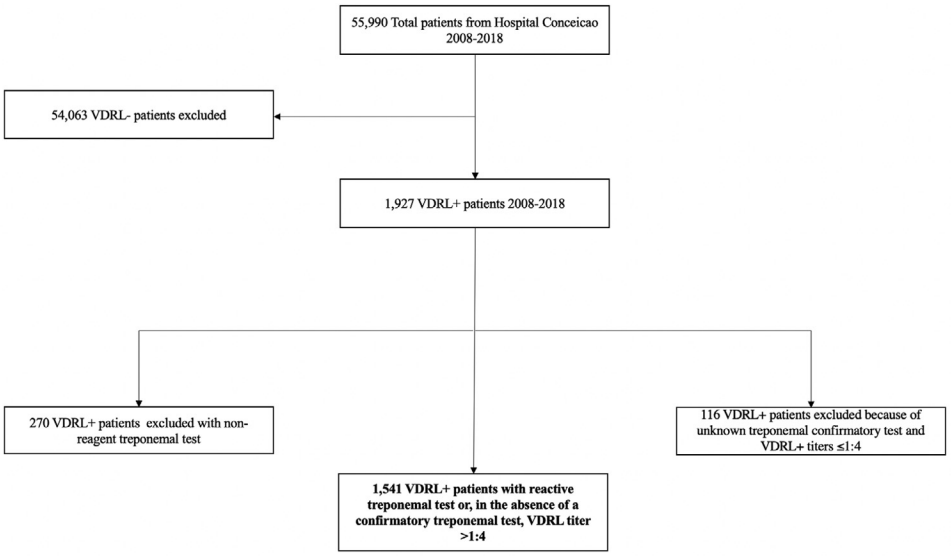
Ethics

We received institutional board review (IRB) approval (IRB protocol 14.124) from the Conceição Hospital in Porto Alegre, Brazil. Obtaining written informed consent was waived because this was a secondary data analysis of deidentified data.

Selection criteria

Maternal syphilis was diagnosed by positive nontreponemal venereal diseases research laboratory (VDRL) results followed by confirmation with an antitreponemal assay such as treponemal pallidum particle agglutination assay or enzyme-linked immunosorbent assay, both routinely used in Brazil. Women with a positive VDRL result during pregnancy and unknown treponemal confirmatory test results were included in the analysis if the titers were >1:4. Titers <1:8 were not considered diagnostic for syphilis if the confirmatory test result was unknown[13,14]; titers <1:8 have been associated with serologic cure.[15,16] False positive VDRL results can present as low titers such as 1:1, 1:2,

FIGURE 1
Pregnant participant selection flowchart



VDRL, venereal diseases research laboratory.

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or even 1:4 during pregnancy or in patients with autoimmune diseases.[17]

Exposure and outcomes

The patients were stratified into syphilis-positive pregnant women treated effectively and syphilis-positive pregnant women treated ineffectively. World Health Organization (WHO) guidelines including the following were used for establishing effective treatment: (1) adequate penicillin treatment provided >30 days before delivery, (2) demonstration of lower syphilis titers after treatment, and (3) use of 2.4 million units of 1-time intramuscular benzathine penicillin G (BPG) (for primary, secondary, or early latent stage disease) or weekly for 3 consecutive weeks (for late or unknown stage disease). Penicillin desensitization is recommended even in the event of penicillin allergy.[2]

The primary outcome was congenital syphilis infection, whereas the secondary outcomes were clinical findings consistent with congenital syphilis in exposed newborns and adverse fetal and neonatal outcomes, including low infant birthweight (≤2500 g), preterm birth (<37 weeks), and fetal loss. Infected newborns were categorized as symptomatic if they displayed any of the following characteristics identified by the Centers for Disease Control and Prevention: deformed bones, severe anemia (low blood count), enlarged liver and spleen, jaundice, brain and nerve problems (blindness or deafness), meningitis, or skin rashes.[18] We examined the adverse outcome differences in pregnant women with partners that were treated vs partners that had unknown or no treatment. Our evaluation of the predictors of congenital syphilis is outlined in the supplemental appendix.

Data management and statistical analysis

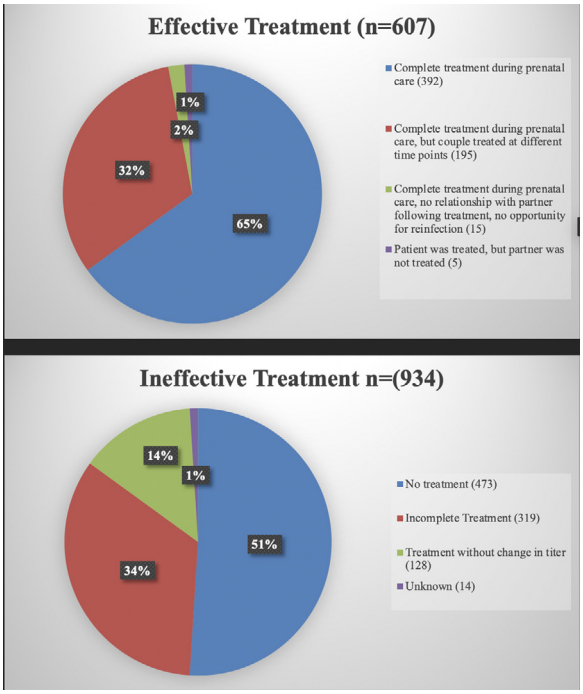
Data were abstracted from the Grupo Hospitalar Conceição SINAN reporting database, which was originally abstracted from medical records for SINAN reporting purposes. The exclusion criteria are noted in the supplemental appendix.

The continuous baseline characteristics were reported as median values and interquartile range (IQR) and were compared with the Welch t test. The categorical variables were reported as a frequency. The relative risk and corresponding 95% confidence intervals (CIs) were generated for potential risk parameters for women who received effective and ineffective syphilis treatment. We conducted an adjusted multivariate Poisson regression for each dichotomous outcome using treatment effectiveness as the main regressor and did a backward removal of covariates found to have a P value <.20 in the crude regression stage of the analysis. Using the Baron and Kenny test, we identified treatment effectiveness and prenatal care as interaction variables. Statistical analysis was performed using Stata statistical software (version 16; StataCorp LLC, College Station, TX), and all statistical significance tests relied on a 2-sided α <0.05.

Results

Over 11 years, 55,990 pregnant women delivered at the Conceição Hospital, of which 96.6% had a negative VDRL titer (Figure 1). Among 1927 participants with a positive VDRL result, 270 (14%) had negative treponemal test results. 116 (6%) participants with no confirmatory treponemal test results available and VDRL titers <1:8 were excluded from further analysis. The remaining study population consisted of 1541 pregnancies with both positive VDRL and treponemal antibody assay results

FIGURE 2
Breakdown of ineffective and effective treatment cohorts by maternal treatment status



VDRL, venereal diseases research laboratory.

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(n=1446) and pregnancies with a positive VDRL titer of >1:4 without a confirmatory treponemal test result (n=95) (Figure 1).

Among 1541 pregnant women diagnosed with maternal syphilis between 2008 and 2018 at Hospital Conceição, 934 (61%) received ineffective syphilis treatment (Figure 2). Total 792 (85%) women in the ineffective syphilis treatment category were either not treated while pregnant or had treatment initiated within 30 days of delivery because of a late diagnosis. An additional 128 (14%) women were treated, but VDRL titers did not decline or increased post treatment. Less than 1% of the women had a syphilis diagnosis during previous pregnancies but no evidence of treatment in the current pregnancy. For 1% of the cohort, there was no record of syphilis treatment.

Table 1 shows the demographics and pregnancy characteristics of the study population stratified by effective vs ineffective treatment. The median age of the study population was 24 (IQR, 20−29), and no significant differences were found between race distributions in the 2 groups. Most of the study population (62.5%) self-identified as White, followed by 25.1% as Black and 12.1% as Mixed, Indigenous, Asian, or other. The educational level differed between the groups; 52.2% of women with ineffective treatment did not have secondary education compared with 39.9% of women with effective treatment ($P<.01$). A higher frequency of prenatal care (at least 1 visit) was observed in the women who received effective syphilis treatment (97.2% vs 69.1%, $P<.01$). Only 54.4% of partners received treatment in the effective treatment cohort; it was significantly higher than the 17.1% of partners treated in the ineffective treatment group ($P<.01$). A greater percentage of women with ineffective treatment were diagnosed at delivery and had elevated VDRL titers than those with effective treatment ($P<.01$). A higher proportion of women had HIV coinfection in the ineffective treatment group as opposed to the effectively treated population (13.1% vs 5.9%, respectively, $P<.01$). The distribution of treatment groups also differed by year of diagnosis ($P<.01$): 6.9% of women received effective treatment and 17.2% did not between 2008 and 2010, compared with 35.6% of women who received effective treatment and 19.3% who did not between 2017 and 2018.

Table 2 evaluates the adverse outcomes among the effective and ineffective treatment groups. Of note, 165 (72.4%) of the fetal losses reported for the ineffective treatment group were attributed to women who received no penicillin treatment before admission for miscarriage. These were generally women who presented to the hospital because of an ongoing miscarriage and were found to be VDRL positive on admission. Overall, 98.1% of the women with ineffective treatment transmitted congenital syphilis, compared with 49.8% of women with effective treatment. Significantly higher rates of fetal loss, congenital syphilis diagnoses, low birthweight, and preterm deliveries were reported in the group of women with ineffective treatment.

Table 3 explores the same adverse outcomes in women that had treated partners vs women with partners that had no or unknown treatment status. Overall, only 31.8% of women reported treated partners. 47.8% of women with treated partners transmitted congenital syphilis compared with 93.6% of women with partners that had no or unknown treatment ($P<.01$). Women with treated partners were significantly less likely to experience any adverse fetal or neonatal outcomes than those who had partners with no or unknown treatment ($P<.01$).

The predictors of adverse outcomes in women with syphilis in Brazil over an 11-year span are shown in Supplemental Table 1 (unadjusted multivariate analysis) and Table 4, which shows the adjusted multivariate analysis of predictors of fetal death, low birthweight, preterm birth, congenital syphilis, and symptomatic newborns. Ineffective treatment (adjusted risk ratio [ARR],

TABLE 1
Baseline demographic and pregnancy characteristics of women diagnosed with maternal syphilis in Porto Alegre, Brazil, 2008 to 2018

Demographic and pregnancy characteristics	Effective treatment	Ineffective treatment	*P* value
N=1541	N (%)	N (%)	
Group total	607 (39)	934 (61)	
Age median (IQR)	24.0 (20.0–28.0)	24.0 (20.0–30)	.09
Age			
<20	121 (19.9)	186 (19.9)	.03
20–29	367 (60.5)	512 (54.8)	
≥30	119 (19.6)	236 (25.3)	
Self-identified race			
White	378 (62.3)	585 (62.6)	.34
Black	155 (25.5)	232 (24.8)	
Mixed, Indigenous, Asian, Other	74 (12.2)	112 (12.0)	
Unknown	0 (0)	5 (0.5)	
Education			
Primary	242 (39.9)	488 (52.2)	<.01
Secondary	220 (36.2)	283 (30.3)	
High school or higher	142 (23.4)	157 (16.8)	
Unknown	3 (0.5)	6 (0.6)	
Year of diagnosis			
2008–2010	42 (6.9)	161 (17.2)	<.01
2011–2013	114 (18.8)	259 (27.7)	
2014–2016	235 (38.7)	334 (35.8)	
2017–2018	216 (35.6)	180 (19.3)	
Number of gestations			
1 Gestation	218 (35.9)	240 (25.7)	<.01
2–4 Gestations	319 (52.6)	514 (55.0)	
≥5 Gestations	70 (11.5)	180 (19.3)	
Prenatal care			
Received care	590 (97.2)	645 (69.1)	<.01
Did not receive care	17 (2.8)	281 (30.1)	
Unknown	0 (0)	8 (0.9)	
Partner treatment			
Received treatment	330 (54.4)	160 (17.1)	<.01
Did not receive treatment	239 (39.4)	649 (69.5)	
Unknown	38 (6.3)	125 (13.4)	
Timing of syphilis Diagnosis			
Prenatal care	564 (92.9)	479 (51.3)	<.01
During delivery	37 (6.1)	440 (47.1)	
After delivery	1 (0.2)	2 (0.2)	
Unknown	5 (0.8)	13 (1.4)	
Syphilis titers			
<1:8	446 (73.5)	390 (41.8)	<.01
1:8–1:32	150 (24.7)	387 (41.5)	
≥1:64	11 (1.8)	154 (16.5)	
Unknown	0 (0.0)	3 (0.2)	
Maternal HIV status			
HIV+	36 (5.9)	122 (13.1)	<.01
HIV–	570 (93.9)	811 (86.8)	
HIV unknown	1 (0.2)	1 (0.1)	

IQR, interquartile range.

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4.52; 95% CI, 2.35–8.69), absence of prenatal care (ARR, 9.31; 95% CI, 3.77–23.0), syphilis diagnosis at delivery (ARR, 3.08; 95% CI, 2.07–4.58), and VDRL titers ≥1:64 (ARR, 1.45; 95% CI, 1.09–1.93) were predictors of fetal loss at any time during pregnancy. Women with ineffective syphilis treatment (ARR, 1.42; 95% CI, 1.05–1.92) and higher syphilis titers ≥1:64 (ARR, 2.92; 95% CI, 2.21–3.87) were at an increased risk of delivering a low birthweight infant. In contrast, women with higher education were at a reduced risk of having a low birthweight infant (ARR, 0.70; 95% CI, 0.51–0.96). Ineffective syphilis treatment (ARR, 1.70; 95% CI, 1.22–2.38) and syphilis titers ≥1:64 (ARR, 3.13; 95% CI, 2.36–4.15) were predictors of preterm birth.

Women with ineffective syphilis treatment had an increased risk of transmitting congenital syphilis (ARR, 1.71; 95% CI, 1.59–1.84) than effectively treated women. Women older than 20 (ARR, 1.08; 95% CI, 1.02–1.15), those diagnosed between 2014 and 2016 (ARR, 1.07; 95% CI, 1.02–1.13), those without prenatal care (ARR, 1.44; 95% CI, 1.17–1.76), and those with syphilis titers >1:4 (ARR, 1.17; 95% CI, 1.12–1.22) were at an increased risk of delivering a baby with congenital syphilis. Alternatively, women with treated partners (ARR, 0.60; 95% CI, 0.55–0.65) and women diagnosed between 2017 and 2018 (ARR, 0.86; 95% CI, 0.79–0.93) had a reduced risk of MTCT syphilis. Higher education (ARR, 1.79; 95% CI, 1.01–3.18), diagnosis between 2017 and 2018 (ARR, 2.57; 95% CI, 1.14–5.79), and titers ≥1:64 (ARR, 2.04; 95% CI, 1.24–3.37) were associated with higher chances of having a symptomatic newborn. Partner treatment (ARR, 0.48; 95% CI, 0.27–0.86) led to reduced risk of a symptomatic newborn.

One hundred fifty eight (10.3%) women with a syphilis diagnosis had a concurrent diagnosis of HIV. One hundred twenty two (13.1%) women with HIV and syphilis were more likely to have ineffective penicillin treatment (which includes 77% of the women with HIV, $P<.01$). However, maternal HIV coinfection was not associated with increased risk of fetal loss, low

TABLE 2
Adverse maternal and fetal outcomes in women diagnosed with syphilis during pregnancy in Porto Alegre, Brazil by maternal syphilis treatment status

Adverse maternal and fetal outcomes	Effective treatment	Ineffective treatment	*P* value
N=1541	N (%)	N (%)	
Group total	607 (39)	934 (61)	<.01
Fetal birth outcome			
Fetal loss at any time during pregnancy	18 (3.0)	228 (24.4)	<.01
Live fetus	589 (97.0)	706 (75.6)	
Congenital syphilis			
Yes	302 (49.8)	916 (98.1)	<.01
No	305 (50.2)	18 (1.9)	
Symptomatic newborn			
Yes	31 (5.1)	59 (6.3)	.55
No	566 (93.3)	854 (91.4)	
Unknown	10 (1.6)	21 (2.3)	
Fetal birthweight			
≤2500 g	67 (11.3)	205 (26.0)	<.01
>2500 g	528 (88.7)	582 (74.0)	
Not included abortions	12	147	
Term of birth			
Preterm birth <37 wk	57 (9.6)	194 (24.6)	<.01
Term ≥37 wk	538 (90.4)	590 (75.0)	
Unknown	0 (0)	3 (0.4)	
Not included abortions	12	147	

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birthweight, preterm birth, congenital syphilis, or symptomatic neonatal infection (Table 3).

Comment

Principal findings

Despite strict adherence to WHO guidelines at this hospital in southern Brazil, only 39% of the 1541 pregnant women diagnosed with syphilis between 2008 and 2018 in our analysis received effective penicillin treatment. Even more concerning is that 51% of women in the ineffective treatment group had no treatment at all. The cause for the vast undertreatment of this population is multifactorial. The absence of prenatal care and lack of follow-up visits puts patients at risk for a missed syphilis diagnosis or inadequate clearance of a previous infection. In women who miscarried, a syphilis diagnosis was generally made concurrently with the miscarriage, often times during the patient's first encounter with the medical system.

Results

Multiple prenatal care visits are essential in retesting for infections throughout pregnancy. Some barriers to prenatal care are lower socioeconomic status, greater travel distances, low maternal schooling, and negative attitudes toward pregnancy.[19–21] Patient follow-up depends both on patient attendance and the effective tracking of patients in the hospital system. It is not unusual for patients to deliver at different locations from where they received prenatal care.[22] Without a smooth transition of care between the ambulatory and delivery teams, the patients may not receive effective treatment. One-thirds of women were placed in the ineffective treatment cohort as a result of incomplete treatment less than 30 days before delivery. Almost half of the patients with ineffective treatment were diagnosed at the time of delivery, suggesting that the main reason why patients were treated ineffectively is because a syphilis diagnosis was made late in pregnancy.

Clinical implications

Although effective treatment was shown to reduce disease transmission, half of effectively treated women still transmitted syphilis. This frequency was higher than expected for the patients who were managed according to the appropriate guidelines and demonstrated VDRL titer decline. We hypothesize that the lack of partner treatment is contributing to these high transmission rates. We also found that women without partner treatment were more likely to have syphilis MTCT. Despite treatment according to the standard of care, pregnant women are at a high risk of reinfection from untreated partners.[1,23] Inadequate partner treatment stems from both institutional and social barriers. Cuba, the first country worldwide to successfully eliminate MTCT of HIV and syphilis, prioritized partner screening and treatment in their public health initiatives.[2] In areas with no standardized partner treatment guidelines, the onus is placed on the women to both notify and counsel their partners to receive treatment.

Failure to disclose diagnoses is an aspect of the untreated partner problem fueling the syphilis epidemic. Andrade and colleagues showed that women with an extramarital encounter or those who had experienced previous domestic violence were more fearful of sharing new diagnoses with their partners.[24] Professional support for navigating such conversations is essential for creating a safe environment for partner notification.[25] Partner reinfection is also the product of risky sexual behaviors such

TABLE 3
Adverse maternal and fetal outcomes in women diagnosed with syphilis during pregnancy in Porto Alegre, Brazil by partner syphilis treatment status

Adverse maternal and fetal outcomes	Partner treatment	No/Unknown Partner Treatment	*P* value
N=1541	N (%)	N (%)	
Group total	490 (31.8)	1051 (68.2)	
Fetal birth outcome			
Fetal loss at any time during pregnancy	21 (4.3)	225 (21.4)	<.01
Live fetus	469 (95.7)	826 (78.6)	
Congenital syphilis			
Yes	234 (47.8)	984 (93.6)	<.01
No	256 (52.2)	67 (6.4)	
Symptomatic newborn			
Yes	13 (2.7)	77 (7.4)	<.01
No	469 (96.5)	951 (91.1)	
Unknown	4 (0.8)	16 (1.5)	
Fetal birthweight			
≤2500 g	51 (10.7)	221 (24.4)	<.01
>2500 g	424 (89.3)	686 (75.6)	
Not included abortions	15	144	
Term of birth			
Preterm birth <37 wk	51 (10.7)	200 (22.0)	<.01
Term ≥37 wk	424 (89.3)	704 (77.7)	
Unknown	0 (0)	3 (0.3)	
Not included abortions	15	144	

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as refusal to engage in regular condom use.[26–28] Regardless of global efforts to address the syphilis epidemic, we found that pregnant women were at increased risk of syphilis MTCT between 2014 and 2016 than between 2008 and 2010. The penicillin shortage of 2014 may explain this increase in diagnoses.[3,29] Increased reports of effective treatment during this time period may be attributed to the prioritization of treatment of pregnant women outlined in the Brazilian Ministry of Health initiative.[30]

Ineffective syphilis treatment coincided with the absence of prenatal care and a diagnosis of syphilis at delivery. Dual screening for HIV and syphilis has been found to be more cost effective than individual rapid tests.[31] Considering that low and middle income countries have been more resistant to aggressively test for both infections because of cost concerns, the money saved from dual testing may be an incentive for adjusting future public health strategies.[32] Our study demonstrated that women with HIV coinfection were more likely to receive ineffective treatment. A cross-sectional study of pregnant women receiving prenatal care in Tanzania showed that women screened earlier during the course of prenatal care presented at delivery with syphilis and HIV seroconversion as a result of reinfection.[9] Standardized HIV and syphilis testing throughout pregnancy in women diagnosed with syphilis during pregnancy may reduce maternal HIV seroconversion.

Research implications

Treatment effectiveness had no significant impact on whether newborns had symptomatic syphilis. Symptomatic illness at birth is a rare phenomenon.[33] Women with higher levels of education were at an increased risk of having symptomatic newborns. Owing to the low frequency of symptomatic newborns in our study, further studies are warranted to determine whether this is a true phenomenon. One possible explanation is that women with higher education have more severe first-time infections. The predictive relationship between higher VDRL titers ≥1:64 and symptomatic newborn syphilis was also shown in our study. Higher-titer syphilis infections are known to be associated with adverse outcomes such as symptomatic disease in the newborn.[29]

Strengths and limitations

Our study further delineates the profile of patients at risk for ineffective syphilis treatment at a large urban hospital in southern Brazil over an 11-year period, allowing us to identify future interventions. A study limitation was that the surveillance system only equated 1 visit to prenatal care, making it difficult to understand how different levels of prenatal care affect syphilis MTCT. Similarly, we did not have specific information regarding the time elapsed between treatment and the control of VDRL titers, making it difficult to discern incorrect or ineffective treatment from reinfection process. No longitudinal data were available for the evaluation of patient and partner contact tracing, and there were no records of maternal treatment during postnatal visits. Without long-term partner follow-up, we could neither identify whether partners were treated adequately nor fully quantify a patient's potential for reinfection from their partner.

Conclusions

Despite efforts to curb the syphilis epidemic, the rates of MTCT and

TABLE 4
Adjusted[a] multivariate analysis of predictors of adverse maternal and fetal outcomes in pregnant women with syphilis in Porto Alegre, Brazil, 2008 to 2018

Predictors of adverse maternal and fetal outcomes	Fetal loss at any time during pregnancy (N=246)	Low birthweight (N=272)	Preterm birth (N=251)	Congenital syphilis (N=1,218)	Symptomatic newborn (N=90)
ARR (95% confidence interval)					
Syphilis treatment					
Effective	ref	ref	ref	ref	ref
Ineffective	4.52 (2.35–8.69)	1.42 (1.05–1.92)	1.70 (1.22–2.38)	1.71 (1.59–1.84)	0.91 (0.55–1.53)
Age					
<20	ref	ref	ref	ref	ref
20–29	0.92 (0.71–1.20)	0.97 (0.73–1.29)	0.77 (0.60–1.00)	1.08 (1.02–1.15)	0.93 (0.54–1.60)
≥30	0.94 (0.70–1.27)	1.22 (0.85–1.75)	1.07 (0.80–1.44)	1.12 (1.04–1.21)	0.55 (0.25–1.19)
Self-identified race					
White	ref	ref	ref	ref	ref
Black		1.11 (0.88–1.40)			
Mixed, Indigenous, Asian, Other		1.12 (0.81–1.53)			
Education					
Primary	ref	ref	ref	ref	ref
Secondary		0.70 (0.51–0.96)		1.06 (1.00–1.12)	1.09 (0.58–2.04)
High school or higher		0.78 (0.55–1.10)		1.02 (0.96–1.09)	1.79 (1.01–3.18)
Year of diagnosis					
2008–2010	ref	ref	ref	ref	ref
2011–2013		0.96 (0.70–1.32)	0.83 (0.60–1.15)	0.97 (0.92–1.02)	1.06 (0.49–2.27)
2014–2016		1.05 (0.77 –1.44)	0.86 (0.63–1.17)	1.07 (1.02–1.13)	1.30 (0.62–2.74)
2017–2018		1.50 (1.01–2.24)	1.06 (0.76–1.49)	0.86 (0.79–0.93)	2.57 (1.14–5.79)
Number of gestations					
1 gestation	ref	ref	ref	ref	ref
2–4 gestations		0.98 (0.76–1.27)		0.93 (0.88–0.98)	0.80 (0.49–1.31)
≥5 gestations		1.00 (0.69–1.44)		0.89 (0.83–0.95)	1.38 (0.68–2.81)
Prenatal care					
Yes	ref	ref	ref	ref	ref
No	9.31 (3.77–23.0)	2.30 (0.82–6.41)	2.65 (0.59–12.0)	1.44 (1.17–1.76)	
Partner treatment					
No	ref	ref	ref	ref	ref
Yes	0.85 (0.54–1.36)	0.76 (0.55–1.04)	0.91 (0.66–1.26)	0.60 (0.55–0.65)	0.48 (0.27–0.86)
Time of syphilis diagnosis					
Prenatal care	ref	ref	ref	ref	ref
During delivery	3.08 (2.07–4.58)	1.06 (0.79–1.42)	1.09 (0.32–3.73)	0.93 (0.88–0.97)	1.43 (0.90–2.26)
Syphilis titers					
<1:8	ref	ref	ref	ref	ref
1:8–1:32	1.26 (0.99–1.60)	1.30 (1.00–1.70)	1.25 (0.95–1.64)	1.17 (1.12–1.22)	1.27 (0.81–1.97)

Swayze. Ineffective treatment and syphilis mother-to-child transmission. Am J Obstet Gynecol Glob Rep 2022. *(continued)*

TABLE 4
Adjusteda multivariate analysis of predictors of adverse maternal and fetal outcomes in pregnant women with syphilis in Porto Alegre, Brazil, 2008 to 2018 *(continued)*

Predictors of adverse maternal and fetal outcomes	Fetal loss at any time during pregnancy (N=246)	Low birthweight (N=272)	Preterm birth (N=251)	Congenital syphilis (N=1,218)	Symptomatic newborn (N=90)
≥1:64	1.45 (1.09–1.93)	2.92 (2.21–3.87)	3.13 (2.36–4.15)	1.11 (1.06–1.16)	2.04 (1.24–3.37)
Maternal HIV					
No	ref	ref	ref	ref	ref
Yes		0.91 (0.67–1.22)	0.93 (0.67–1.29)	0.99 (0.94–1.05)	
Interaction variable					
No prenatal care and ineffective treatment	0.18 (0.07–0.43)	0.65 (0.3–1.81)	0.47 (0.10–2.20)	0.65 (0.53–0.80)	0.54 (0.12–2.41)

ARR, adjusted risk ratio; *ref*, reference group.

[a] Covariates were established for each outcome using predictors that yielded a *P* value of <.20 in the crude analysis shown in Supplemental Table 1.

Swayze. Ineffective treatment and syphilis mother-to-child transmission. Am J Obstet Gynecol Glob Rep 2022.

associated adverse outcomes are on the rise in Brazil. A significant proportion of pregnant mothers with syphilis do not receive effective treatment, placing them at an increased risk of syphilis MTCT and HIV seroconversion in the future. New initiatives emphasizing effective syphilis treatment in both pregnant women and their partners may be pivotal in reducing congenital syphilis and future maternal HIV seroconversion. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2022.100050.

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