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Authors

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BRIEF REPORT

Adverse Neonatal Outcomes Associated With Maternal Sexually Transmitted Infections From a Public Health Clinic Cohort in Southern Brazil

Huan Vinh Dong,[1] Mei Leng,[2] Regis Kreitchmann,[3,4] Jeffrey D. Klausner,[5] Karin Nielsen-Saines,[6] and Nava Yeganeh[6]

[1]Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, California, USA, [2]Department of Medicine, Biostatistics at UCLA, Los Angeles, California, USA, [3]Irmandade da Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Brazil, [4]Federal University of Health Sciences, Porto Alegre, Brazil, [5]Division of Preventative Medicine, USC Keck School of Medicine, Los Angeles, California, USA and [6]Division of Pediatric Infectious Diseases, David Geffen School of Medicine, Los Angeles, California, USA

Pregnant women at public medical centers in Porto Alegre, Brazil, were recruited for a study on screening and treatment of sexually transmitted infections (STIs). STIs were detected in 79 (23%) of 350 pregnant women and were found to be associated with infant low birth weight (adjusted odds ratio 5.8; 95% confidence interval 1.9-18).

Key words. adverse infant birth outcomes; congenital syphilis; low birth weight; pregnancy; sexually transmitted infection.

Sexually transmitted infections (STIs) adversely impact and disproportionately affect women of reproductive age and their newborns [1]. Though bacterial and protozoan STIs are curable with appropriate antimicrobials, these infections are associated with significant maternal morbidity and adverse neonatal outcomes such as stillbirth, low birth weight (LBW), and premature birth [2]. Approximately 50% of infants born to mothers with untreated genital *Chlamydia (C.) trachomatis* or *Neisseria (N.) gonorrhoeae* infection can become infected with conjunctivitis or pneumonia, Maternal infection also increases the infant's risk of vertical HIV acquisition [2]. Infants with congenital syphilis can have multi-organ failure, with serious complications in the skeletal, pulmonary, and central nervous systems, which can result in death [3].

STI burden varies geographically for pregnant women, with *N. gonorrhoeae* prevalence ranging from 1.2% in Latin America to 4.6% in Southern Africa; syphilis ranging from 1.1% in Asia to 6.5% in South Africa; *C. trachomatis* ranging from 0.8% in Asia to 11.2% in Latin America; and *T. vaginalis* ranging from 3.9% in Latin America to 24.6% in Southern Africa [4]. In Brazil, pregnant women are screened for HIV, syphilis, and hepatitis B and C per Brazilian Ministry of Health and World Health Organization (WHO) guidelines. Infections from *C. trachomatis, N. gonorrhoeae*, or *T. vaginalis* are often treated based on reported symptoms instead of diagnosing the etiology, which has poor sensitivity and specificity [5]. Our report aimed to elucidate associations between confirmed maternal STIs and neonatal birth outcomes.

DATA COLLECTION

Prospective demographic and laboratory data from 400 pregnant women enrolled in an STI screening protocol between September 2018 and November 2019 at the Santa Casa Hospital and 10 surrounding public prenatal clinics in the city of Porto Alegre, south Brazil, were collected as previously described [6]. All women (and their participating male partners) diagnosed with STIs were offered treatment within 24 hours of diagnosis, although there was no "test of cure" performed at the end of treatment or before delivery [7]. Infant birth data (gestational age, birth weight, length, head circumference, sex, delivery modality, and physical examination) were collected from health system records until the last enrolled patient delivered (February 2020).

Statistical Analysis

The final study size was a sample of convenience based on the availability of mother-infant dyad information [6]. Primary endpoints for this report were adverse infant outcomes (prematurity, LBW, or small for gestational age [SGA]).

Women 35 years of age or older were categorized as advanced maternal age (AMA). For syphilis infection, in the presence of a positive treponemal rapid test, venereal disease research laboratory (VDRL) titers of at least 1:1 or "indeterminate" were considered positive, whereas positive treponemal results in the presence of a non-reactive VDRL were considered negative. LBW was defined as weighing less than 2500 g at birth. Preterm delivery was defined as delivery before 37 weeks of gestational age. LBW/SGA/preterm composite outcome category was included to address the potential confounding effects of prematurity on infant birth weight. SGA was defined using

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Corresponding Author: Nava Yeganeh, MD, MPH, 10833 Le Conte Ave. MDCC22-442, Los Angeles, CA 9009-1752, USA. E-mail: nyeganeh@mednet.ucla.edu.

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the INTERGROWTH-21st criteria, weight-for-age *Z*-score of less than −1.28, calculated using "igrowup"-package for STATA.

Two-sample *T*-test and Pearson chi-square or Fisher's exact test were used to compare mother-baby parameters in those with laboratory-confirmed STI when compared with those testing negative. Previously reported independent variables (age, ethnicity, alcohol use, drug use, educational attainment, sexual activity during pregnancy, presence of urogenital symptoms, and mode of delivery) [6] were used to assess the relationship of maternal factors with newborn baby outcomes (prematurity, LBW, infant sex, and physical examination findings). Variables trending toward significance ($P < .1$) to an adverse infant outcome were included in a multivariate logistic regression model to adjust for any interactions. All computations were done using SAS 9.4 and Stata 14.2.

RESULTS

A total of 350 pregnant women-infant pairs were included in the final analysis; 50 pairs were excluded due to insufficient infant birth information because of delivery at an outside institution or loss to follow-up.

Maternal characteristics and infant outcomes are summarized in **Table 1**. Of the 79 women who tested positive for an STI, 33 (9.4%) tested positive for *C. trachomatis*, 32 (9.4%) for syphilis, 19 (5.4%) for *T. vaginalis,* 7 (0.2%) for HIV, and 4 (1.1) for *N. gonorrhoeae*.

Analyses are summarized in **Table 2**. Both AMA and maternal STI were significantly associated with increased odds of LBW in multivariate regression (adjusted odds ratio [aOR] 5.0, 95% confidence interval [CI] 1.5-17 and aOR 5.8, 95% CI 1.9-18, respectively). AMA also remained associated with increased odds of SGA (aOR 2.7; 95% CI, 1.2-6.1) as well as any adverse infant outcome (LBW, SGA, or prematurity) (relative risk [RR] 2.0; $P < .03$, aOR 2.5, 95% CI, 1.2-5.4). Infant male sex was protective for prematurity (RR 0.4, $P < .05$, aOR 0.35, 95% CI 0.14-0.88) as well as for any adverse infant outcomes (RR 0.51, $P < .01$, aOR 0.4, 95% CI 0.23-0.83). In this cohort, C-sections were not associated with LBW (RR 2.4, aOR 2.5, 95% CI 0.86-7.4) or preterm delivery (RR 2.2, aOR 2.0, 95% CI 0.8-4.8).

DISCUSSION

Our longitudinal prospective study involving 350 pregnant women focused on the prevalence of STIs and associated infant outcomes. This was a population of young women with self-reported low levels of education and a high nonwhite representation in a city in south Brazil, where most of the population is white.

Compared with those with laboratory-confirmed STIs, nearly twice as many women (39%) reported urogenital symptoms, which potentially represented symptoms from urinary tract infections, vaginitis, STIs such as Herpes Simplex Virus or *Ureaplasma urealyticum* not specifically tested for in our study, or noninfectious urinary changes associated with pregnancy. More than half of the women (65%) in our study who tested positive for any STI reported to be asymptomatic. Reports from multiple regions indicate that urogenital symptoms are poor

Table 1. Maternal Characteristics and Neonatal Birth Outcomes (N = 350)

Maternal Characteristics	Mean Value	Standard Deviation
Maternal age at enrollment (years)	27	SD ± 6
Gestational age at enrollment (weeks)	26	SD ± 10
	N	%
White Race	190	54
Alcohol use during pregnancy	95	27
Drugs use during pregnancy	32	9.1
Education (completed elementary school)	230	66
Symptoms of STI (Yes)	137	39
Negative STI tests	103	30
Diagnosed with STI (Yes)	79	23
Asymptomatic	51	15
One STI	68	19
Two concurrent STIs	6	1.7
Three concurrent STIs	5	1.4
Diagnosed GA 0-12 weeks	10	2.9
Diagnosed GA 13-28 weeks	36	10
Diagnosed GA 29-40 weeks	30	8.6
Neonatal Birth Outcomes	**Mean Value**	**Standard Deviation**
Age/gestational age (weeks)	38.5	±1.7
Birth weight (g)	3260	±501
Length (cm)	48	±2.5
Head circumference (cm)	34	±1.8
	N	%
Female infant	166	47
LBW	17	4.9
Small for gestational age	42	12
Preterm (total, GA <37 weeks)	24	6.9
Late preterm (GA 34-36 weeks)	21	6
Early preterm (GA 32-34 weeks)	2	0.6
Very early preterm (GA <32 weeks)	1	0.3
Cesarean delivery	15	4.3
Vaginal delivery	9	2.6
LBW or SGA or Preterm	50	14
Stillborn	2	0.6
Cesarian Delivery	147	42
Abnormal physical exams after birth[a]	38	11
Jaundice	17	4.9
Respiratory distress	13	3.7
Neonatal sepsis	7	2
Congenital cardiac anomaly	4	1.1
Corpus callosum agenesis	1	0.2
Obstructive uropathy	1	0.2
Neonatal abstinence syndrome	1	0.2
Petechiae	1	0.2
Meconium aspiration	1	0.2

Low birth weight (LBW) defined as less than 2500 g; Small for gestational age (SGA) = -1.28 *Z*-score for sex/gestational age.

GA, gestational age.

[a]Some infants were reported by examining pediatrician to have multiple abnormal findings: 3 had jaundice and respiratory distress, 1 had jaundice and cardiac anomaly, 1 with sepsis and cardiac anomaly, and 4 with sepsis and respiratory distress/dysfunction.

Table 2. Relative Risks and Adjusted Odds Ratios for Associations Between Maternal or Birth Characteristics and Infant Birth Outcomes (N = 350)

		Infant Birth Outcome							
		LBW		SGA		Preterm		LBW or SGA or Preterm	
	N *(%)*	RR (*P*-value)	aOR (95% CI)	RR (*P*-value)	aOR (95% CI)	RR (*P*-value)	aOR (95% CI)	RR (*P*-value)	aOR (95% CI)
Maternal age >35 years	48 *(14)*	**3.3 (.021)**	**5.0 (1.5-17)**	1.9 (.055)	**2.7 (1.2-6.1)**	2.5 (.059)	2.7 (1.0-7.4)	**2.0 (.025)**	**2.5 (1.2-5.4)**
Nonwhite Ethnicity	160 *(46)*	1.7 (.32)	—	1.1 (.82)	—	1.0 (1.0)	—	1.1 (.72)	—
Low education	120 *(34)*	1.7 (.30)	—	1.47 (.24)	—	0.97 (1.0)	—	1.2 (.56)	—
Alcohol use	95 *(27)*	0.35 (.17)	—	0.71 (.36)	—	1.1 (.82)	—	0.83 (.54)	—
Drug use	32 *(9.1)*	1.5 (1.0)	—	1.3 (1.0)	—	2.3 (.71)	—	1.5 (.59)	—
Maternal STI(any)	78 *(22)*	**3.0 (.032)**	**5.8 (1.9-18)**	1.7 (.089)	2.1 (1.0-4.3)	1.1 (.80)	—	1.3 (.32)	—
Infant male sex	179 *(52)*	0.72 (.61)	—	**0.56 (.050)**	0.52 (0.26-1.0)	**0.4 (.050)**	**0.35 (.14–.88)**	**0.51 (.014)**	**0.4 (.23–.83)**
Cesarean Delivery	149 *(43)*	2.5 (.078)	2.5 (.86-7.4)	1.1 (.72)	—	2.2 (.055)	2.0 (.80-4.8)	1.2 (.44)	—

LBW, low birth weight; SGA, small for gestational age; STI, sexually transmitted infection; RR, relative risk; aOR, adjusted odds ratio; CI, confidence interval.

"—" = not included in multivariate model. Bolded numbers represent significant *P*-value or CIs. For "Drug use" = only Marijuana and Cocaine were reported in this study population. Low education is defined as having not completed elementary school.

predictors of laboratory-confirmed STIs, and previous analysis suggests that syndromic diagnosis of STIs during pregnancy is not well correlated with laboratory-confirmed diagnosis [5, 6].

Prevalence of a cesarean delivery in our cohort was 43%, which, despite being high, is still below the Brazilian national average of 55%, likely reflecting the lower socioeconomic and education status of women in our study [8]. Iatrogenic prematurity is a concern for populations with high C-section rates but was not observed in our cohort [8].

Like other reports, we found that AMA and maternal STI significantly correlated with one or more adverse outcomes in our univariate analysis [9]. Female sex was more significantly associated with adverse infant outcomes, which is contrary to general studies demonstrating that boys tend to have worse birth outcomes [10]. After logistic regression, AMA was significant for all adverse outcomes of interest including LBW and SGA, and the "any adverse outcome" category, which is congruent with other reports from Brazil [9]. Given the association between AMA and LBW, our lower prevalence of LBW when compared with regional surveys may underscore a mostly young cohort of women.

The presence of any laboratory-confirmed maternal STI demonstrated the strongest association with LBW, with nearly a 6-fold increase. Few studies have evaluated these outcomes, though one report in a cohort of HIV-positive pregnant women found that *C. trachomatis* and *N. gonorrhoeae* were more significantly associated with adverse infant outcomes than either mono-infection [11]. Recent systematic reviews highlight this association between STIs and adverse infant outcomes, including LBW and prematurity [2, 12]. Though precise pathogenesis is unclear, it is thought that infection with accompanying cytokine release causes a local inflammatory response that adversely impacts placental integrity and function [4]. Some studies describe homology between human and chlamydial heat-shock proteins, hypothesized to be involved with premature rupture of membranes, miscarriage, preterm labor, fallopian tube damage, and embryonic rejection [2].

Furthermore, studies have shown reductions in LBW and SGA when pregnant women were treated for *C. trachomatis* [13]. Women in our study received treatment for their infection when detected on screening; however, a strong risk still remained for their infants. Most women were in their second or third trimesters at the time of enrollment; perhaps earlier detection and treatment could have improved outcomes. Furthermore, having an STI could represent a constellation of confounding factors not explored in our study, including increased risk-taking behaviors, limited health-seeking behaviors, limited healthcare access, or healthcare infrastructural limitations for STI screening and treatment. Though our study did not capture sufficient events to stratify analysis by each STI, we hope to evaluate this in future studies.

There were 2 infant deaths: one from complications of Trisomy 13 and the other of unknown cause. We were unable to draw

any statistically relevant conclusions regarding those tragic outcomes. Urogenital symptoms were twice as often reported than confirmed STIs; thus, there could be other processes impacting infant morbidity such as urinary tract infections or other urogenital infections. The confounding impact of comorbidities such as gestational hypertension, metabolic derangements, pre-eclampsia, and other conditions affecting maternal-infant outcomes was unavailable for analysis. Although well-validated modalities to identify pathogens with high sensitivity and specificity were used, we cannot rule out false positives or false negatives, which may impact the final analyses [14].

CONCLUSION

In a population of mostly nonwhite, young women-infant dyads in a low-income setting in Brazil, maternal STI positivity was a strong predictor of LBW by nearly 6-fold. Even when mothers were screened and treated for STIs, a statistically significant risk for LBW was observed.

Notes

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Potential conflicts of interest. Past 12 months, J. D. K. has received consulting fees from Abbott, Cepheid, Curative, Danaher, Roche, Talis Bio, and Visby Medical. The remaining authors reported no conflicts of interest.

All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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