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CLINICAL ARTICLE

Gestational syphilis and stillbirth in Latin America and the Caribbean



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ABSTRACT

Objective: To measure the association between gestational syphilis and stillbirth in Latin America and the Caribbean. **Methods:** In a retrospective study, data on stillbirth and gestational syphilis extracted from the Sistema Informático Perinatal database were analyzed for deliveries in 11 countries between January 1, 2009, and December 31, 2012. Potential confounders were examined, and binary logistic regression analysis was performed to assess the association between gestational syphilis and stillbirth. **Results:** Among 368 151 deliveries, 3875 (1.1%) were by women with a positive syphilis test, and 1461 (0.4%) were stillbirths. Among the stillbirths, 29 (2.0%) were delivered by women with a positive syphilis test. After controlling for country, congenital anomalies, gestational age at labor, maternal age, and previous stillbirth, gestational syphilis was significantly associated with stillbirth (odds ratio 1.88, 95% confidence interval 1.25–2.83; $P = 0.002$). **Conclusion:** Gestational syphilis contributes to stillbirth in Latin America and the Caribbean. Interventions targeting gestational syphilis are highly cost-effective and should be implemented across the region.

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1. Introduction

WHO estimates that 1.36–2 million pregnancies are affected by syphilis every year [1–3], of which 50%–80% will result in adverse outcomes without proper treatment [2,4–6]. Prominent among these outcomes is stillbirth, which occurs in 25%–40% of cases [4–6]. Globally, syphilis is the main cause of more than 212 000 stillbirths annually [2,3,7], and, in areas with a high prevalence of syphilis, as many as half of all stillbirths can be attributed to this infection [5,8].

Worldwide, Latin America and the Caribbean (LAC) has the highest incidence of syphilis, and accounts for up to 25% of the 2 million annual cases of gestational syphilis [1,9]. The prevalence of gestational syphilis in LAC varies from 0.08% to 7.0% by country [2,10]. Every year, an estimated 100 000 stillbirths in the region are attributable to congenital syphilis, which is defined as a neonate delivered to a mother who was untreated or inadequately treated for syphilis during pregnancy, or a neonate with a positive syphilis test [1,10,11].

The Pan American Health Organization (PAHO) approved the Regional Elimination of Congenital Syphilis Plans of Action in 1995 and 2010, in which elimination is defined as an incidence of 0.5 or fewer cases of congenital syphilis, including stillbirths, per 1000 deliveries [1,9,10]. Elimination of congenital syphilis is possible with proper treatment—one dose of penicillin is almost 100% effective at preventing syphilis-associated adverse outcomes in pregnancy [2,5,7,9,12]. Moreover, the cost-effectiveness of prenatal syphilis screening

and treatment has been shown repeatedly and is considered one of the most cost-effective interventions available [2,4,5,10,12].

Nevertheless, syphilis-attributable stillbirths are still occurring in LAC. There are few studies on the relationship between gestational syphilis and stillbirth in LAC. Two previous studies in the region showed that the risk of stillbirth increases with exposure to gestational syphilis: one [13] reported that women with a positive syphilis test in Jamaica have a 3.04-fold increased odds of fetal death, whereas the other [14] indicated that women with a positive syphilis test in LAC countries have a 2.41-fold higher risk of fetal death. Generally, research in LAC has focused on the prevalence of gestational syphilis and calls to action to test and treat pregnant women [14], rather than examining factors that influence the relationship between gestational syphilis and stillbirth, and only one study has approached the problem at the regional level [13,15–19].

Sistema Informático Perinatal (SIP) is a PAHO/WHO database, developed by the Latin American Center for Perinatology and Human Development (CLAP), which includes a set of standardized instruments designed for obstetric and neonatal health services [14]. Every entry in SIP corresponds to a birth record containing data on maternal demographics; family and obstetric history; prenatal visits, delivery, and postpartum details; and discharge information for both the mother and neonate. Information is prospectively recorded at the clinic level during prenatal, delivery, and postnatal care. In addition to recording clinical data, SIP facilitates the electronic storage of information for further processing and analysis for managerial, epidemiologic, and other purposes.

The primary aim of the present study was to use SIP data for deliveries occurring from 2009 to 2012 to measure the association between gestational syphilis and stillbirth at the regional level, with adjustments

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for potential confounding factors. A secondary aim was to identify high-risk groups through tests for confounders, mediators, and effect measure modifiers, to focus future gestational syphilis interventions both in LAC and globally.

2. Materials and methods

In a retrospective study, SIP data on stillbirth and gestational syphilis were analyzed for deliveries recorded in LAC countries between January 1, 2009, and December 31, 2012. Because data were extracted via a computer-generated identification code that was not linked in any way to patients, the study was exempt from institutional review board approval and informed consent was not needed.

Use and coverage of SIP varies within the LAC region and within countries. Data collection and entry are done at the institutional level, and data are reported to CLAP through the respective national ministry of health. Deliveries in 15 LAC countries that use SIP and share their data with CLAP were considered for the present study. Of these countries, four did not have syphilis data recorded for the time period of the study and so were excluded. The 11 countries included in our study were: Argentina, Bolivia, Colombia, Ecuador, Guyana, Haiti, Honduras, Nicaragua, Paraguay, El Salvador, and Uruguay. The countries were randomly labeled with letters to maintain confidentiality because the study aim was not to compare specific countries, but to carry out a regional analysis of the relationship between gestational syphilis and stillbirth.

For the analysis, data were extracted from the SIP records on syphilis test results, delivery outcome, and potential confounders that might biologically influence the relationship between gestational syphilis and stillbirth (Box 1). Records that were not complete were excluded from the study.

The definition of stillbirth varies by study [5,8,12,13,15]. In line with recent studies [5,12], for the present analysis, stillbirth was defined as the neonate being dead at delivery. Gestational syphilis was defined as a positive result on the mother's most recent prenatal non-treponemal or treponemal syphilis test [19]. The results from at least one syphilis test for the mother during pregnancy were available for all included deliveries. Traditionally, syphilis screening has been carried out in laboratories with non-treponemal tests, the results of which can take a

few weeks to be delivered in rural areas [20]. New point-of-care (POC) treponemal tests react to antibodies for *Treponema pallidum*, which usually remain in an individual's system even after successful treatment and require only 20 minutes for detection [20]. Use of a treponemal or non-treponemal syphilis test, and what constituted a positive response for gestational syphilis, was determined at the institutional level.

Among the SIP variables analyzed, "previous stillbirth" indicated that the mother had one or more previous stillbirths. Congenital anomalies were classified at the institutional level in SIP as "no," "minor," or "major," and were analyzed as an ordinal variable. Both gestational age at labor and maternal age were analyzed as continuous variables, and then were grouped in accordance with international norms [21,22] for comparison.

Statistical analyses were performed with SPSS version 17.0 (SPSS Inc, Chicago, IL, USA). After extraction of delivery outcome, gestational syphilis exposure, and all potential confounders from SIP, an unadjusted binomial logistic regression analysis was carried out for gestational syphilis and stillbirth. Each potential covariate was then analyzed separately with syphilis and delivery outcome in unique binary logistic regression models.

Syphilis and all variables that were significantly associated with stillbirth when controlling for syphilis in their respective binary logistic regression model were then analyzed in a larger model, which also adjusted for syphilis exposure status. Covariates that were not significant in the larger model were excluded, resulting in a final model. All independent variables in the final model were tested for multicollinearity with linear regression by using dummy variables for all nominal variables.

In the final model, confounding among covariates not thought to be in the causal pathway (all but gestational age at labor) was checked with Pearson χ^2 tests of the covariate with syphilis and birth outcome separately, and the crude and Mantel-Haenszel odds ratios (ORs) were compared. Covariates that were not confounders, but also not in the causal pathway, were examined for statistical evidence of effect measure modification with calculations of the difference in the syphilis–stillbirth relationship across strata of the covariate with the beta for the interaction term (covariate*syphilis) in a binary logistic regression, in which syphilis, the covariate, and the interaction term are the independent variables. For the variable thought to be in the causal pathway—

Box 1

Covariates tested for significance in the relationship between gestational syphilis and stillbirth.

Active smoker	Urinary tract infection	Passive smoker
Maternal age	Drug use	Planned pregnancy
Alcohol use	Education	Pregnancy-induced hypertension
Rubella vaccine	Ethnic origin	Presentation at labor
Group B streptococcus carrier	Gestational age at labor	Previous body mass index
Tetanus vaccine	Hemorrhage	Previous pregnancies
Bacteriuria	Family history of diabetes	Previous live births
Birth weight	Maternal history of diabetes	Previous stillbirths
Cervix check	Family history of eclampsia	Premature rupture of membranes
Chagas disease	Maternal history of eclampsia	Rupture of membranes <37 wk
Chronic hypertension	Maternal history of heart disease	Syphilis test treponemal
Civil status	Family history of hypertension	Syphilis test non-treponemal
Companion at delivery	Maternal history of hypertension	Mother lives alone
Companion at labor	Maternal history of kidney disease	Three consecutive spontaneous abortions
Congenital defect	Family history of preeclampsia	Toxoplasmosis
Contraceptive failure	Maternal history of preeclampsia	Violence to mother
Country	History of violence toward mother	Treated for syphilis
Chorioamnionitis infection	HIV infection	Partner treated for syphilis
Diabetes	Hospitalized during pregnancy	Week of syphilis test non-treponemal
Eclampsia	Intrauterine growth restriction	Week of syphilis treatment
Heart disease	Literate	Week of syphilis test treponemal
Kidney disease	Multiple pregnancy	
Pre-eclampsia	Number of antenatal visits	

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