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SECTION: ORIGINAL ARTICLE

Impact of implementation of rapid treponemal testing in prenatal care on incidence and severity of congenital syphilis

Impacto da implementação do teste treponemal rápido no pré-natal na incidência e na gravidade da sífilis congênita

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Abstract

Objective: to compare the incidence of congenital syphilis (CS) before and after the introduction of the rapid treponemal test and to determine whether there were changes in the clinical characteristics and severity of this disease.

Methods: a cross-sectional study was conducted in the community of Viamão, Brazil. Reported cases of CS identified by maternal screening with a nontreponemal test (group I) and those identified by screening with a rapid treponemal test (group II) were compared. Data were obtained from the Notifiable Diseases Information System (SINAN).

Results: 302 cases of CS were detected in the sample, with an incidence of 7.7 ‰ live births (80 / 10,369) in group I and 23.2 ‰ (222 / 9,538) in group II (p=0.000). After the introduction of the rapid treponemal test, there was a slightly higher proportion of pregnant women (1 (2.0 %) x 14 (8.8 %); p = 0.12) and their sexual partners (6 (11.8 %) x 38 (24.0 %); p = 0.12) who received adequate treatment during prenatal care, there were fewer newborns with clinical manifestations (11 (16.7%) x 12 (6. 2%); p = 0.02) and proven or highly probable CS (16 (24.2%) x 29 (14.8%); p = 0.10). The incidence per group of proven or highly probable CS was 1.5 and 3.0 ‰ live births, and possible CS was 4.7 and 16.6 ‰ (p = 0,10), respectively.

Conclusion: screening with the rapid treponemal test was associated with a slight improvement in maternal management and fewer clinically affected neonates, although the incidence of CS increased significantly. This raises doubts about the quality of prenatal care for gestational syphilis.

Keywords: congenital syphilis, congenital infections, epidemiology, diagnosis, treatment.

Resumo

Objetivo: comparar a incidência de sífilis congênita (SC) antes e depois da introdução do teste rápido treponêmico e verificar alterações nas características clínicas e na gravidade dessa doença.

Métodos: foi realizado um estudo transversal na cidade de Viamão, Brasil. Foram comparados os casos notificados de SC identificados pela triagem materna com teste não treponêmico (grupo I) e aqueles identificados pela triagem com teste treponêmico rápido (grupo II). Os dados foram obtidos no Sistema de Informação de Agravos de Notificação (SINAN).

Resultados: foram detectados 302 casos de SC na amostra, com incidência de 7,7‰ nascidos vivos (80/10.369) no grupo I e 23,2‰ (222/9.538) no grupo II (p=0,000). Após a introdução do teste treponêmico rápido, houve uma proporção ligeiramente maior de gestantes (1 (2,0%) x 14 (8,8%); p = 0,12) e de seus parceiros sexuais (6 (11,8%) x 38 (24,0%); p = 0,12) que receberam tratamento adequado durante o pré-natal, houve menos recém-nascidos com manifestações clínicas (11 (16,7%) x 12 (6,2%); p = 0,02) e SC comprovada ou altamente provável (16 (24,2%) %) x 29 (14,8%). A incidência por grupo de SC comprovada ou altamente provável foi de 1,5 e 3,0‰ nascidos vivos, e de SC possível foi de 4,7 e 16,6‰ (p = 0,10), respectivamente.

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Conclusão: a triagem com teste treponêmico rápido foi associada a uma ligeira melhora no manejo materno e a menos neonatos clinicamente afetados, embora a incidência de SC tenha aumentado significativamente. Isso levanta dúvidas sobre a qualidade da assistência pré-natal para sífilis gestacional.

Palavras-chave: sífilis congênita, infecções congênitas, epidemiologia, diagnóstico, tratamento.

Introduction

Syphilis is a chronic, systemic, preventable, and treatable infectious disease that has challenged humanity for centuries. It is caused by the spirochete bacterium Treponema pallidum and is transmitted by sexual contact, transplacentally and, rarely, by transfusion of blood products. Treponemal infection during pregnancy has major implications for fetal health, family life and social costs. Early diagnosis and timely treatment of pregnant women with penicillin G are the most effective measures to prevent vertical transmission (1-4).

The classic approach to prenatal syphilis screening, and the only one used in Brazil until 2012, consists of serological screening of pregnant women with a nontreponemal test. In Brazil, the Venereal Disease Research Laboratory (VDRL) test is used, and all cases must be confirmed by a serum treponemal test, usually the Fluorescent Treponemal Antibody Absorption Test (FTA-ABS), except for those pregnant women with a prior history of syphilis (1, 4-8). Since 2013, the reverse-sequence screening protocol has been progressively implemented by the Ministry of Health. It consists of a rapid treponemal point-of-care test (POCT) (immunochromatography lateral flow assays) on capillary blood samples, followed by VDRL for monitoring of treatment response when positive. In pregnant women with no previous history of syphilis and at risk of loss to follow-up, guidelines recommend immediate treatment when a rapid treponemal test is positive (4, 6, 8, 9).

Reverse-sequence prenatal screening for syphilis has a favorable cost-benefit ratio, and its implementation was designed to improve the quality of care and expand access to timely diagnosis for pregnant women and their sexual partners (5, 10). While the nontreponemal test typically requires two steps to provide a conclusive result, the treponemal POCT can provide results in a single step, resulting in a quicker response time. However, concurrently with this gradual implementation, there was a substantial increase in the incidence of congenital syphilis (CS) in Brazil, consistent with global trends (8, 11-14). To date, it is unclear whether the change in screening algorithm has contributed in any way to the increased incidence of CS.

Early detection of syphilis in pregnant women is required to prevent CS in newborns but laboratory resources are often limited in many parts of the world. Thus, a syphilis POCT for use in pregnant women is a potential solution to this problem. The present study aimed to compare the incidence of CS in periods before and after the implementation of syphilis POCT during prenatal care and to assess whether there were modifications in the clinical-laboratory characteristics and severity of neonates with CS.

Methods

A cross-sectional study of all cases of CS reported in the municipality of Viamão was conducted in two periods: 2012 to 2014 (group I) and 2016 to 2018 (group II). Viamão is in the metropolitan region of Porto Alegre, Rio Grande do Sul, the southernmost state of Brazil, and has an estimated population of 253,000, a municipal human development index of 0.717, and a predominantly white population (15).

Data were obtained from the Notifiable Diseases Information System (SINAN), which is provided by the Municipal Health Department, and maintained by the Information Technology Department of Public Health Care System (DATASUS). Cases diagnosed after the neonatal period, and pregnancies without prenatal care were excluded.

Group I corresponded to the period during which conventional maternal screening was performed, i.e., initial use of a nontreponemal test (VDRL), whereas group II corresponded to the period during which reverse-sequence screening

(syphilis POCT first) was already implemented. Cases reported in 2015 were not included in the study, as the year represented a transition between the two screening methods.

The outcome variable was the diagnostic classification of CS, adapted from the U.S. Centers for Disease Control and Prevention (CDC) protocol (1, 3, 8). The following CS classifications were considered for newborns whose mothers had positive serologic tests for syphilis during pregnancy:

I) Proven or highly probable CS: a) physical examination abnormal and consistent with CS; or b) serum VDRL titer at least fourfold the maternal level; or c) VDRL-positive in CSF; or d) radiographic changes in long bones consistent with CS.

II) Possible CS: normal physical examination, serum VDRL equal to or less than fourfold the maternal titer, negative VDRL in CSF sample, and no radiographic changes in the long bones, but born to a mother who: a) received no treatment; or b) was treated with inadequate doses of penicillin G or was treated with an antibiotic other than penicillin G; or c) started treatment less than 4 weeks before delivery; or d) treatment response has not been demonstrated by a fourfold decrease in the VDRL titer; or e) has no documentation of having received treatment.

III) CS less likely: normal physical examination and serum VDRL equal to or less than fourfold the maternal titer and both of the following criteria: a) mother was treated during pregnancy with penicillin G, in doses appropriate for the stage of infection, and treatment was initiated more than 4 weeks before delivery; and b) mother has no evidence of reinfection or relapse.

IV) CS unlikely: normal physical examination and serum VDRL titer equal to or less than fourfold the maternal titer and both of the following criteria: a) adequate maternal treatment before pregnancy; and b) low and stable maternal VDRL (≤1:2) during pregnancy and at delivery.

The doses of benzathine penicillin G considered adequate for the treatment of pregnant women were 2,400,000 IU in syphilis of less than one year's duration and 2,400,000 IU in three weekly doses for a total of 7,200,000 IU in syphilis of more than one year's duration or unknown duration, and the treatment regimen was initiated ≥28 days before delivery (1, 3, 8, 9).

Maternal variables of interest were age, ethnicity, educational level, VDRL and treponemal serologic test results during antenatal care and at delivery, and treatment history (own and partner's). Neonatal variables were reported clinical and radiographic manifestations, serum, and cerebrospinal fluid (CSF) VDRL, treatment, and outcome.

Categorical variables were expressed as absolute frequencies and percentages, and continuous variables, as mean and standard deviation (when normally distributed) or as median and interquartile range (when asymmetrically distributed). Statistical analyses were performed with the chi-square test or Fisher's exact test to compare proportions, Student's *t*-test to compare normally distributed quantitative variables, and the Mann–Whitney *U* test for asymmetrically distributed variables. The significance level was set at $p \leq 0.05$. Data were entered into Microsoft Excel and analyzed in IBM SPSS 26.0.

The study protocol was submitted to the Brazilian National Health Council *Plataforma Brazil* registry and approved by the Pontifical Catholic University of Rio Grande do Sul Research Ethics Committee (Opinion number 4,113,401). Given the retrospective nature of the study and use of secondary data, informed consent was waived, and the authors instead signed a data use and confidentiality agreement. This study was conducted in accordance with Brazilian National Health Council Resolution No. 466 of December 12, 2012 (on research involving human subjects) and followed all provisions of the World Medical Association 1994 Declaration of Helsinki and its subsequent revisions.

Results

There were 10,369 live births in the municipality of Viamão from 2012 through 2014 and 9,538 from 2016 through 2018. During these periods, 302 cases of CS were reported (80 in group I and 222 in group II). The incidence of CS was 7.7/1,000

live births in group I and 23.2 / 1,000 live births in group II (p = 0.000).

Overall, 40 reports were excluded: 39 pregnancies without antenatal care (14 in group I and 25 in group II), and 1 case due to missing data in the Notifiable Diseases Information System (group II). Thus, the final sample size consisted of 262 cases of CS: 66 in group I and 196 in group II. The sample power was 80.1 %.

Table 1 presents maternal sociodemographic variables and the dates of syphilis screening and treatment for both mothers and their sexual partners. The mean maternal age was 23.2 ± 6.4 years in group I and 24.6±6.3 years in group II (p = 0.11). A total of 154 (83.2 %) pregnant women were aged 20 to 30 years. There were no illiterate mothers in the entire sample. The median (IQR) of maternal VDRL at delivery was 1:8 (1:2-1:16) and was the same in both periods (p = 0.26). Of 212 untreated sexual partnerships (group I = 59; group II = 153), in 164 (77.4 %) cases (45 (76.3 %) in group I and 119 (77.8 %) in group II, p = 0.86), the pregnant woman was diagnosed with syphilis during prenatal care.

TABLE 1. Data on maternal sociodemographic profile, time of diagnosis of gestational syphilis, maternal treatment and sexual partnership and maternal syphilis screening at birth.

Variable, n (%)	**Group I** (n = 66)	**Group II** (n = 196)	**Total** (n = 262)	**p**[a]
Skin color				
White	46 (75.4)	115 (65.4)	161 (67.9)	0.16
Black	11 (18.0)	30 (17.0)	41 (17.3)	
Brown	4 (6.6)	31 (17.6)	35 (14.8)	
Total	61 (100)	176 (100)	237 (100)	
Educational attainment				
Primary (4th-grade level or less)	12 (20.7)	4 (2.6)	16 (7.5)	0.001
Primary (5th- to 8th-grade level)	25 (43.1)	81 (52.2)	106 (49.8)	
Secondary	21 (36.2)	64 (41.3)	85 (39.9)	
Higher	0 (0.0)	6 (3.9)	6 (2.8)	
Total	58 (100)	155 (100)	243 (100)	
Maternal diagnosis				
Prenatal	51 (72.3)	158 (80.6)	209 (79.8)	0.60
At delivery	15 (22.7)	38 (19.4)	53 (20.2)	
Maternal treatment in prenatal care[b]				
Appropriate	1 (2,0)	14 (8.8)	15 (7.2)	0,12
Inappropriate	42 (82,3)	115 (72.8)	157 (75.1)	
Not performed	7 (13.7)	17 (10.8)	24 (11.9)	
Ignored	1 (2,0)	12 (7.6)	13 (6,2)	
Partner treated in prenatal care[b]	6 (11.8)	38 (24.0)	44 (21.0)	0.074
Maternal treponemal test at delivery	52 (78.8)	158 (80.6)	210 (80.1)	0,97

[a]Chi-square test or Fisher's exact test.
[b]percentage calculated from the total number of maternal diagnoses in prenatal care.

Table 2 presents data on laboratory and radiographic investigations, clinical manifestations and treatment of the newborn and the diagnostic classification of CS. The median VDRL at birth of newborns in group I was 1:8 (IQR = 1:2-1:4) and in group II it was 1:8 (IQR = 1:2-1:8) (p = 0.18).

TABLE 2. Data on laboratory and radiographic evaluation, clinical manifestations and treatment of exposed neonates and classification of CS cases.

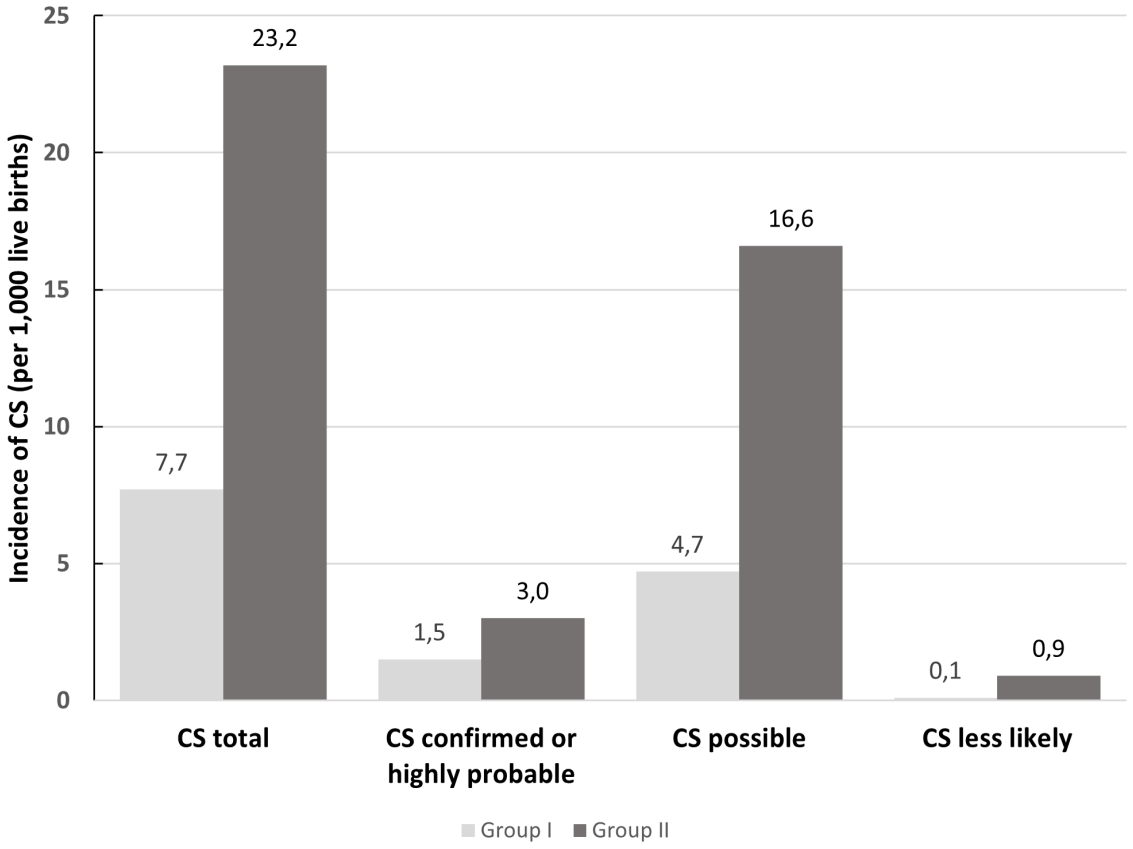
Variable, n (%)	**Group I** (n = 66)	**Group II** (n = 196)	**Total** (n = 262)	**p**[a]
VDRL >4x maternal titer[b]	1 (1.5)	11 (5.6)	12 (4.6)	0.30
CSF performed	53 (80.3)	172 (87.7)	225 (85.9)	0.19
Neurosyphilis[c]	11 (16.7)	28 (14.4)	39 (14.9)	0.69
CSF positive for VDRL[c]	3 (5.7)	8 (4.6)	11 (4.9)	0.72
Other CSF changes[c]	8 (17.8)	20(10.2)	28(14.3)	0.82
Long bone radiographs performed[d]	50 (75.8)	158 (80.6)	208 (79.4)	0.39
Abnormal radiographs	6 (12.0)	14 (8.8)	20 (9.6)	0.25
Clinical manifestations associated with CS	11 (16.7)	12 (6.2)	23 (8.9)	0.02
Newborn treatment				
Crystalline benzylpenicillin	43 (65.2)	131 (66.8)	174 (68.5)	0.28
Procaine benzylpenicillin	3 (4.5)	14 (7.1)	17 (6.7)	
Benzathine benzylpenicillin	12 (18.2)	23 (11.8)	35 (13.8)	
Ceftriaxone and/or ampicillin	3 (4.5)	20 (10.2)	23 (9.1)	
Ignored	5 (4.7)	8 (4.1)	13 (2.0)	
CS classification				
Confirmed or highly probable	16 (24.2)	29 (14.8)	45 (17.2)	0.10
Possible	49 (74.2)	158 (80.6)	207 (79.0)	
Less likely	1 (1.5)	9 (4.6)	10 (3.8)	

CS, congenital syphilis.
[a]Chi-square test or Fisher's exact test.
[b]14 notifications without information: group I = 1; group II = 13.
[c] percentage calculated on the total number of CSF analysis tests performed.
[d] percentage calculated on the total number of radiological exams performed.

It was observed that, of the 15 appropriately treated pregnant women, five neonates exhibited one or more criteria to be classified as proven or highly probable CS: three newborns had a serum VDRL at least fourfold higher than the maternal titer, (one of whom also had reactive VDRL in the CSF), one had VDRL-positive CSF, one had visible changes on long-bone radiographs, and one was reported as symptomatic, with cholestatic jaundice. Overall, 214 (81.7%) neonates received intravenous antibiotic therapy.

We calculated the incidence of CS per 1,000 live births, broken down by diagnostic classification (**Figure 1**). Two (1.0 %) neonatal deaths due to CS were observed in group II (mortality coefficient = 20.1 / 100,000 live births). One was born to an untreated mother, and the other received inappropriate treatment.

Figure 1. Incidence of CS (per 1,000 live births) among neonates born to mothers who received prenatal care, stratified by diagnostic classification, during each period of analysis. Group I indicates 2021 to 2014; Group II, 2016 to 2018. CS, congenital syphilis.



Discussion

This study confirms the increase in the incidence of CS over the past decade. This disease remains an important public health problem at the end of the second decade of the 21st century. Although the reverse sequence algorithm performed with the rapid treponemal test suggests a lower severity of CS, there was no increase in the rate of syphilis treatment for mothers and their sexual partners during prenatal care. This suggests an inadequate application of this protocol in the primary health care network in this municipality. It is highly likely that the same is happening in many other places in Brazil.

The incidence of CS in Viamão tripled in the last three years of analysis as compared to the first period studied. In addition, the incidence was well above the regional and national averages, which also increased between these two periods. The incidences of SC in the state of Rio Grande do Sul between 2012 and 2014 and between 2016 and 2018 were 6.8 and 13.8 cases / 1,000 live births respectively, while the countrywide incidence was 4.8 and 8.3 cases / 1,000 live births, respectively (13). This substantial increase in the number of CS cases can be attributed to several factors, among them an increase in reporting, the improvement of diagnosis by expanded screening after implementation of the syphilis POCT, and even to an increase in the population-wide prevalence of syphilis (11, 12, 16).

We found that 13.0% of pregnant women in the initial sample did not receive any prenatal care. These women corresponded to an important

portion of the cases of gestational and CS, which is consistent with nearly all previous studies (17-19). These patients were excluded from the analysis because they had not undergone any form of syphilis screening, which was the focus of the study. Among the mothers who received prenatal care, we were unable to analyze the number of visits, since there is no field to enter this information in the CS reporting form. On the other hand, about one-fifth of the mothers who received prenatal care were diagnosed with syphilis at the time of delivery or in the immediate postpartum period. Some studies have shown that syphilis was detected at the time of delivery in about half of pregnant women who received adequate prenatal care but was not diagnosed in time to prevent CS (17, 20).

Syphilis POCT has become routine so that pregnant women who test positive can be treated immediately upon diagnosis, especially those in whom monitoring will be difficult or who are expected to be lost to follow-up (5, 9, 10, 21). In this study, contrary to expectations, many mothers and her sexual partners remained untreated, even after the implementation of the rapid testing. Similarly, low rates of appropriate treatment have been reported by other authors (22, 23). In Brazil, only 4% of pregnant women received adequate treatment for syphilis in 2016, the first year of our second analysis period (13), which is significantly associated with the presence of newborns with CS.

During the second period of analysis, the treponemal test was performed on almost all pregnant women at the time of delivery or postpartum, contrary to what was expected, which indicates an unnecessary duplication of treponemal tests for diagnosis of syphilis despite implementation of the reverse-sequence protocol. Blood treponemal testing is used to determine exposure to *T. pallidum* and is useful for ruling out false-positive VDRL results in the traditional screening protocol (1, 3, 7-9). Treponemal tests generally remain reactive for life, even after infection has cleared, which contraindicates their use for follow-up. In the reverse-sequence protocol, once a syphilis POCT is found to be positive, VDRL should be performed immediately. Subsequent serial titration will allow evaluation of treatment efficacy. Serum treponemal tests are only indicated in case of discrepancy between the first two tests (positive syphilis POCT, negative nontreponemal test) (3, 7–9). Performing treponemal testing without VDRL not only delays therapeutic decisions and prevents proper control of CS, but also increases healthcare costs because of its higher cost. This may indicate that primary care providers were not properly informed about the purpose and proper use of the rapid treponemal test.

The proportion of more symptomatic CS cases and with more severe alterations – such as neurosyphilis – tended to decrease after introduction of rapid testing, despite the rising incidence of CS between the two periods of analysis. This data may be related to the earlier diagnosis provided by the rapid testing and, hence the timely start of treatment. It is a fact that the treatment of the pregnant women, even incomplete, can mitigate the symptoms of neonatal syphilis (24). Furthermore, the cases classified as CS less likely occurred in a greater proportion in group II (with the use of the syphilis POCT), and 14 of the 15 pregnant women with adequate treatment belonged to group II. However, fatal cases only occurred during the second period, accounting for 6.5 % of syphilis-related deaths in children under one year of age in Rio Grande do Sul. The mortality rate was approximately 2.5 times higher than both the state and national rates (13). This statement raises concerns about potential issues with the application of POCT, including the possibility of erroneous interpretation or application, which could result in inappropriate clinical decisions. Therefore, a more thorough analysis of prenatal care and potential corrective measures may be necessary.

A study was conducted among pediatricians from public maternity hospitals in Teresina - PI to evaluate their knowledge about the CS evaluation and treatment protocol. The study found that 59% of the pediatricians believed that the Syphilis POCT was not a treponemal test, 34 % thought it

could be used to monitor response to treatment or cure, and 42 % had insufficient knowledge about the CS case definition (25).

The occurrence of symptomatic newborns or those with VDRL titers at least four times higher than the maternal titer among mothers who received full treatment (during or before pregnancy) can also be explained by non-compliance with the Ministry of Health protocol (9), leading to failure to detect maternal reinfection during pregnancy (generally due to lack of monthly VDRL control.

Some studies have shown maternal reinfection in the same pregnancy (26) and children with CS (27) in pregnant women who received adequate treatment, without identifying possible reasons for treatment failure or other conditions that might explain the clinical findings. Furthermore, CDC data indicate that one in three women who transmitted syphilis to their children were tested during pregnancy and contracted the disease after this test, which emphasizes the need to repeat syphilis testing in each trimester of pregnancy as well as at delivery (28).

Nearly 80% of newborns were hospitalized for CS treatment with intravenous antibiotic therapy, and some cases treated with ceftriaxone and ampicillin may be related to the temporary shortage of crystalline penicillin in the state of Rio Grande do Sul between July 2015 and June 2016.

The limitations of this study are those inherent to the use of a notifiable diseases database. Despite advances in record-keeping in the last 10 years, flaws in reporting and inappropriate form completion remain significant challenges. Nevertheless, reporting of notifiable diseases is a sensitive indicator of the health conditions of a population (22). Although the present study obtained data directly from the municipal health department to ensure the best possible quality, it is important to emphasize that the use of secondary data has inherent limitations, such as the possibility of inadequate records, errors in filling out the form, and incompleteness. data from the notification form. Despite advances in recording over the past decade, there are still gaps in reporting and underreporting (23, 29). Despite these difficulties, notifications represent the health status of a population.

Our study aimed to address an important issue, particularly for resource-limited health care settings around the world. Early detection of syphilis in pregnant women is essential to prevent CS in newborns, but laboratory resources are limited in many parts of the world. A rapid syphilis POCT that can be used during pregnancy may be a potential solution to this problem. The study found that the introduction of the rapid treponemal test did not result in the expected improvement in the early diagnosis and timely treatment of syphilis in pregnant women and their sexual partners. Additionally, the incidence of CS increased significantly between the periods studied in the municipality of Viamão. Furthermore, some data indicate that the reverse protocol is not being applied in the most correct way, which would have a better cost-benefit ratio and probably a lower incidence of CS, even if acquired syphilis shows an increasing prevalence. This highlights the urgent need for better training of health professionals in the diagnosis, treatment and appropriate antenatal care of pregnant women and their partners.

Notes

This study is part of the result of a master's thesis in the Postgraduate Program in Pediatrics and Child Health at the Pontifical Catholic University of Rio Grande do Sul, by one of the authors (EG), entitled ""Comparison of cases of congenital syphilis before and after implementation of the rapid test"".

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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