CASE REPORT

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Reinfection caused by gestational syphilis: A case report and systematic review of the literature

Reinfección por sífilis gestacional: reporte de caso y revisión sistemática de la literatura

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ABSTRACT

Objective: To present a case of gestational syphilis (GS) caused by reinfection, and conduct a systematic review of the literature regarding the frequency, diagnosis, treatment, and follow-up reinfection.

Materials and methods: A 21-year-old immigrant woman was hospitalized for preeclampsia and bacterial vaginosis. She reported having been diagnosed and treated for GS in the first trimester, with a subsequent decrease in Venereal Disease Research Laboratory (VDRL) titers, followed by a new elevation detected at 39 weeks. She was diagnosed with syphilis reinfection and treated again with benzathine penicillin. A diagnosis of syphilis reinfection was made, and she was treated again with benzathine penicillin. The newborn presented a positive VDRL test with a titer of 1:2, but without clinical signs or sequelae of Treponema pallidum infection. The infant was diagnosed with Congenital Syphilis (CS), and treated with intravenous crystalline penicillin G, with satisfactory outcomes. A systematic review of the literature was conducted from the inception of each database until November 2023 in Medline (PubMed), Embase, Scopus, Web of Science, and Lilacs. Case reports, case series, and cohorts of pregnant women with syphilis reinfection were selected. Two authors independently selected the studies and extracted the data. Study characteristics, population details, diagnostic features, GS treatment, and reinfection frequency were described. A descriptive analysis was performed.

Results: A total of 208 potentially relevant titles were identified, of which 12 were reviewed in full text. Ultimately, six articles were included. In total, 85 women experienced syphilis reinfection during pregnancy ranged from 1.5% to 7.3%. Diagnosis was predominantly made using nontreponemal tests (83.3%). Available information regarding the treatment of pregnant women with reinfection, follow-up, partner treatment, and perinatal outcomes was limited.

Conclusions: Active and individualized monitoring of treated GS cases is crucial, as it enables the identification of reinfection and ensures treatment of sexual partners to prevent recurrence. Prospective studies are needed to assess the magnitude of this problem, its perinatal consequences, and potential resistance to penicillin.

Key words: Syphilis; syphilis congenital; pregnancy; reinfection; case report.

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RESUMEN

Objetivos: presentar un caso de reinfección por sífilis gestacional (SG) y realizar una revisión sistemática de la literatura sobre la frecuencia, el diagnóstico, el tratamiento y el seguimiento de la reinfección.

Materiales y méto: mujer de 21 años, inmigrante, quien es hospitalizada por preeclamsia y vaginosis bacteriana. Refiere que fue diagnosticada y tratada por SG en el primer trimestre, con posterior disminución de los títulos de Venereal Disease Research Laboratory (VDRL), y nueva elevación de los mismos detectada a la semana 39. Se hace el diagnóstico de reinfección por sífilis y recibe nuevamente tratamiento con penicilina benzatínica. El recién nacido presenta VDRL positivo, dilución (1:2), sin signos clínicos ni secuelas de infección por *Treponema Pallidum*; se hace diagnóstico de Sífilis Congénita (SC) y recibió tratamiento con penicilina G cristalina intravenosa, con evolución satisfactoria. Se realizó una revisión sistemática de la literatura desde el inicio de registro de cada base de datos hasta noviembre de 2023, en Medline (PubMed), Embase, Scopus, Web of Science y Lilacs. Se seleccionaron reportes de caso, series de casos y cohortes de mujeres gestantes con reinfección por sífilis. Dos autores seleccionaron los estudios y extrajeron los datos de manera independiente. Se describen las características del estudio, la población, las características del diagnóstico, el tratamiento de la SG y la frecuencia de casos de reinfección. Análisis descriptivo.

Resultados: se identificaron 208 títulos potencialmente relevantes, de los cuales 12 fueron evaluados en texto completo. Finalmente, se incluyeron seis artículos. En total, 85 mujeres presentaron una reinfección por sífilis durante la gestación (3,8 %). La incidencia de reinfección por sífilis durante el embarazo varía entre el 1,5 y 7,3 %. El diagnóstico se realizó en mayor medida con pruebas no treponémicas (83,3 %). La información disponible respecto al tratamiento de la gestante con reinfección, el seguimiento, el tratamiento del compañero y los resultados perinatales es limitada.

Conclusiones: la vigilancia activa e individual de los casos de SG tratada es importante porque permite no solo identificar la reinfección, sino también garantizar el tratamiento de los compañeros sexuales para prevenirla. Se requieren estudios prospectivos para evaluar la magnitud de este problema, sus consecuencias perinatales y la posible resistencia a la penicilina.

Palabras clave: sífilis; sífilis congénita; embarazo; reinfección; reporte de caso.

INTRODUCTION

Syphilis is an infection caused by *Treponema pallidum* (TP) (1). The main forms of transmission are through sexual intercourse, the bloodstream, or vertical transmission through the placenta from the mother to the fetus, infecting the fetus and the neonate, in what is called congenital syphilis (CS) (2). As of 2022, the global prevalence of syphilis was reported at 0.6%, with nearly eight million new cases in women and men between 15 and 49 years of age (3), and a higher frequency than the one reported in 2016 at 0.5%, affecting Africa and America mainly (5). The Weekly Epidemiological Newsletter (*Boletín Epidemiológico Semanal*) published by the Colombian Ministry of Health and the National Institute of Health, reported 7,570 cases of gestational syphilis (GS) and 906 cases of CS in the first 40 weeks of 2024 (6).

Serological tests are the mainstay of diagnosis. They include nontreponemal tests (NTT) used to detect total antibodies against cardiolipin and lecithin, and treponemal tests, which are more specific for the detection of anti-TP antibodies (7). In the traditional diagnostic algorithm, although the opposite algorithm is also used in which TTs are used before NTTs, particularly in pregnant women (8). Syphilis is classified according to stages, namely, primary, secondary, latent (early or late), and tertiary. This classification has therapeutic implications. However, considering that TP replication is relatively protracted, penicillin is generally used as first-line treatment, either as benzathine penicillin (9). Benzathine penicillin G

(BPG) is used in all the previously described stages; however, in neurosyphilis or central nervous system involvement, crystalline penicillin G (CPG) is used as it crosses the blood-brain barrier. Its effectiveness is close to 90% (10). The treatment of gestational syphilis is the same as that of non-pregnant women (11).

CS accounts for the highest burden of the disease, as it is the main cause of miscarriage, early and late fetal demise, preterm delivery, low birthweight and congenital malformations (12). CS occurs when the woman is already affected by GS, either because the infection is acquired during pregnancy, in which case the odds of fetal transmission are 90 to 100%, particularly in the primary or secondary stage; or when the woman has latent syphilis and becomes pregnant, in which case the probability of fetal transmission ranges between 40 and 70% (13).

CS is entirely preventable when diagnosed and treated early during the course of prenatal care. A single 2,400,000-unit ampoule of BPG administered to the mother is 97% effective in preventing CS (14). The main reasons for CS cases to occur are: 1) failure to attend prenatal care visits; 2) failure to perform screening tests; 3) failure to receive timely treatment; and 4) reinfection during pregnancy (15).

Reinfection is defined as occurring in an individual diagnosed with syphilis who receives the required treatment according to the stage but in whom genital or skin lesions consistent with the disease are identified during follow-up, or when rising titers are found in two-dilution tests (four-fold) or when titers fail to come down (at least two dilutions) after six months of treatment (16). Little is known about syphilis reinfection frequency during gestation (17), particularly considering the high frequency of non-treatment of the sexual partner, a situation still present in Colombia. (6,18). This case report and systematic literature review aims to present a case of reinfection GS and conduct a systematic review of the literature regarding *T. pallidum frequency*, treatment and perinatal prognosis.

CASE PRESENTATION

A 21-year-old primigravida, migrant, living in the city of Bogota since 2023, with a history of gestational syphilis diagnosed by a positive NTT in a 1:16 dilution at 15 weeks + 4 days of gestation. She had received treatment for syphilis consisting of three doses of 2,400,000 units of BPG during an unknown period of time. The last dose had been given within the next 15 days following diagnosis with intention to cure, in accordance with the Colombian Clinical Practice Guideline (16), based on a positive follow-up NTT in a 1:2 dilution at 19 weeks of gestation. No evidence of treatment given to the sexual partner was documented in the clinical record.

The patient attended a general, intermediate complexity public hospital located in Bogota which provides care to a population covered under the state-subsidized regime of the General Social Security System (GSSS) in Colombia. She was diagnosed with stage II gestational hypertension (149/100 mmHg). Laboratory tests included a reactive NTT in a 1:16 dilution, negative HIV test and vaginal smear suggestive of bacterial vaginosis.

The patient was found to have a hypertensive disorder and bacterial vaginosis, and to meet the criteria for syphilis reinfection during pregnancy. She was admitted and treatment for her and her partner was started with 2,400,000 units of BPG. She was also prescribed a single dose of metronidazole and oral antihypertensive medication. During hospitalization, the patient developed severe preeclampsia with fetoplacental unit compromise, prompting cesarean section delivery on October 20, 2023. A second BPG dose was administered on the following week.

The male neonate had a birthweight of 2,615 g, length of 50 cm, and an APGAR score of 8-9-9/10. It presented with respiratory distress syndrome (Silverman 3/10) due to transient tachypnea which required oxygen supplementation and resolved during the hospital stay. The neonatal TT test was positive, with a positive NTT in a 1:2 dilution. The cerebrospinal fluid sample was VDRL-negative with normal leukocyte and protein counts and slightly elevated transaminase levels. Congenital syphilis was diagnosed based on the epidemiological

connection, given that the treatment was considered inadequate according to the national guidelines (16), less than 30 days after birth. No signs of ocular syphilis were found on neonatal ophthalmological assessment. Neonatal management was initiated with 130,000 units of PenG every 12 hours for three days, followed later by a single prophylactic dose of BPG 50,000 units/kg based on the opinion of the infectious disease specialist and the history of maternal reinfection. The recommendation of the national guideline was not followed. No evidence of the administration of a third treatment dose to the mother was documented in the clinical record and neither were tests to identify TP resistance to penicillin performed (Figure 1).

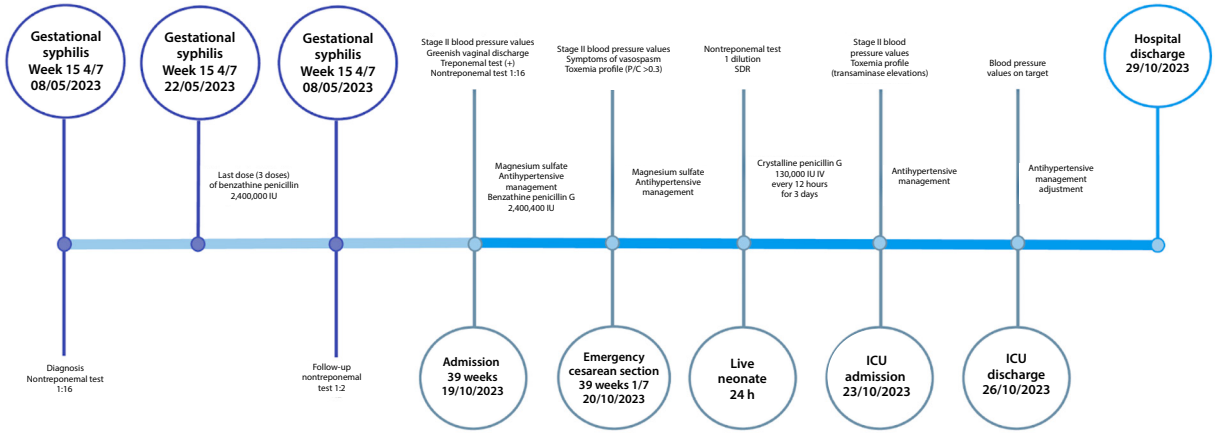

Figure 1. Case report timeline.
Source: Authors.

Ethical considerations. The patient provided her written informed consent for this case report. Additionally, the health research ethics requirements for Colombia were met (19).

MATERIALS AND METHODS

A systematic review was conducted in accordance with the guidance of the Cochrane Handbook for Systematic Reviews (20), reporting the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), based on the following questions: What is the frequency of reinfection gestational syphilis?, how is reinfection gestational syphilis diagnosed and treated? and what is its prognosis?(21).

Inclusion criteria. By type of study: case reports and case series, cross-sectional or cohort studies. Type of population: women with GS diagnosed in the first or second trimester of pregnancy, with adequate treatment for the infection.

A systematic search was carried out in the Medline via PubMed, Embase, Scopus, Web of Science and Lilacs databases using the indexed and relevant search terms *"Syphilis", "Treponema pallidum"*, "Pregnancy" and "Reinfection". Additional searches were conducted in Google Scholar and Open Grey (Supplementary Material 1). The snowball method was also applied to conduct an additional search based on the references of the identified studies, limited to papers in Spanish, English and Portuguese from the inception of the records in each database until November 1, 2023.

Study selection and data extraction. Studies were initially selected based on title and abstract review. The full text was then analyzed in order to determine suitability for inclusion. Three of the researchers carried out these procedures in matched form. One of the authors was responsible for data extraction, with independent

cross-checking carried out by a different author. Disagreements were resolved by consensus. The information extracted from the articles included author and publication year, number of women with a diagnosis of GS, screening and syphilis confirmation methods, NTT titers, treatment received, proportion of treated partners, follow-up serology after treatment, number of women diagnosed with syphilis reinfection during pregnancy, method used to diagnose reinfection, serological titers at the time of reinfection, treatment received for reinfection, perinatal outcomes, and one and five-year follow-up.

Quality assessment. Included studies were independently assessed by two of the authors using the Joanna Briggs Institute tool (22). They were rated for selection bias risk (items 1, 4, 5), measurement bias (items 2, 3, 6, 7), generalization of the results (item 8) and quality of the analysis (item 9).

Results are presented in descriptive form with a meta-aggregative approach to the synthesis. The information focuses on the methodology and the study population consisting of pregnant women with syphilis reinfection.

RESULTS

Search and study selection. The search identified 203 potentially relevant studies, plus another five which were selected as part of the snowball search, for a total of 208 titles (Figure 2). Following title and abstract review, five duplicate studies and 191 which did not meet the inclusion criteria were eliminated. Twelve studies were assessed in full-text, but six did not meet the inclusion criteria and were disregarded (Supplementary material 2). Ultimately, six studies were included for information analysis.

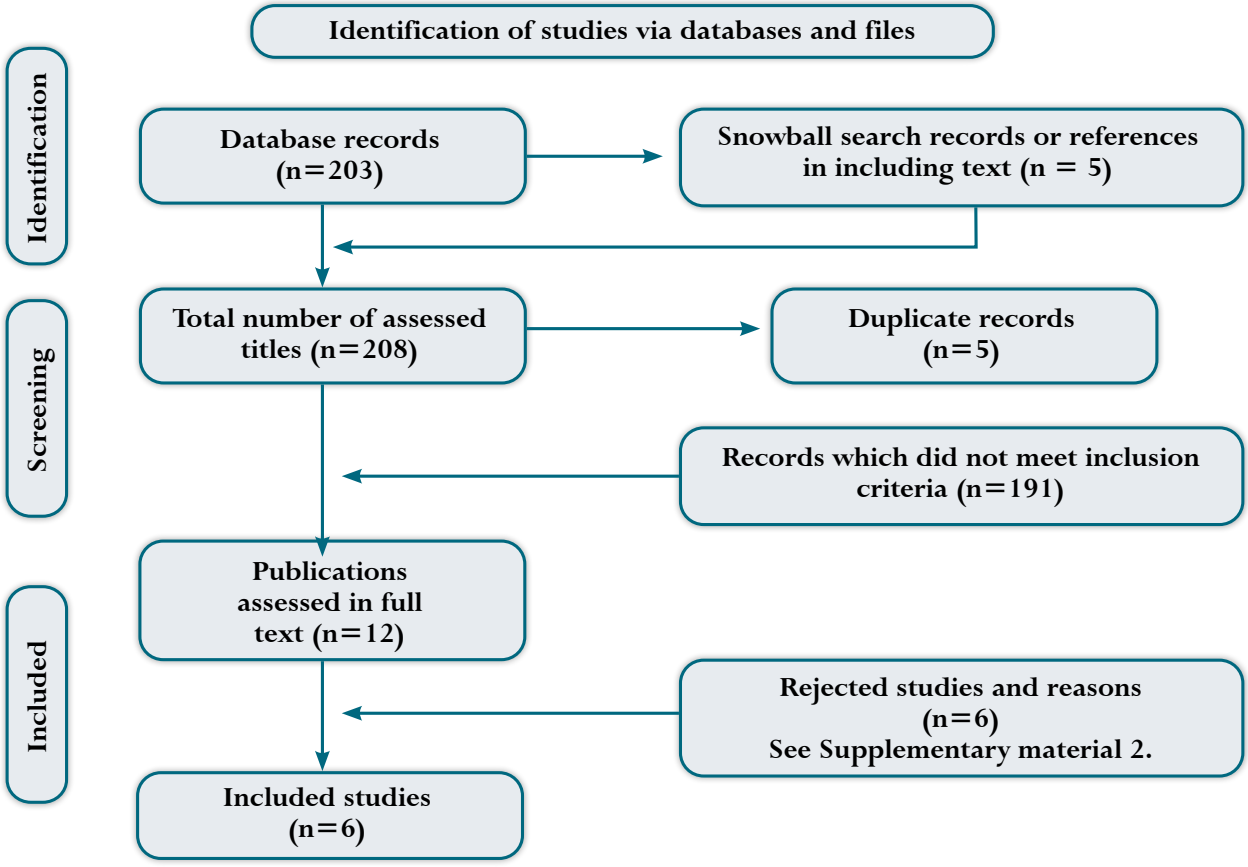

Figure 2. Flow diagram.
Source: Authors.

Study designs. The six studies were surveillance system-based cohort studies (23-28). The funding source was reported in only one study (n = 1, 16.6%) (26). Conflict of interest disclosures were found in all the studies (23-28). All of the studies were carried out in the United States, half of them in Florida (50%) (23,25,27) and the other half in New York (24,28) (33.3%) and Arizona (16.7%) (26). As for chronology, these studies had been published between 2012 and 2022. The general characteristics of the included studies are summarized in Table 1.

Table 1.
Characteristics of the included studies..

Author and year	Matthias et al., 2017 (23)	Slutsker et al., 2018 (24)	Matthias et al., 2021 (25)	Sykes et al., 2021 (26)	Matthias et al., 2022 (27)	Patel et al., 2012 (28)
Design	2013-2014 surveillance system-based cohort	2010-2016 surveillance system-based cohort	2018 surveillance system-based cohort	2017-2018 surveillance system-based cohort	2018-2019 surveillance system-based cohort	2000-2009 surveillance system-based cohort
Number of diagnosed and treated women	321	578	369	205	551	190
Maternal age	14-45 years	15-44 years	16-43 years	13-45 years	14-45 years	17,7-45,2 years
Syphilis stage	Early (primary, secondary and early latent): 38%	Unknown duration or late: 74.6% Secondary 21.8% Prima-ry 1.0%	No information	Primary, secondary and early: 61.4% Late latent: 26.3%	Primary or secondary: 13% Unknown duration: 62%	Unknown duration: 36% Late latent: 35% Latent primary: 26%
Confirmation method and NTT dilutions	Range 1:2-1:32	No dilutions reported	Median 1:32 (1:4-1:28)	No dilutions reported	Range 1:2-1:32	No dilutions reported
Treatment received	No information	Penicillin (no dose specified)	No information	No information	No information	Penicillin (no dose specified)
Proportion of treated partners	No information	No information	No information	No information	No information	No information
Serology follow-up	No information	No information	Reduced dilutions: Range: 2-64	No information	No information	No information

Source: Authors.

The number of women diagnosed with GS included in each study ranged between 191 to 578, for a total of 2,214 participants, with an age range of 13 to 45 years. The initial diagnosis was made using only NTTs (23-28); three studies reported titers between 1:2 and 1:32 (23,25,27), while the remaining studies did not provide this information.

Of the total number of pregnant women, 58% (n = 1,281) had no information regarding the duration of the condition; 22% (n = 481) had primary, secondary or early latent syphilis; 3.74% (n = 83) late latent syphilis, and in 16.66 % (n = 369) the stage was not reported. Two of the studies (33.3%) described the use of penicillin as the initial treatment (24,28), albeit with no information

regarding the precise management regimen. Only one study (16.6%) reported infection of three sexual partners but provided no information on whether they had received treatment or not (25). Diagnosis or treatment of the partners was not reported in the rest of the studies. Serologic follow-up was reported only in one study (16.6%), with a eight-fold median reduction in NTT titers (25).

Syphilis reinfection during pregnancy and congenital syphilis. In terms of reinfection, between 5 and 27 cases were identified per study, for a total of 85 women with this diagnosis (3.84%). Incidence ranged between 1.5 and 7.3%. In three studies (50%) the criterion to establish a reinfection diagnosis was at least a four-fold increase in titers on the NTT after initial treatment for GS (23,25,27); in one of those studies, the criterion was any increase (24), while the criterion was not clearly defined in the remaining studies (26,28) (Table 2). Only one study reported the treatment received by the women with reinfection (16.6%) (25), where 11 patients received a single dose of 2,400,000 units of BPG and five patients received three doses (25). Finally, none of the studies included information on maternal follow-up, perinatal outcomes, or treatment failure after reinfection.

Table 2.
Detailed reinfection information.

Author and year	Matthias et al., 2017 (23)	Slutsker et al., 2018 (24)	Matthias et al., 2021 (25)	Sykes et al., 2021 (26)	Matthias et al., 2022 (27)	Patel et al., 2012 (28)
Number of women with reinfection diagnosis	Five cases (1.5% of the population) and 6% of the neonates with congenital syphilis occurred due to reinfection or therapeutic failure	15 cases (2.5% of the population) and 71.4% of congenital syphilis cases	19 cases (5.1%)	Five cases (2.4% of the population) and 8.8% of the congenital syphilis cases	27 cases (4.9% of the population) and 10% of the neonates with congenital syphilis occurred due to reinfection or therapeutic failure	14 cases (7.3%)
Reinfection diagnostic method	NTT	NTT	NTT	No information	NTT	NTT
Serology titers at the time of reinfection	Four-fold increase in titers after the initial treatment	Titer increase (non-specified amount)	Four-fold increase in titers after the initial treatment	No information	Four-fold increase in titers after the initial treatment	No information
Treatment received for reinfection	No information	No information	11 patients received one dose of benzathine penicillin 2,400,000 IU Five patients received three doses of benzathine penicillin 2,400,000 IU	No information	No information	No information
Perinatal outcome	No information	No information	No information	No information	No information	No information
Follow-up	No information	No information	No information	No information	No information	No information

Source: Authors.

Quality assessment. The quality scores for the studies ranged between 4/10 and 7/10. The risk of selection bias was low, although complete information regarding participant inclusion was lacking in two studies (23,26). The risk of measurement bias was high given that no information was provided regarding follow-up of patients with a syphilis reinfection diagnosis or of the neonates. Four studies did not describe the statistical analysis (23,26-28) (Table 3).

Table 3.
Quality assessment results.

Author and year	Matthias et al., 2017 (23)	Slutsker et al., 2018 (24)	Matthias et al., 2021 (25)	Sykes et al., 2021 (26)	Matthias et al., 2022 (27)	Patel et al., 2012 (28)
JBI Cirteria	**Evaluaton**					
1. Was there a clear case inclusion criterion? (Selection bias)						
2. Was the measure condition standardized and reliable for all participants included in the case series? (Measurement bias)						
3. Were validated methods used to identify all the participants included in the case series? (Measurement bias - Misclassification)						
4. Did the case series include participants from a consecutive series? (Selection bias)						
5. Was participant inclusion in the case series complete? (Selection bias)						
6. Were demographic reports clear for all the participants in the study? (Measurement bias)						
7. Were clinical reports clear for all the par-ticipants? (Measurement bias)						
8. Were follow-up re-sults for cases clearly reported? (Measurement bias - Lost data)						
9. Were demographic data reports of the presentation sites/clinics clear? (Results generaliza-tion)						
10. Was the statistical analysis appropri-ate? (Quality of the analysis)						
Rating	**4-oct**	**7-oct**	**6-oct**	**6-oct**	**4-oct**	**7-oct**
Color information	**Yes**	**No**	**Not clear**	**Not applicable**		

Source: Authors.

CONCLUSIONS

Active, individualized surveillance in treated cases of GS is important as it does not only allow to detect reinfection but also ensure treatment for sexual partners in order to prevent it. Prospective studies are needed to assess the magnitude of this problem, its perinatal consequences and potential penicillin resistance.

AUTHOR'S CONTRIBUTIONS

HV, NV and DMB: Conceptualization, data acquisition, formal analysis, initial draft, writing, proofreading and editing, approval.

JMC: Research, methodology, formal analysis, initial draft, writing, proofreading and editing, approval.

HGD: Methodology, formal analysis, initial draft, writing, proofreading and editing, approval.

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Supplementary material 1

Search algorithms and results by database

Search Report # 1	
Database	MEDLINE
Platform	PubMed
Date range	1966/10-2023
Language restrictions	English, Spanish and Portuguese
Date search	01/11/2023
Search	1. Syphilis[MeSH Terms] (29.761) 2. "Treponema pallidum"[Title/Abstract] OR "syphilis"[Title/Abstract] OR "syphil*"[Title/Abstract] (36,384) 3. #1 OR #2 (42,659) 4. Pregnancy[MeSH Terms] (1,015,658) 5. pregnan*[Title/Abstract] OR Gestation[Title/Abstract] (682,252) 6. #4 OR #5 (1,184,176) 7. reinfection[Title/Abstract] OR "re-infection"[Title/Abstract](13,075) 8. #3 AND #7(288) 9. #6 AND #8 (35)
Results	**35**

Search Report # 2	
Database	Embase
Platform	Embase
Date range	1947-2023
Language restrictions	Spanish, Portuguese and English
Date search	01/11/2023
Search	1. 'syphilis'(52,660) 2. 'treponema pallidum':ab,ti OR 'syphilis':ab,ti OR 'syphil*':ab,ti(39,622) 3. #1 OR #2(55,119) 4. 'pregnancy'(1,141,688) 5. pregnan*:ab,ti OR gestation:ab,ti(893,276) 6. #4 OR #5(1,272,612) 7. reinfection:ab,ti OR 're-infection':ab,ti(16,450) 8. #3 AND #7(415) 9. #6 AND #8 (62)
Results	**62**

Search Report # 3	
Database	Scopus
Platform	Scopus
Date range	2004-2023
Language restrictions	Spanish, Portuguese and English
Date search	03/11/2023
Search	TITLE-ABS-KEY ((syphilis OR ("treponema pallidum" OR "syphilis" OR "syphil*")) AND (pregnancy OR (pregnan* OR gestation)) AND (reinfection OR "re-infection"))) (69)
Results	**69**

Search Report # 4	
Database	Lilacs
Platform	Lilacs
Date range	1985-2023
Language restrictions	Spanish, Portuguese and English
Date search	03/11/2023
Search	((syphilis OR ("Treponema pallidum" OR "syphilis" OR "syphil*")) AND ((pregnancy OR (pregnan* OR gestation)) AND (reinfection OR "re-infection"))) AND (db:("LILACS")) (13)
Results	**13**

Search Report # 5	
Database	Web of Science
Platform	Web of Science (Core collection)
Date range	2000-2023
Language restrictions	Spanish, Portuguese and English
Date search	03/11/2023
Search	1. TS=(Syphilis OR "Treponema pallidum" OR "syphilis" OR "syphil*")(15,792) 2. TS=(Pregnancy OR pregnan* OR Gestation)(511,905) 3. TS=(reinfection OR "re-infection")(11,037) 4. #1 AND #3(167) 5. #2 AND #4 (24)
Results	**24**

Source: Authors.

Supplementary material 2

Rejected articles and reason for rejection

Table 1.
Characteristics of the included studies.

#	Reference	Title	Reason for rejection
1	Williams, et al., 2011	Partner notification and treatment for maternal syphilis in Lima, Peru: Knowledge, attitudes, and practices of health providers and patients	Does not meet exposure criterion
2	Oleg, 2017	Syphilis in pregnant women and elimination of congenital syphilis in Belarus	Does not meet exposure criterion
3	Serpa, et al., 2018	Epidemiology of partner treatment in the prognosis of gestational syphilis in the federal district	Does not meet population or exposure criteria
4	Parkes-Ratanshi, et al., 2020	Low male partner attendance after syphilis screening in pregnant women leads to worse birth outcomes: The Syphilis Treatment of Partners (STOP) randomized control trial	Does not meet exposure criterion
5	Caldeira, et al., 2022	Perfil das gestantes diagnosticadas com sífilis durante o pré-natal ou parto admitidas em maternidade de Belo Horizonte MG	Does not meet exposure criterion
6	Farias, et al., 2023	The crucial role of the partner in the incidence of cases of congenital syphilis in the state of Sergipe: an analysis in 17 years	Does not meet population or exposure criteria

Source: Authors.