

UNIVERSIDADE FEDERAL DE MINAS GERAIS  
FACULDADE DE MEDICINA  
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE – SAÚDE DA  
CRIANÇA E DO ADOLESCENTE

LORENA BATISTA PASCOAL

**DETERMINANTES DA ASSISTÊNCIA OBSTÉTRICA E NEONATAL PARA  
SÍFILIS CONGÊNITA NO SEGUIMENTO CLÍNICO EM AMBULATÓRIO DE  
REFERÊNCIA**

Belo Horizonte

2023

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Orientadora: Profa. Roberta Maia de Castro Romanelli

Coorientadora: Profa. Ericka Viana Machado Carellos

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UNIVERSIDADE FEDERAL DE MINAS GERAIS  
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SAÚDE DA CRIANÇA E DO ADOLESCENTE  
**ATA DE DEFESA DE DISSERTAÇÃO**

Às treze horas e trinta minutos do dia quinze de dezembro de dois mil e vinte e três na sala 526 (Sala de Videoconferência do CPG), 5º andar da Faculdade de Medicina da Universidade Federal de Minas Gerais, realizou-se a sessão pública para a defesa da dissertação de Mestrado de **LORENA BATISTA PASCOAL**, número de registro 2021652526, graduada no curso de MEDICINA, como requisito parcial para a obtenção do grau de Mestre em CIÊNCIAS DA SAÚDE, pelo Programa de Pós-Graduação em Ciências da Saúde-Saúde da Criança e do Adolescente. A Presidência da sessão coube à Prof.<sup>a</sup> Roberta Maia de Castro Romanelli - Orientadora (UFMG). Inicialmente a Presidente após dar conhecimento aos presentes sobre o teor das Normas Regulamentares do trabalho final de Pós-Graduação, fez a apresentação da Comissão Examinadora, assim, constituída pelas seguintes Professoras Doutoras: Roberta Maia de Castro Romanelli – Orientadora, Presidente (UFMG), Eleonor Gastal Lago (PUC-RS), que participou através da videoconferência da Plataforma LifeSize, Leni Marcia Anchieta (UFMG) e Ericka Viana Machado Carellos, Coorientadora (UFMG). Em seguida, a Presidente autorizou a aluna para iniciar a apresentação de seu trabalho final intitulada “DETERMINANTES DA ASSISTÊNCIA OBSTÉTRICA E NEONATAL PARA SÍFILIS CONGÊNITA NO SEGUIMENTO CLÍNICO EM AMBULATÓRIO DE REFERÊNCIA”. Seguiu-se à arguição pela comissão Examinadora, com a respectiva defesa da aluna. Logo após a Comissão reuniu-se sem a presença da candidata e do público para julgamento e expedição do resultado da avaliação do trabalho final da aluna e decidiu considerar a dissertação Aprovada. O resultado final foi comunicado publicamente à aluna pela Presidente da Comissão. Nada mais havendo a tratar, a Presidente encerrou a sessão e lavrou a presente ata que, após lida, será assinada eletronicamente por todos os membros da Comissão Examinadora presente através do SEI (Sistema Eletrônico de Informações) do Governo Federal.

Belo Horizonte, 15 de dezembro de 2023.



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Ao meu filho, Davi, por colorir meus dias.

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## RESUMO

**Introdução** – Apesar de ser uma doença antiga e tratável, a sífilis permanece como um problema de saúde pública no Brasil e no mundo. Dentre suas complicações, está a sífilis congênita (SC), que resulta da transmissão da espiroqueta *Treponema pallidum* da gestante infectada ao conceito. A única forma de prevenção da SC é o diagnóstico e o tratamento oportuno da gestante infectada. Dessa forma, a identificação de variáveis associadas à transmissão vertical da sífilis é uma medida importante para a construção de políticas direcionadas à população de risco e a consequente correção das falhas assistenciais.

**Objetivo** – Identificar e analisar os fatores associados à assistência obstétrica e ao recém-nascido (RN), que possam servir como preditores de SC.

**Métodos** – Estudo de coorte retrospectivo realizado no Centro de Referência e Treinamento em Doenças Infecciosas e Parasitárias (CTR) Orestes Diniz, no período de 2017 a 2022. Foi utilizada amostragem não probabilística e incluídas crianças atendidas devido à exposição vertical à sífilis. A definição de SC confirmada foi baseada na presença de um teste treponêmico positivo após os 18 meses de vida e SC descartada definida com um teste treponêmico negativo. A análise estatística dos dados foi conduzida utilizando o *software Statistical Package for Social Sciences* (SPSS) 21.0 (IBM, Armonk, NY).

Na análise descritiva, variáveis contínuas foram expressas como média e desvio-padrão ou mediana e intervalo interquartil, dependendo da sua distribuição. Variáveis categóricas foram apresentadas como frequência e percentual. A análise comparativa das variáveis entre os grupos de crianças com diagnóstico de SC confirmado e descartado incluiu o teste de Mann-Whitney, para variáveis contínuas, e o teste exato de Fisher, para as variáveis categóricas. A significância estatística foi considerada quando  $p < 0,05$  e a medida da magnitude da associação foi avaliada pelo *odds ratio* (OR) e intervalo de confiança (IC) de 95%. O estudo é um braço do Projeto de Pesquisa aprovado no Comitê de Ética e Pesquisa (COEP) da UFMG intitulado “Diagnóstico de infecções congênitas e correlação com o acometimento fetal e evolução clínica de crianças infectadas por transmissão vertical”.

**Resultado** – De 867 pacientes elegíveis, 377 crianças foram incluídas na análise comparativa, sendo que dez delas (2,7%) tiveram o diagnóstico confirmado de SC e 367 (97,3%) descartado. A prevalência de SC no nosso estudo foi de 1,15% (10/377). O diagnóstico de sífilis foi

confirmado em 221 mães (58,6%) e o tratamento para sífilis foi considerado adequado em 58 mães (17,7%). Manifestações clínicas foram documentadas em 77 crianças (20,4%), a saber, esplenomegalia (n=3), hepatomegalia (n=6), exantema (n=2), icterícia (n=61), petéquias (n=2) e atraso do desenvolvimento neuropsicomotor (n=3), e o tratamento para sífilis instituído em 81,2% dos pacientes (n=306). Três variáveis foram associadas, independentemente, à SC: ausência de tratamento materno com penicilina benzatina (OR=4,29; IC 95% 1,13-18,96), presença de manifestações clínicas no período neonatal ou na 1ª consulta (OR=4,97; IC 95% 1,30-18,96) e titulação de VDRL (*Venereal Disease Research Laboratory*) do recém-nascido coletado na maternidade > 1:2 (OR=11,28; IC 95% 1,42-94,44).

**Conclusão** – A SC, apesar de ser uma doença prevenível, permanece um problema de saúde pública. O alto percentual de mães inadequadamente tratadas reflete as dificuldades no manejo da gestante infectada, o que, por sua vez, aumenta significativamente o risco de ocorrência da SC. Além disso, embora as manifestações clínicas no período neonatal tenham sido identificadas como fatores associados à SC, a inespecificidade desses achados contribui para a complexidade do manejo adequado dos recém-nascidos expostos verticalmente à sífilis. O resultado alterado do VDRL no neonato, identificado como uma variável independente associada ao diagnóstico final de SC, ressalta a importância de valorizar esse exame na decisão de tratar o recém-nascido na maternidade.

Palavras-chave: sífilis congênita; gestantes; cuidado pré-natal; fatores de risco; transmissão vertical de doenças infecciosas.

## ABSTRACT

**Introduction** – Despite being an old and treatable disease, syphilis remains a public health problem in Brazil and around the world. Among its complications is congenital syphilis (CS), which results from the transmission of the spirochete *Treponema pallidum* from the infected pregnant woman to the conceptus. The only form of prevention of CS is the diagnosis and timely treatment of the infected pregnant woman. Thus, the identification of variables that are associated with vertical transmission of syphilis is an important measure for the creation of policies focusing on the risk population and the consequent correction of failures in health care procedures.

**Objective** – To identify and analyze the factors associated with obstetric and newborn (NB) care that can serve as predictors of CS.

**Method** – A retrospective cohort study was carried out at the Reference and Training Center in Infectious and Parasitic Diseases (RTC) Orestes Diniz, from 2017 to 2022. Non-probabilistic sampling was used, and children treated due to vertical exposure to syphilis were included. The definition of confirmed CS was based on the presence of a positive treponemal test after 18 months of life, and discarded CS was defined as having a negative treponemal test. The statistical analysis of the data was conducted using the Statistical Package for Social Sciences (SPSS) 21.0 software (IBM, Armonk, NY).

In the descriptive analysis, continuous variables were expressed as mean and standard deviation or median and interquartile range, depending on their distribution. Categorical variables were presented as frequency and percentage. The comparative analysis of the variables between the groups of children with confirmed and discarded CS diagnoses included the Mann-Whitney test for continuous variables and the exact Fisher test for categorical variables. Statistical significance was considered at  $p < 0.05$ , and the measure of the magnitude of the association was evaluated by the odds ratio (OR) and confidence interval (CI) of 95%. The study is a branch of the Research Project approved by the Ethics and Research Committee (COEP) of UFMG entitled “Diagnosis of congenital infections and correlation with fetal involvement and clinical evolution of children infected by vertical transmission”.

**Results** – Of 867 eligible patients, 377 children were included in the comparative analysis, of which ten (2.7%) had a confirmed diagnosis of CS and 367 (97.3%) had it discarded. The

prevalence of CS in our study was 1.15% (10/377). The diagnosis of syphilis was confirmed in 221 women (58.6%), and the treatment for syphilis was considered adequate in 58 (17.7%). Clinical manifestations were documented in 77 children (20.4%), namely splenomegaly (n=3), hepatomegaly (n=6), exanthema (n=2), jaundice (n=61), petechiae (n=2) and delay in neuro-psychomotor development (n=3) and treatment for syphilis was carried out in 81.2% of patients (n=306). Three variables were independently associated with CS: absence of maternal treatment with benzathine penicillin (OR=4,29; CI 95% 1,13-18,96), clinical manifestations present in the neonatal period or at the first clinic appointment (OR=4,97; CI 95% 1,30-18,96), and titration of VDRL (*Venereal Disease Research Laboratory*) of the NB collected at the maternity > 1:2 (OR=11,28; CI 95% 1,42-94,44).

**Conclusion** – Despite being a preventable disease, CS remains a public health problem. The high percentage of inadequately treated mothers reflects the difficulties in managing infected pregnant women, which in turn significantly increases the risk of CS occurrence. Furthermore, although clinical manifestations in the neonatal period have been identified as factors associated with CS, the non-specificity of these findings contributes to the complexity of the proper management of NBs exposed vertically to syphilis. The altered VDRL result in the newborn, identified as an independent variable associated with the final diagnosis of CS, highlights the importance of valuing this test in the decision to treat the RN at the maternity hospital.

**Keywords:** congenital syphilis; maternal syphilis; prenatal care; risk factors; vertical infectious disease transmission.

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## LISTA DE ABREVIATURAS E SIGLAS

|                   |                                                                                        |
|-------------------|----------------------------------------------------------------------------------------|
| CDC               | <i>Centers for Disease Control and Prevention</i>                                      |
| CTR Orestes Diniz | Centro de Referência e Treinamento em Doenças Infecciosas e Parasitárias Orestes Diniz |
| FTA-ABs           | <i>Fluorescent treponemal antibody absorption test</i>                                 |
| IC                | Intervalo de confiança                                                                 |
| IST               | Infecção sexualmente transmissível                                                     |
| LCR               | Líquido cefalorraquidiano                                                              |
| OMS               | Organização Mundial de Saúde                                                           |
| OPAS              | Organização Pan-Americana da Saúde                                                     |
| OR                | <i>Odds ratio</i>                                                                      |
| RN                | Recém-nascido                                                                          |
| SC                | Sífilis congênita                                                                      |
| SINAN             | Sistema de Informação de Agravos de Notificação                                        |
| TTPA              | <i>Treponema pallidum particle agglutination assay</i>                                 |
| VDRL              | <i>Venereal Disease Research Laboratory</i>                                            |

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## 1. INTRODUÇÃO

A sífilis é uma infecção sexualmente transmissível (IST), causada pelo espiroqueta *Treponema pallidum*. A origem da doença é incerta, mas ela ganhou destaque histórico no final do século XV, quando se espalhou pela Europa, principalmente entre soldados franceses e italianos, em decorrência de guerras para conquista de territórios.<sup>1</sup> O agente etiológico foi descoberto no início do século XX, em 1905, por Schaudinn e Hoffman, e, um ano depois, Landsteiner introduziu o método da microscopia de campo escuro. Em 1910, Wasserman apresentou o primeiro teste que detectava anticorpos não específicos, porém, somente em 1949 foi criado, por Nelson e Mayer, o primeiro teste que detectava anticorpos específicos para *T. pallidum*.<sup>1</sup> Já o tratamento com a penicilina, antibiótico que mudaria radicalmente o prognóstico da doença, foi utilizado pela primeira vez apenas em 1943.<sup>2</sup>

Apesar de ser uma doença antiga e tratável, a sífilis permanece como um problema de saúde pública há mais de 100 anos. Um dos maiores impactos dessa infecção é a sífilis congênita (SC), que resulta da transmissão do *T. pallidum* da gestante infectada ao concepto, principalmente pela via transplacentária e, raramente, durante o parto.<sup>3</sup>

A sífilis pode ser transmitida ao feto em qualquer momento da gestação e a probabilidade da transmissão vertical está diretamente relacionada ao estágio clínico no qual a mãe se encontra (sífilis precoce resulta em maior transmissão do que a sífilis latente tardia) e à idade gestacional na qual a mulher adquiriu a sífilis (o risco de transmissão aumenta com o avançar da gestação).<sup>3</sup>

Fatores de risco maternos para SC incluem pré-natal inadequado, mulheres jovens, baixo nível socioeconômico, prostituição e o uso de drogas ilícitas.<sup>4</sup> Além disso, outros fatores documentados também foram assinalados, como a presença de outra infecção sexualmente transmissível e ter relações sexuais com mais de um parceiro nos últimos 12 meses.<sup>5</sup> No Brasil, um estudo baseado em uma coorte nacional hospitalar mostrou maior prevalência de sífilis em gestantes com menos de oito anos de escolaridade, que se declararam pretas ou pardas, em mulheres sem pré-natal e em gestantes atendidas em serviços públicos ou mistos.<sup>6</sup>

Gestantes com sífilis não tratada podem apresentar desfechos gestacionais adversos, como perda fetal, natimorto, morte neonatal, prematuridade, baixo peso ao nascer e evidência clínica de SC.<sup>7</sup>

A extensão do dano fetal depende do estágio de desenvolvimento em que ocorreu a infecção e do tempo decorrido antes do início do tratamento. A infecção do concepto no início da gravidez e na ausência de tratamento pode levar à morte fetal com aborto espontâneo (geralmente após

o primeiro trimestre) ou natimorto, mas também pode ocorrer parto prematuro ou morte neonatal. No entanto, cerca de dois terços dos nascidos vivos com SC são assintomáticos ao nascimento e, nas crianças sintomáticas, a maioria das manifestações clínicas são inespecíficas, como hepatomegalia, esplenomegalia, icterícia e exantema.<sup>3</sup>

Um modelo epidemiológico, ajustado para vigilância sentinela, indicou que a prevalência global estimada de sífilis em gestantes, em 2016, foi de 0,69% (IC 95% 0,57 - 0,81%), resultando em uma taxa global de SC de 473 casos (IC95% 385-561) por 100.000 nascidos vivos.<sup>8</sup>

Em 2020, os países das Américas registraram 29.149 casos de SC, correspondendo a uma taxa de incidência de 2,01 para cada 1.000 nascidos vivos, conforme dados divulgados pela Organização Pan-Americana da Saúde (OPAS). O Brasil foi identificado como o responsável por uma expressiva parcela desses casos, contabilizando 76% do total notificado no período.<sup>9</sup>

Conforme os dados epidemiológicos mais recentes, divulgados pelo Boletim do Ministério da Saúde de 2022, referentes ao ano de 2021, o Sistema de Informação de Agravos de Notificação (SINAN) registrou, no Brasil, 74.095 casos de sífilis em gestantes e 27.019 casos de SC, resultado em 192 óbitos por SC. Embora a taxa de incidência de SC tenha demonstrado um decréscimo modesto, entre 2018 e 2020, observou-se um acréscimo significativo de 14,6% entre 2020 e 2021.<sup>10</sup>

A Organização Mundial de Saúde (OMS) iniciou, em 2007, um programa de estratégias para a eliminação da transmissão vertical da sífilis, cuja última atualização foi publicada em 2021, com o objetivo de alcançar essa meta até o ano de 2030. Para validar a eliminação da SC, foi estabelecida a meta de redução das taxas para 50 casos, ou menos, de SC para cada 100.000 nascidos vivos. O processo para isso ocorrer envolve dois outros objetivos:  $\geq 95\%$  das gestantes testadas para sífilis e  $\geq 95\%$  dessas gestantes soropositivas tratadas adequadamente.<sup>11</sup> Atualmente, 15 países e territórios no mundo receberam a validação da OMS, sendo que Cuba, em 2015, foi o primeiro deles e Omã, por sua vez, o último, em 2022.<sup>12</sup> Isto demonstra que, a partir de políticas públicas bem estruturadas e consistentes, é possível erradicar a SC em países de baixa e média renda.

A taxa de incidência de SC, em 2021, no Brasil, foi 9,9 casos/1.000 nascidos vivos,<sup>10</sup> número quase 20 vezes maior que o alvo estabelecido pela OMS, revelando o quão longe o país se encontra da eliminação da transmissão vertical da sífilis.

A única medida eficaz para prevenir a SC é o tratamento das gestantes infectadas com penicilina G parenteral. Analisando o tratamento para sífilis no pré-natal, Alexander *et al*<sup>13</sup> demonstraram a eficácia de 99,7% (339/340) na cura da infecção na gestante e 98,2% (334/340) na prevenção da SC, considerando todas as fases clínicas da sífilis na gestante.

Na ausência de identificação da gestante infectada e subsequente tratamento adequado, o manejo do recém-nascido (RN), exposto verticalmente à sífilis, torna-se um desafio. Como citado anteriormente, a maioria das crianças com SC são assintomáticas ao nascimento. Somado a isso, não há disponibilidade de um exame sorológico que confirme, ou determine, com precisão o diagnóstico de sífilis no RN, o que impõe a prática de algoritmos para guiar a equipe assistencial. A abordagem envolve, assim, uma combinação de elementos: informações sobre o tratamento materno na gestação, comparação de testes não-treponêmicos do binômio mãe-filho e a avaliação clínico-laboratorial da criança.<sup>14</sup> Frequentemente, essa estratégia requer a realização de exames invasivos e, em algumas situações, internação prolongada para tratamento do RN.

Considerando os desafios citados acima, o presente estudo foi estruturado com o objetivo de identificar e analisar variáveis maternas e neonatais que fossem preditoras para o desfecho da SC. De acordo com a resolução 03/2010, do Programa de Pós-graduação em Ciências da Saúde, Área de Concentração Saúde da Criança e do Adolescente, da Faculdade de Medicina da Universidade Federal de Minas Gerais, a revisão da literatura e os resultados serão apresentados sob a forma de artigo de revisão e artigo original, respectivamente.

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## 2. REVISÃO DA LITERATURA

Artigo de revisão – versão em word do artigo publicado disponível no ANEXO 1.

### **Maternal and perinatal risk factors associated with congenital syphilis**

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**Keywords:** Pregnant Woman; Syphilis, Congenital; Prenatal Care

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## ABSTRACT

**Objective:** Mother-to-child transmission of syphilis remains an important global public health problem. Untreated intrauterine infection may result in adverse events for the fetus or newborn (NB). Maternal risk factors, such as prenatal care, early diagnosis, and appropriate treatment, significantly impact the likelihood of vertical transmission of syphilis. The purpose of this review is to evaluate maternal risk factors for congenital syphilis and the characteristics of exposed NB.

**Methods:** A total of 14 studies were evaluated, including 8 cohort studies, 4 cross-sectional and 2 control cases. 12,230 women were included, with confirmed or highly probable congenital syphilis outcome, and 2,285 NB. The studies evaluated risk factors for congenital syphilis, which were maternal, demographic, obstetric factors and characteristics of the exposed NB.

**Results:** Included in the risk factors studied, inadequate prenatal care and late onset, as well as inadequate or late treatment of maternal syphilis were significant risk factors for the outcome of congenital syphilis. When the time set of maternal diagnosis was correlated with neonatal infection, there was a tendency to worsen prognosis (more infected NB) in women diagnosed later in pregnancy, as well as women who underwent few prenatal consultations and inadequate treatment. Women with recent syphilis with high VDRL titres had a higher rate of vertical transmission. The prior history of syphilis with adequate treatment was identified as a protective factor, resulting in lower rates of congenital syphilis. Among the epidemiological and demographic aspects surveyed, it was observed that low age, lower schooling, unemployment, low family income and no fixed residence were associated with higher risk of congenital syphilis.

**Conclusions:** The association of syphilis with adverse socio-economic conditions and inadequate prenatal care suggests that the improvement of the population's living conditions and equitable access to quality health services may have an impact on the reduction of congenital syphilis.

## INTRODUCTION

Congenital syphilis (CS) is the result of the transplacental transmission of the spirochete *Treponema pallidum* from the infected pregnant woman to the conceptus, during any time of pregnancy, and, rarely, during childbirth. Untreated intrauterine infection may result in abortion, stillbirth, Hydrops fetalis, premature delivery, perinatal death, in addition to clinical

manifestations in the postnatal period. [1, 2]. Prenatal care programs that include testing and treatment of pregnant women have been shown to be effective in reducing adverse pregnancy outcomes. [1]. Early screening for maternal syphilis during pregnancy associated with immediate treatment with benzathine penicillin of infected mothers leads to mother and baby healing and prevents the main complications associated with vertical transmission of syphilis [3].

Despite being an ancient and preventable disease, CS remains a public health problem in several countries. In 2016, the worldwide estimated prevalence of syphilis in pregnant women was 0.69% (95% CI 0.57 - 0.81%) resulting in an overall congenital syphilis rate from 473 (385-561) to 100,000 live births and a total of 661,000 cases of CS, including 355,000 cases of adverse outcomes related to pregnancy or birth [4].

In Brazil, the 2020 detection rate of syphilis in pregnant women was 21.6/1,000 live births. The incidence rate of congenital syphilis was 7.7/1,000 live births and the mortality rate due to CS was 6.5/100,000 live births. [5]

Vertical transmission of syphilis has been well documented for several decades, but the diagnosis of CS remains a demanding situation. Most newborns (NB) are asymptomatic at birth and gold standard tests for diagnosis, such as dark field *Treponema* research and polymerase chain reaction (CRP), are not available in clinical practice. The detection of IgG antibodies against *Treponema* in newborns does not allow the diagnosis of congenital infection due to the maternal-fetal transfer of these antibodies, and it is not possible to distinguish maternal antibodies from endogenous antibodies produced by the offspring. The detection of specific IgM *treponemal* antibodies, which do not cross the placental barrier, would confirm fetal infection, however, these laboratory tests have low sensitivity, so they are not validated for commercial use [6].

There is no further evaluation that could accurately determine the infection in the newborn. Non-treponemal tests are generally used in the evaluation of neonates with suspected CS because they provide quantitative results that can be compared with maternal results. They are also recommended to monitor diseases after treatment. These tests, however, are not specific and are not automated, and differences in the results in testing at alternate times can be observed. [6,7]

Hence, for the management of newborns exposed vertically to syphilis and the consequent decision to treat or not the baby, the CS case definition should follow validated criteria defined

by the World Health Organization or official protocols from Health Ministry of several countries. These criteria consider the combination of clinical, laboratory and epidemiological evaluation, including the presence of known risk factors for CS. In this sense, several studies evaluating maternal and neonatal factors associated with CS have been published. This systematic review was accomplished to critically compile and analyze the results published to date with the aim of improving the health care of pregnant women and newborns.

## METHODS

The PECO question was defined as: Population: infants exposed to syphilis during pregnancy and their mothers; Exposure: risk factors in prenatal and perinatal time; Control: infants without risk factors; Outcome: congenital syphilis (confirmed or probable).

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol was used to construct this systematic review. Registration in PROSPERO: CRD42021279652.

### *Search strategy*

A systematic search was conducted in the main electronic online databases (Medline, EMBASE, SciELO and Cochrane Library) of all articles registered until February 2021, without language restriction. The search terms used were "Syphilis Serodiagnosis", "treponemal infections", "pregnant women", "prenatal care", "risk factors" and "congenital syphilis".

The search performed in each of the bases with the boolean descriptors and operators are described below:

- Pubmed: ((Syphilis Serodiagnosis) OR (Treponemal Infections)) AND ((Pregnant Women) OR (Prenatal Care) OR (risk factors)) AND (Syphilis, Congenital)
- EMBASE: ('syphilis serology' OR treponematosi OR 'treponemal infection') AND ('pregnant woman' OR 'prenatal care' OR 'risk factor') AND 'congenital syphilis'.
- Cochrane: ((Syphilis Serodiagnosis) OR (Treponemal Infections)) AND ((Pregnant Women) OR (Prenatal Care)) AND (Syphilis, Congenital).
- SciELO ("Syphilis Serodiagnosis" OR "Treponemal Infections") AND ("Pregnant Women" OR "Prenatal Care" OR "risk factors") AND "Syphilis Congenital"

In addition, we manually reviewed the bibliographic citations of the included studies to verify possible articles identified in the initial research.

### *Selection criteria*

Observational studies (cross-sectional, case-control and prospective and retrospective cohort) that investigated risk factors for congenital syphilis in children exposed to syphilis were included. The presence of a treponemal and a non-treponemal positive test during pregnancy or delivery were considered a diagnosis of maternal syphilis, or if the criteria for congenital syphilis were met for the neonates of the mothers in the study. Congenital syphilis was defined according to CDC/USA surveillance criteria [8] for confirmed and highly probable congenital syphilis or use of IgM treponemal test at birth and/or IgG at 18 months.

Exclusion criteria included studies in which the population was not pregnant, or studies that had unclear statistical analysis methods, or that did not present data possible to be extracted for analysis, in addition to duplicates and studies presenting overlapped data. Articles whose population studied was specific as pregnant women with HIV or deprived of liberty were also removed, since the variable considered in this review was to evaluate exposure or not to certain risk factors. In addition, studies that used possible or unlikely definitions of congenital syphilis according to the CDC criteria [9], or that were not clear regarding the inclusion criteria of children were excluded.

Two researchers (LBP, BSFS) performed the selection and extraction of the data independently. Discrepancies were resolved by a consensus among all authors.

### *Data extraction and quality analysis*

Each author conducted the individual reading of the articles, followed by a detailed review of all studies that met the inclusion criteria for data extraction, such as author name, year of publication, study design, sample size, main characteristics of the population, as well as location, period, and limitations of the studies. These characteristics were grouped for analysis and shown in Table 1.

The risk of bias was assessed using the Newcastle-Ottawa scale [10] for control and cohort case studies and an adapted form of this scale for cross-sectional studies [11]. Stars are considered to evaluate study quality, with nine to ten stars indicating “very good” quality, seven to eight stars indicating “good” quality, five to six stars indicating “satisfactory” quality, and zero to four stars indicating “unsatisfactory” quality. A maximum of 9 stars are considered for case-control studies and cohorts and a maximum of 7 stars are considered for cross-sectional studies.

The quality of the studies was evaluated by two reviewers (LBP, BSF) severally using the described scale and any disagreement was consensually resolved with two other reviewers (MRR, EC). Study practicalities have also been described.

### *Statistical analysis*

The information was synthesized in table 3 with descriptive variables including the sample size and the comparative analysis that register measures of association (relative risk and odds ratio) with respective confidence intervals at 95% and p-value.

## **RESULTS**

### *Studies Selection*

Our search identified 775 publications in the databases. Four articles cited in the references of the included studies were added. After removing the duplications (190) and excluding the studies after reading the title and abstract (415), 174 articles were considered potentially relevant and independently reviewed. Of these, 14 studies met the eligibility criteria, 8 cohort studies, 4 cross-sectional and 2 control cases (Figure 1).

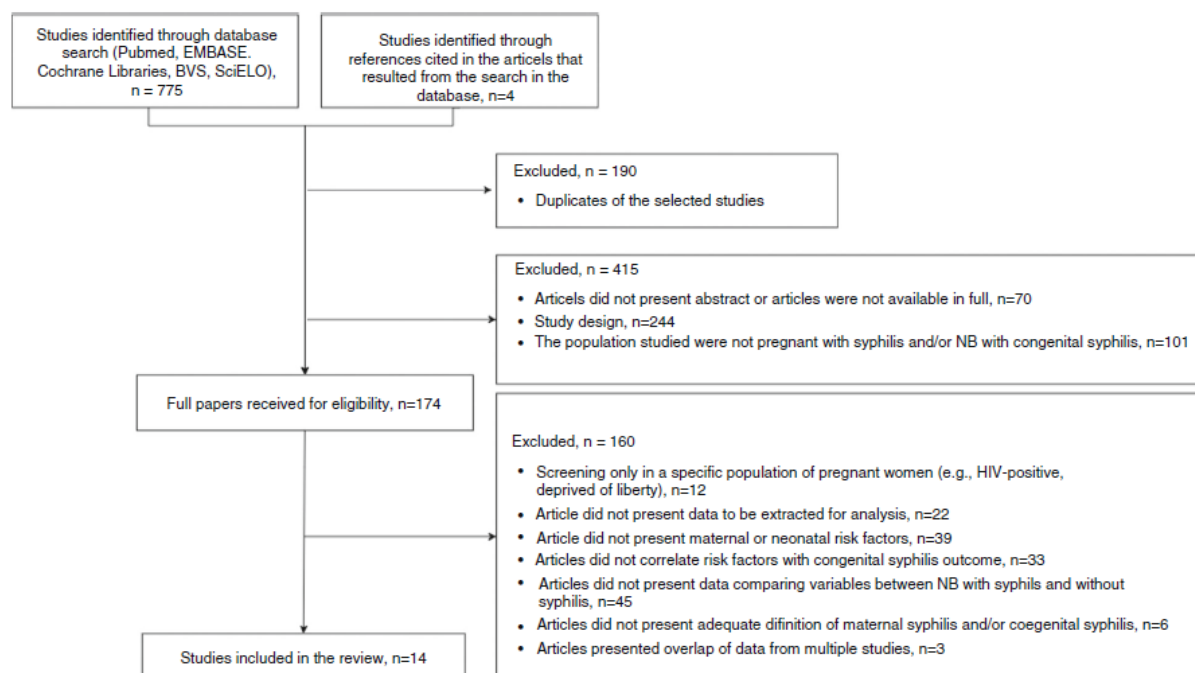


**Figure 1:** Flowchart of the study selection process.

Six studies were from the U.S., four from China and four from other countries. A total of 12,230 women who were diagnosed with syphilis in the current pregnancy were added, resulting in 2,285 children diagnosed with confirmed or presumed syphilis. The main characteristics of the included studies are presented in Table 1.

**Table 1** - Main features of the studies included in the review

| <b>Reference</b>                           | <b>Design of experiment</b> | <b>Study location</b> | <b>Study duration</b> | <b>Number of pregnant women diagnosed with syphilis</b> | <b>Number of newborns with presumed or confirmed syphilis</b> |
|--------------------------------------------|-----------------------------|-----------------------|-----------------------|---------------------------------------------------------|---------------------------------------------------------------|
| Rawstron et al <sup>23</sup> (1993)        | Cohort                      | U.S.                  | 1988 -1989            | 397                                                     | 75                                                            |
| McFarlin et al <sup>24</sup> (1994)        | Cohort                      | U.S.                  | 1991 - 1992           | 190                                                     | 72                                                            |
| Risser and Hwang <sup>21</sup> (1997)      | Cross-sectional             | U.S.                  | 1990 - 1992           | 1070                                                    | 694                                                           |
| Mobley et al <sup>15</sup> (1998)          | Cohort                      | U.S.                  | 1991 - 1993           | 673                                                     | 186                                                           |
| Tikhonova et al <sup>28</sup> (2003)       | Cohort                      | Russia                | 1995 - 1999           | 715                                                     | 544                                                           |
| Lago et al <sup>12</sup> (2004)            | Case-control                | Brazil                | 1998 - 1999           | 118                                                     | 77                                                            |
| Liu et al <sup>18</sup> (2010)             | Cohort                      | China                 | 2002- 2007            | 554                                                     | 29                                                            |
| Kirkcaldy et al <sup>20</sup> (2011)       | Cross-sectional             | U.S.                  | 2004 -2008            | 242                                                     | 78                                                            |
| Tridapalli et al <sup>19</sup> (2012)      | Cohort                      | Italy                 | 2006 - 2007           | 203                                                     | 51                                                            |
| Qin et al <sup>14</sup> (2014)             | Cohort                      | China                 | 2007 - 2012           | 2.671                                                   | 96                                                            |
| Hong et al <sup>13</sup> (2017)            | Cohort                      | China                 | 2003-2014             | 4746                                                    | 162                                                           |
| Biswas et al <sup>16</sup> (2018)          | Cross-sectional             | U.S.                  | 2012 - 2014           | 427                                                     | 164                                                           |
| Wang et al <sup>17</sup> (2019)            | Caso-control                | China                 | 2011 - 2014           | 155                                                     | 27                                                            |
| Anugulruengkitt et al <sup>22</sup> (2020) | Cross-sectional             | Thailand              | 2013 - 2017           | 69                                                      | 30                                                            |

Of the 14 selected studies, one was classified as very good, four as good, six satisfactory and four unsatisfactory (Table 2).

**Table 2** - Quality analysis of studies that evaluated maternal, obstetric, and neonatal risk factors associated with congenital syphilis according to the Newcastle-Ottawa scale

| Reference                                  | Design of experiment             | Selection | Comparability | Exposure* | Outcome** | Quality        |
|--------------------------------------------|----------------------------------|-----------|---------------|-----------|-----------|----------------|
| Lago et al <sup>12</sup> (2004)            | Case-control                     | ★★★       | ★             | ★         | -         | Satisfactory   |
| Wang et al <sup>17</sup> (2019)            | Case-control                     | ★★★       | ★★            | ★★★       | -         | Good           |
| Rawstron et al <sup>23</sup> (1993)        | Cohort                           | ★★★       | ★             | -         | ★★        | Satisfactory   |
| McFarlin et al <sup>24</sup> (1994)        | Cohort                           | ★★        | ★             | -         | ★         | Unsatisfactory |
| Mobley et al <sup>15</sup> (1998)          | Cohort                           | ★★★★      | ★             | -         | ★★        | Good           |
| Tikhonova et al <sup>28</sup> (2003)       | Cohort                           | ★★★       | ★             | -         | ★★        | Satisfactory   |
| Liu et al <sup>18</sup> (2010)             | Cohort                           | ★★★★      | ★             | -         | ★★★       | Good           |
| Tridapalli et al <sup>19</sup> (2012)      | Cohort                           | ★         |               | -         | ★★        | Unsatisfactory |
| Qin et al <sup>14</sup> (2014)             | Cohort                           | ★★★★      | ★★            | -         | ★★★       | Very good      |
| Hong et al <sup>13</sup> (2017)            | Cohort                           | ★★★★      | ★             | -         | ★★★       | Good           |
| Risser and Hwang <sup>21</sup> (1997)      | Cross-sectional <sup>&amp;</sup> | ★★        | ★★            | -         | ★★        | Satisfactory   |
| Kirkcaldy et al <sup>20</sup> (2011)       | Cross-sectional <sup>&amp;</sup> | ★★        | ★             | -         | ★★        | Satisfactory   |
| Biswas et al <sup>16</sup> (2018)          | Cross-sectional <sup>&amp;</sup> | ★★        | ★             | -         | ★★        | Satisfactory   |
| Anugulruengkitt et al <sup>22</sup> (2020) | Cross-sectional <sup>&amp;</sup> | ★★        | ★             | -         | ★★        | Satisfactory   |

\* *Exposure: cohort studies do not have “exposure” according to study design and scoring criteria in Newcastle-Ottawa scale.*

\*\* *Outcome: case-control studies do not present “outcome” according to and scoring criteria in Newcastle-Ottawa scale.*

In women diagnosed with syphilis during pregnancy or childbirth with the outcome of confirmed or probable congenital syphilis the variables identified were:

- Demographics and maternal history (residence, education, income, occupation, immigration; age, race, marital status, history of other sexually transmitted infection (STIs), number of sexual partners, treatment for syphilis prior to pregnancy, HIV co-infection);
- Obstetrics (previous pregnancy, history of pregnancy with adverse outcome, previous abortion, prenatal abortion, treatment during pregnancy, gestational age at the time of treatment, gestational age at the time of diagnosis, non-treponemal test result, syphilis stage, and information on prenatal funding);
- Neonatal: gender, birth weight, gestational age, Apgar, intensive care unit stay (ICU), head circumference, cerebrospinal fluid, blood count and long bones radiographs.

Table 3 presents the studies according to the significant variables evaluated and the magnitude of risk found.

| Table 3 - Maternal and obstetric factors related to congenital syphilis |                                          |                                                                                                                                                   |   |                                                                                                                                                                                |
|-------------------------------------------------------------------------|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Socio-Demographic                                                       | Reference                                | Variables                                                                                                                                         | P | RR or OR (IC95%)                                                                                                                                                               |
| Age                                                                     | Qin et al <sup>14</sup><br>(2014)        | Mother age <ul style="list-style-type: none"> <li>• &lt;25 years</li> <li>• 25-30 years</li> <li>• 30-35 years</li> <li>• &gt;35 years</li> </ul> | - | OR non adjusted:<br>0,62 (0,49-0,78) <ul style="list-style-type: none"> <li>• 1</li> <li>• 0,44 (0,27-0,70)</li> <li>• 0,27 (0,14-0,49)</li> <li>• 0,34 (0,17-0,69)</li> </ul> |
|                                                                         | Tridapalli et al <sup>19</sup><br>(2012) | Mother age < 20 years                                                                                                                             | - | RR: 3,44 (1,63-7,27)                                                                                                                                                           |
| Ethnicity                                                               | Mobley et al <sup>15</sup><br>(1998)     | Black ethnicity                                                                                                                                   | - | OR adjusted: 4,5 (1,3-15,5)                                                                                                                                                    |
|                                                                         | Risser and Hwang <sup>21</sup> (1997)    | Hispanic ethnicity                                                                                                                                | - | OR 1,8 (1,3-2,5)                                                                                                                                                               |

|                       |                                         |                                                                                                                                                                                    |          |                                                                                                                                                            |
|-----------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                       | Qin et al <sup>14</sup><br>(2014)       | Chinese minority ethnicity (' <i>non Han</i> ')                                                                                                                                    | -        | OR non adjusted: 1,13<br>(1,01-1,25)                                                                                                                       |
| <b>Income</b>         | Lago et al <sup>12</sup><br>(2004)      | Income < US\$ 30/per month                                                                                                                                                         | -        | OR adjusted: 2,8 (1,1-7,4)                                                                                                                                 |
| <b>Location</b>       | Hong et al <sup>13</sup><br>(2017)      | Antenatal clinic in less development area                                                                                                                                          | p <0,001 | OR adjusted: 1,62 (1,38-1,91)                                                                                                                              |
|                       | Mobley et al <sup>15</sup><br>(1998)    | Rural areas resident                                                                                                                                                               | -        | OR adjusted: 2,0 (1,4-2,9)                                                                                                                                 |
| <b>Marital status</b> | Qin et al <sup>14</sup><br>(2014)       | Marital status: single                                                                                                                                                             | -        | OR non adjusted: 2,88<br>(1,64-5,05)                                                                                                                       |
|                       | Lago et al <sup>12</sup><br>(2004)      |                                                                                                                                                                                    | -        | OR adjusted: 2,8 (1,1-7,8)                                                                                                                                 |
| <b>Migration</b>      | Wang et al <sup>17</sup><br>(2019)      | Immigrant                                                                                                                                                                          | -        | OR non adjusted: 4,9 (1,7-17,7)                                                                                                                            |
|                       | Tikhonova et al <sup>28</sup><br>(2003) |                                                                                                                                                                                    | p<0,001  | -                                                                                                                                                          |
| <b>Education</b>      | Hong et al <sup>13</sup><br>(2017)      | Education: primary education or without schooling                                                                                                                                  | p<0,001  | OR adjusted 1,5 (1,17-1,92)                                                                                                                                |
|                       | Biswas et al <sup>16</sup><br>(2018)    | Any level of higher education or more as a protective factor                                                                                                                       | p 0,006  | -                                                                                                                                                          |
|                       | Lago et al <sup>12</sup><br>(2004)      | 10 years of education or more as a protective factor                                                                                                                               | -        | OR adjusted: 0,2 (0,1-0,7)                                                                                                                                 |
|                       | Qin et al <sup>14</sup><br>(2014)       | Education: <ul style="list-style-type: none"> <li>• Complete and incomplete primary</li> <li>• Middle school</li> <li>• Technical education</li> <li>• Higher education</li> </ul> | -        | OR non adjusted: <ul style="list-style-type: none"> <li>• 1</li> <li>• 0,27 (0,17-0,45)</li> <li>• 0,23 (0,12-0,42)</li> <li>• 0,40 (0,19-0,83)</li> </ul> |
| <b>Drug</b>           | Mobley et al <sup>15</sup><br>(1998)    | Use of cocaine                                                                                                                                                                     | -        | OR non adjusted 9,3 (2,6-33,1)                                                                                                                             |
| <b>Sex partners</b>   | Qin et al <sup>14</sup><br>(2014)       | Number of sexual partners in the 6                                                                                                                                                 | -        | 1,50 (1,01-2,22) <ul style="list-style-type: none"> <li>• 1</li> <li>• 3,82 (1,11-13,18)</li> </ul>                                                        |

|                                              |                                     | months prior to pregnancy                                                                                                                                          |                    |                                   |
|----------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------------------------|
|                                              |                                     | <ul style="list-style-type: none"> <li>• 1</li> <li>• <math>\geq 3</math></li> </ul>                                                                               |                    |                                   |
| <b>Previous Syphilis</b>                     | Hong et al <sup>13</sup> (2017)     | Treatment for pre-pregnancy syphilis                                                                                                                               | p<0,001            | OR adjusted: 1,65 (1,36-2,02)     |
|                                              | Rawstron et al <sup>23</sup> (1993) |                                                                                                                                                                    | p<0,026            | -                                 |
|                                              | Qin et al <sup>14</sup> (2014)      | Past history of syphilis                                                                                                                                           | -                  | OR non adjusted: 0,24 (0,11-0,53) |
| <b>Pregnancy loss</b>                        | Lago et al <sup>12</sup> (2004)     | Stillborn prior to current pregnancy                                                                                                                               | -                  | OR non adjusted: 4,6 (1,2-17,8)   |
|                                              | Mobley et al <sup>15</sup> (1998)   | $\geq 1$ gestational loss                                                                                                                                          | -                  | OR adjusted 0,3 (0,2-0,6)         |
| <b>HIV positivity</b>                        | Hong et al <sup>13</sup> (2017)     | HIV co-infection                                                                                                                                                   | p 0,039            | OR adjusted: 4,01 (1,08-14,93)    |
|                                              | Lago et al <sup>12</sup> (2004)     |                                                                                                                                                                    | -                  | OR non adjusted: 16,0 (3,1-109,5) |
| Variable related to prenatal care            | Reference                           | Variables                                                                                                                                                          | P                  | RR or OR (IC95%)                  |
| <b>Prenatal care service</b>                 | Biswas et al <sup>16</sup> (2018)   | Service where prenatal care was held: <ul style="list-style-type: none"> <li>• Private</li> <li>• No health insurance</li> </ul>                                   | p<0,001            | -                                 |
|                                              | Biswas et al <sup>16</sup> (2018)   | Prenatal care as a protective factor <ul style="list-style-type: none"> <li>• Any time</li> <li>• <math>\geq 40</math> days before delivery</li> </ul>             | p<0,001<br>p<0,001 | -                                 |
| <b>GA at the first prenatal consultation</b> | Biswas et al <sup>16</sup> (2018)   | GA at the first prenatal consultation <ul style="list-style-type: none"> <li>• 1st trimester as a risk factor</li> <li>• 3rd trimestre as a risk factor</li> </ul> | p<0,001            | -                                 |

|                                                |                                          |                                                                                      |         |                                   |
|------------------------------------------------|------------------------------------------|--------------------------------------------------------------------------------------|---------|-----------------------------------|
| <b>Prenatal care</b>                           | Tikhonova et al <sup>28</sup><br>(2003)  | GA at the first prenatal consultation $\leq$ 20 weeks                                | p<0,001 | -                                 |
|                                                | Hong et al <sup>13</sup><br>(2017)       | GA at the first prenatal consultation $\geq$ 28 weeks                                | p<0,001 | OR adjusted: 21,47 (18,07-25,50)  |
|                                                | Biswas et al <sup>16</sup><br>(2018)     | Prenatal care as a protective factor                                                 | p<0,001 | -                                 |
|                                                | Risser and Hwang <sup>21</sup> (1997)    |                                                                                      | p<0,001 | -                                 |
|                                                | Mobley et al <sup>15</sup><br>(1998)     | Absence of prenatal care                                                             | -       | OR adjusted: 2,7 (1,3-5,5)        |
|                                                | Qin et al <sup>14</sup><br>(2014)        |                                                                                      | -       | OR non adjusted: 4,00 (2,64-6,05) |
|                                                | Tikhonova et al <sup>28</sup><br>(2003)  |                                                                                      | p<0,001 | OR ajustado: 2,8 (1,7-4,7)        |
|                                                | Risser and Hwang <sup>21</sup> , 1997    |                                                                                      | -       | OR: 6,0 (3,9-9,2)                 |
|                                                | Rawstron et al <sup>23</sup><br>(1993)   |                                                                                      | p<0,001 | -                                 |
|                                                | Lago et al <sup>12</sup><br>(2004)       | < 6 prenatal consultations                                                           | -       | OR adjusted: 3,2 (1,3-8,1)        |
| <b>Prenatal visit</b>                          | Tikhonova et al <sup>28</sup><br>(2003)  | $\leq$ 3 prenatal consultations                                                      | p<0,001 | -                                 |
|                                                | Tridapalli et al <sup>19</sup><br>(2012) | Absence of screening for syphilis in prenatal care                                   | -       | RR: 3,1 (1,47-6,21)               |
|                                                | Biswas et al <sup>16</sup><br>(2018)     |                                                                                      | p<0,001 | -                                 |
|                                                | Biswas et al <sup>16</sup><br>(2018)     | 1st test for syphilis < 40 days before delivery                                      | p<0,001 | -                                 |
|                                                | Kirkcaldy et al <sup>20</sup><br>(2011)  | First test for syphilis performed in the 1st or 2nd trimester as a protective factor | p<0,001 | -                                 |
| <b>Screening for syphilis in prenatal care</b> |                                          |                                                                                      |         |                                   |

|                                        |                                     |                                                                                                             |         |   |
|----------------------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------------------|---------|---|
| <b>Maternal treatment for syphilis</b> | McFarlin et al <sup>24</sup> (1994) | Maternal treatment for syphilis before pregnancy or early in pregnancy (14 weeks GA) as a protective factor | p 0,005 | - |
|----------------------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------------------|---------|---|

| Syphilis diagnosis                              | Reference                                  | Variables                                                                                                                                                           | P       | RR or OR (IC95%)                                                                                                                                                                                                  |
|-------------------------------------------------|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>GA at diagnosis</b>                          | Wang et al <sup>17</sup> (2019)            | GA at diagnosis > 36 weeks                                                                                                                                          | -       | OR non adjusted: 24,1 (3,6- >1000)                                                                                                                                                                                |
| <b>Screening for syphilis</b>                   | Tikhonova et al <sup>28</sup> (2003)       | Screening for syphilis ≥ 28 weeks                                                                                                                                   | p<0,001 | OR adjusted: 4,0 (2,6-6,0)                                                                                                                                                                                        |
|                                                 | Tikhonova et al <sup>28</sup> (2003)       | Screening for syphilis ≤ 27 weeks                                                                                                                                   | p<0,001 | -                                                                                                                                                                                                                 |
|                                                 | Anugulruengkitt et al <sup>22</sup> (2020) | Positive serology for syphilis in the 3rd trimester                                                                                                                 | p<0,001 | -                                                                                                                                                                                                                 |
| <b>Titers of nontreponemal antibodies tests</b> | Liu et al <sup>18</sup> (2010)             | Logarithm (1/titer of nontreponemal antibodies)<br>*Values have been transformed using the reciprocal TRUST title log                                               | p<0,001 | OR non adjusted: 11,18 (5,16-24,24)                                                                                                                                                                               |
|                                                 | Qin et al <sup>14</sup> (2014)             | Titers of nontreponemal antibodies tests<br><ul style="list-style-type: none"> <li>• 1:1</li> <li>• 1:8</li> <li>• 1:16</li> <li>• 1:32</li> <li>• ≥1:64</li> </ul> | -       | OR non adjusted: 2,07 (1,83-2,34)<br><ul style="list-style-type: none"> <li>• 1</li> <li>• 2,66 (1,06-6,63)</li> <li>• 10,38 (4,66-23,12)</li> <li>• 13,56 (5,93-31,02)</li> <li>• 38,75 (16,08-93-39)</li> </ul> |
|                                                 | Qin et al <sup>14</sup> (2014)             | Titers of nontreponemal antibodies test<br><ul style="list-style-type: none"> <li>• &lt;1:8</li> <li>• ≥1:8</li> </ul>                                              | -       | OR non adjusted:<br><ul style="list-style-type: none"> <li>• 1</li> <li>• 10,62 (6,69-16,85)</li> </ul>                                                                                                           |
|                                                 | McFarlin et al <sup>24</sup> (1994)        | High VDRL titer in diagnosis                                                                                                                                        | p<0,001 | -                                                                                                                                                                                                                 |

|                                                  | McFarlin et al <sup>24</sup><br>(1994)   | High VDRL titer in delivery                                                                                                                         | p<0,001  | -                                                                                                                                     |
|--------------------------------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------------------------------------------------------------------------------------------------------------------------------------|
|                                                  | Rawstron et al <sup>23</sup><br>(1993)   | RPR titers: <ul style="list-style-type: none"> <li>• Geometric mean: 1:4.5</li> <li>• Mean: 1:182</li> </ul>                                        | p<0,001  | -                                                                                                                                     |
| <b>Stage of syphilis</b>                         | Qin et al <sup>14</sup><br>(2014)        | Primary syphilis                                                                                                                                    | -        | OR non adjusted: 65,90 (38,29-113,44)                                                                                                 |
|                                                  | Kirkcaldy et al <sup>20</sup><br>(2011)  |                                                                                                                                                     | p 0,001  | -                                                                                                                                     |
|                                                  | Liu et al <sup>18</sup> (2010)           | Early syphilis (< 2 years)                                                                                                                          | p 0,001  | OR non adjusted: 5,01 (2,15-11,69)                                                                                                    |
|                                                  | Tikhonova et al <sup>28</sup><br>(2003)  | Primary or secondary syphilis versus latent syphilis                                                                                                | p<0,001  | OR adjusted: 3,7 (2,4-5,7)                                                                                                            |
|                                                  | Risser and Hwang <sup>21</sup> (1997)    | Clinical stage of syphilis: <ul style="list-style-type: none"> <li>• Primary or secondary</li> <li>• Early latent</li> <li>• Late latent</li> </ul> |          | OR (multivariate analysis): <ul style="list-style-type: none"> <li>• 1,0</li> <li>• 1,9 (1,3-2,9)</li> <li>• 3,4 (1,9-5,9)</li> </ul> |
|                                                  |                                          | Reinfection                                                                                                                                         |          | OR (univariate analysis): 2,4 (1,5-3,8)                                                                                               |
| <b>Maternal treatment</b>                        | <b>Reference</b>                         | <b>Variables</b>                                                                                                                                    | <b>P</b> | <b>RR or OR (IC95%)</b>                                                                                                               |
| <b>Inadequate maternal treatment</b>             | Hong et al <sup>13</sup><br>(2017)       | No treatment for syphilis                                                                                                                           | p<0,001  | OR adjusted: 68,28 (29,64-157,28)                                                                                                     |
|                                                  | Biswas et al <sup>16</sup><br>(2018)     |                                                                                                                                                     | p<0,001  | -                                                                                                                                     |
|                                                  | Biswas et al <sup>16</sup><br>(2018)     | Inadequate maternal treatment (latent syphilis only)                                                                                                | p<0,001  | -                                                                                                                                     |
|                                                  | Qin et al <sup>14</sup><br>(2014)        | Treatment <ul style="list-style-type: none"> <li>• Incomplete</li> <li>• Non-penicillin</li> </ul>                                                  | -        | OR non adjusted: <ul style="list-style-type: none"> <li>• 11,00 (6,46-18,72)</li> <li>• 3,24 (1,50-6,97)</li> </ul>                   |
|                                                  | Tridapalli et al <sup>19</sup><br>(2012) | Inadequate maternal treatment                                                                                                                       | p 0,0001 | RR: 15,32 (5,22-47,31)                                                                                                                |
| <b>Maternal treatment as a protective factor</b> | Rawstron et al <sup>23</sup><br>(1993)   | Any maternal treatment as a protective factor                                                                                                       | p<0,001  | -                                                                                                                                     |

|                          |                                            |                                                                                                                                               |         |                                                                                                                      |
|--------------------------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------------------------------------------------------------------------------------------------------------|
|                          | Anugulruengkitt et al <sup>22</sup> (2020) | Adequate maternal treatment as a protective factor                                                                                            | p<0,001 | -                                                                                                                    |
| <b>Time of treatment</b> | Kirkcaldy et al <sup>20</sup> (2011)       | Median GA week of maternal treatment: 36 weeks (6-42 week interval)                                                                           | p<0,001 | -                                                                                                                    |
|                          | Liu et al <sup>18</sup> (2010)             | GA at the time of maternal treatment for syphilis                                                                                             | p<0,001 | OR non adjusted: 1,1 (1,06-1,15)                                                                                     |
|                          | McFarlin et al <sup>24</sup> (1994)        |                                                                                                                                               | p 0,005 | --                                                                                                                   |
|                          | Qin et al <sup>14</sup> (2014)             | GA in the 1st treatment <ul style="list-style-type: none"> <li>• &lt;12 weeks</li> <li>• &gt;29 weeks</li> </ul>                              | -       | OR non adjusted: 2,67 (1,99-3,59) <ul style="list-style-type: none"> <li>• 1</li> <li>• 6,50 (2,36-17,86)</li> </ul> |
|                          | Hong et al <sup>13</sup> (2017)            | Benzathine penicillin started after 28 weeks of gestation                                                                                     | -       | OR adjusted: 8,06 (2,93-22,21)                                                                                       |
|                          | Biswas et al <sup>16</sup> (2018)          | Initiation of treatment <30 days before delivery                                                                                              | p<0,001 | -                                                                                                                    |
|                          | Qin et al <sup>14</sup> (2014)             | Time between the end of the 1st treatment and delivery <ul style="list-style-type: none"> <li>• &gt;4 weeks</li> <li>• &lt;4 weeks</li> </ul> | -       | OR non adjusted: <ul style="list-style-type: none"> <li>• 1</li> <li>• 16,89 (8,46-33,73)</li> </ul>                 |
| <b>Outcome</b>           | McFarlin et al <sup>24</sup> (1994)        | Outcome in current pregnancy: stillborn                                                                                                       | p<0,001 | -                                                                                                                    |

| Perinatal and neonatal variables | Reference                                  | Variables                  | P        | RR or OR (IC95%)               |
|----------------------------------|--------------------------------------------|----------------------------|----------|--------------------------------|
| <b>GA at birth</b>               | Mobley et al <sup>15</sup> (1998)          | 32-37 GA weeks             | -        | OR non adjusted: 2,0 (1,2-3,2) |
|                                  | Tridapalli et al <sup>19</sup> (2012)      | Prematurity                | p 0,0001 | RR: 5,72 (2,93-11,18)          |
|                                  | Anugulruengkitt et al <sup>22</sup> (2020) |                            | p 0,004  | -                              |
|                                  | Rawstron et al <sup>23</sup> (1993)        | < 34 GA weeks              | p 0,0004 | -                              |
| <b>Birth weight</b>              | Mobley et al <sup>15</sup> (1998)          | Birth weight: 1500 - 2499g | -        | OR non adjusted: 2,1 (1,3-3,2) |

|                               |                                               |                                              |          |                        |
|-------------------------------|-----------------------------------------------|----------------------------------------------|----------|------------------------|
|                               | Tridapalli et al <sup>19</sup><br>(2012)      | Birth weight < 2000g                         | p 0,0001 | RR: 7,85 (4,37-14,11)  |
|                               | Anugulruengkitt<br>et al <sup>22</sup> (2020) | Low Birth weight                             | p 0,009  | -                      |
|                               | Rawstron et al <sup>23</sup><br>(1993)        | Small newborns for<br>gestational age (p<10) | p 0,0001 | -                      |
| <b>Complementary<br/>exam</b> | Tridapalli et al <sup>19</sup><br>(2012)      | Change in<br>cerebrospinal fluid             | -        | RR: 11,05 (4,71-17,55) |
|                               | Tridapalli et al <sup>19</sup><br>(2012)      | Changes in<br>radiography of long<br>bones   | -        | RR: 3,51 (1,72-6,88)   |

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GA: Gestational age

The most studied maternal risk factors were age, race/color, marital status, history of another sexually transmitted infection, number of sexual partners, treatment for syphilis prior to pregnancy; co-infection with HIV, educational level, residence, income, occupation, and evaluation on immigration. Other factors such as menarche age, sexarche age, condom use before pregnancy and whether the woman was deprived of freedom or were a sex worker were less studied factors and did not obtain significance in any study.

Seven studies evaluated the level of education [12-18], one of them with statistical significance, demonstrating that the lower the level of education, the higher the risk of congenital syphilis [13]. In three of these studies [12, 14, 16], having more than 10 years of schooling was a protective factor (OR 0.2 [0.1-0.7]). The variable occupation was evaluated by four studies [12, 14, 17, 19], but none of them with statistical significance. The income variable was evaluated only by one study showing higher risk (OR 2.8 - 1.1 - 7.4) [12]. The variable “immigration” was evaluated by three studies [17, 19, 20] conducted in three different countries, China, U.S., and Italy. Only in the Chinese study [17] there was an association with higher risk for CS.

The history/treatment of syphilis prior to pregnancy was identified in two studies and it was associated to lower incidence of congenital syphilis. Qin et al evaluated maternal history of syphilis as a protective factor (OR=0.24, 0.11-0.53), probably due to previous treatment [14]. In the study by Hong et al, the incidence was 0.22% (95% CI, 0.05%-0.66%), with OR 1.6 (1.36-2.02) among babies born to women seropositive for syphilis and who were adequately treated before pregnancy, demonstrating that previous treatment may be inadequate or that reinfection may occur [13].

The obstetric factors assessed were previous pregnancy, history of pregnancy with adverse outcome, previous abortion, prenatal care, treatment during pregnancy, gestational age at diagnosis and treatment, results of non-treponemal tests, stages of syphilis and type of prenatal funding. The non-performance or late onset of prenatal care were risk factors for the outcome of CS in eight studies, all of them presenting statistical significance [12-16, 21, 23, 28]. Risser et al [21] evaluated the incidence of CS in the absence of prenatal care with OR 6.0 (3.9-9.2) and Hong et al [13] that evaluated this incidence with the beginning of prenatal care after 28 weeks of gestation with OR 21.47 (18.07-25.50). Another factor widely studied and with statistical significance was both incomplete or late treatment of maternal syphilis, as demonstrated by Qin et al who evaluated incomplete treatment during pregnancy with OR 11.00 (6.46- 18.72) and its onset after 29 weeks of gestation with OR 6.50 (2.36-17.86) [14].

The clinical characteristics of newborns with a confirmed diagnosis or with a probable infection of congenital syphilis have been described in five studies [15, 19, 22-24], and prematurity and low birth weight have been shown to be related to the chance of vertical transmission. As Tridapalli et al compared infected children and all other cases born to HIV-positive mothers for syphilis, prematurity (RR 5.72, 95% CI 2.93 to 11.18) and birth weight less than 2000g (RR 7.85, 95% CI 4.37 to 14.11) are presented as risk factors for CS [19]. Rawstron et al studied the same variables and demonstrated that newborns with congenital syphilis had significantly lower average birth weight ( $p$  0.001) and were more likely to be small for gestational age ( $p$  0.0001). The mean gestational age of infected infants was lower, with more than 34 weeks of gestation ( $p$  0.0004) [23]. Other characteristics such as gender, Apgar, history of hospitalization, other clinical manifestations, and alterations of complementary tests of the NB were less evaluated.

## DISCUSSION

The proper management of maternal syphilis during prenatal care and at the time of delivery is essential for the prevention of congenital syphilis and clinical attention of newborns exposed vertically to syphilis. In this systematic review, it was observed that, among the demographic, maternal, obstetric, and neonatal risk factors, the variables of greatest relevance for the outcome of CS were mainly factors related to prenatal care and adequate maternal treatment.

Therefore, prenatal care as well as its early onset are important factors for implementing measures in the control of CS [25, 26]. Among the 458 cases of CS reported to the Centers for Disease Control and Prevention in 2014, almost a quarter were born to mothers who did not

receive prenatal care [27]. In this systematic review, six studies demonstrated an association between absence of prenatal care and CS [14, 15, 21, 23, 28], and in the work of Risser and Hwang, the risk of CS was six times higher when the mother did not have this kind of assistance [21].

In this systematic review, six studies showed that the late onset of prenatal care was associated with congenital syphilis [12-16, 28].

The importance of adequate prenatal care in CS prevention is the early detection of syphilis and treatment in pregnant women [29], with a higher risk of adverse outcome in pregnancy when the woman is screened in the third trimester compared to the first and second trimester [26]. Wang et al demonstrated that mothers with syphilis diagnosed with gestational age greater than 36 weeks were approximately 25 times more likely to have a newborn with CS than women who were diagnosed with syphilis with gestational age less than or equal to 12 weeks [17].

In addition to early diagnosis, some studies in this systematic review have demonstrated statistical significance among high titers of non-treponemal tests of the mother and CS [14, 23, 24]. In the study by Qin et al, almost three quarters of children with CS were born to mothers with elevated titres ( $\geq 1:8$ ) of nontreponemal antibodies. The authors demonstrated that the risk increased as the titres also increased, reaching the risk magnitude of 38 times when they were  $\geq 1:64$ . Despite the wide amplitude of the CI values, the minimum limit was 16, indicating that it is a high-risk variable for CS. By dividing the population into two, putting the cutoff point at 1:8, this same study demonstrated a risk almost 11 times higher when maternal titres were  $\geq 1:8$  [14]. Although this factor cannot be analyzed in isolation in maternal history, attention should be taken to the risk of CS in children born to mothers with high non-treponemal test titres.

## **Treatment**

Adequate treatment for syphilis during pregnancy is the only measure that leads to the prevention of vertical transmission in infected women [25]. This is well established and was demonstrated in the study by Hong et al, who observed a 68 times higher risk of CS when the mother did not receive treatment during pregnancy, despite presenting a wide CI [13]. With this data, it is noteworthy that all newborns of untreated mothers should be considered as having probable CS and they should be submitted to evaluation and treatment.

The antimicrobial for the treatment of syphilis during pregnancy recommended by the Centers for Disease Control and Prevention (CDC) is benzathine G penicillin, being considered 98%

effective in the prevention of CS [25]. Qin et al demonstrated a three-fold higher risk of CS when the pregnant woman received treatment with an antimicrobial other than penicillin [14]. Moreover, it is known that, although penicillin applied at any time during pregnancy treats the woman, this may not occur with the fetus as demonstrated in the study by Rawstron et al, in which nine mothers who had a history of treatment during pregnancy had children with CS and five mothers with a history of treatment before pregnancy had stillborn [23]. This may have occurred not due to therapeutic failure, but to the possibility that treatment was inadequate or that the woman had reinfectd. For this reason, the main global protocols recommend evaluation of information on the treatment of sexual partners to assess the risk of reinfection in treated women [25, 30].

In the study by Rawstron et al, any treatment before and during pregnancy showed statistical significance among children with and without CS [23]. However, although the study gave the definitions of adequate treatment during pregnancy, it did not evaluate the association between the adequacy of maternal treatment and the diagnosis of CS. Adequate treatment during pregnancy is crucial for the prevention of syphilis transmission, being one of the factors considered in the protocols to evaluate the indication of treatment of the child. The data published that evaluated whether the treatment of pregnancy was adequate, following the criteria of international protocols, corroborated the statement in literature. In the study by Tridapalli et al, the risk of CS reached 15 times when the mother received inadequate treatment, even with a CI with wide variation (CI 5.22-47.31) [19]. This systematic review endorses, therefore, that the child of a mother with treatment considered inadequate should be evaluated as presenting suspected CS.

Another factor considered relevant to evaluate the quality of maternal treatment is gestational age at the beginning of treatment, considering that physiological changes at the end of pregnancy lead to increased creatinine clearance and reduced protein concentration in the plasma, thus altering the pharmacokinetics of penicillin. For that, the guidelines consider that the treatment that ends up to 30 days before delivery could be considered adequate [9]. One study found that the initiation of treatment less than 30 days before delivery was significantly associated with CS ( $p < 0.001$ ) [16], but the authors did not present the measures of magnitude of effect and confidence interval, which limits our conclusions. On the other hand, Qin et al observed that the completion of treatment up to four weeks before delivery was significantly associated with the CS outcome, demonstrating a 16-fold risk of CS when treatment was completed less than four weeks (CI 8.46-33.73) before delivery [14]. Hong et al evaluated the

risk of congenital syphilis by comparing different moments of treatment of pregnant women [13]. The study used 28 weeks of GA as a cutoff point of treatment and presented lower incidence of CS among women who received treatment before this period. CS was 8 times more common in women treated after 28 weeks and 68 times more in untreated women compared to those treated before that date. This association was also observed in the study by Qin et al, demonstrating that treatment started from 29 weeks of gestation was associated with a 6.5-fold risk of CS [14], with a broad CI, but with a considerably significant minimum limit (CI 2.36-17.86). Moreover, according to the results of the univariate logistic analysis published in the study by Liu et al, each week of delay in the treatment of pregnant women would increase the risk of CS by about 10% [18].

### **Adverse pregnancy outcome**

Maternal syphilis is associated with adverse gestational outcomes, such as miscarriage, stillbirth, premature delivery, neonatal death, and low birth weight [31]. Five studies of this systematic review found an association between the variable's prematurity and birth weight with CS [15, 19, 22, 24]. This information may contribute to the decision of the clinical management of NB, considering that in some cases the only alteration presented may be low birth weight or prematurity.

Although CS may be related to prematurity and restriction of intrauterine growth, these manifestations are nonspecific and may be related to other maternal factors, such as the use of illicit drugs.

### **Clinical signs in the newborn**

The presence of cerebrospinal fluid (CSF) alterations is associated with CS with high magnitude in the study by Tridapalli et al, although it is not mentioned what alterations were found [19]. The absence of changes in cerebrospinal fluid, however, does not exclude the diagnosis of neurosyphilis in NB, according to a study conducted by Michelow et al. A total of 148 neonates were evaluated for the presence of infection in the central nervous system. The authors found that the alteration of only one parameter (VDRL reagent or high protein levels or pleocytosis) presented maximum sensitivity of 56% and, when more than one alteration was present, sensitivity reached 82% [32]. The low sensitivity demonstrated in the study reveals the difficulties inherent in the evaluation of CSF in NB. Therefore, given the presence of changes

in cerebrospinal fluid analysis, the NB should be treated for neurosyphilis. In addition, findings in CSF analysis may be present in approximately 8% of asymptomatic infants born to mothers with untreated early syphilis [33], showing the importance of subjecting this group of patients to lumbar puncture (spinal tap).

Another important consideration related to complementary tests refers to long bone radiography, which is important for the evaluation of CS in symptomatic or non-symptomatic neonates [33]. Tridapalli et al found an increased risk of CS in infants with alteration in this imaging exam [19]. However, the authors do not specify what these features were.

McFarlin et al compared NB with CS and NB without CS evidence and demonstrated that newborns with CS were more likely to be admitted to the neonatal intensive care unit or progressive care unit with longer length of stay (11 vs 5.5 days), besides presenting higher morbidity [24]. The study makes it clear that maternal treatment during pregnancy can reduce the severity of the disease for the newborn without eradicating adverse outcomes, since in the group of mothers adequately treated for syphilis during pregnancy, 28% had deliveries before 37 weeks of gestation.

### **Limitations and bias**

This systematic review is based on the analysis of observational studies, some of them with unsatisfactory methodological quality, as presented in Newcastle evaluation. The design of the studies may result in potential selection bias.

While demographic factors are well defined in the literature, there is still a gap in relation to the diagnosis of syphilis in the vertically exposed infant, which impacts the conduction of studies since the diagnosis of CS is often presumptive.

Limitation of the analysis was that most of the selected studies did not include stillbirths attributable to maternal syphilis, potentially resulting in underestimation of the risk of developing CS, particularly among the group of women who did not receive treatment for syphilis.

### **CONCLUSION**

The association of syphilis with adverse socio-economic conditions and inadequate prenatal care suggests that the improvement of the population's living conditions and equitable access

to quality health services may have an impact on the reduction of congenital syphilis. Interventions directed to pregnant women and their sexual partners, such as health education, preventive measures of syphilis and other STIs, monitoring and management of prenatal follow-up should be maintained as a focus of health care for the timely management and treatment of these pregnant women and their offspring.

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### 3. JUSTIFICATIVA

Os dados epidemiológicos mais recentes do Brasil revelam uma preocupante tendência de aumento na taxa de gestantes com sífilis, atingindo 27,1 casos por 1.000 nascidos vivos em 2021. Embora haja um esforço para identificar mais gestantes infectadas, infelizmente, o tratamento adequado e outras medidas preventivas de reinfecção ainda não estão sendo implementados de maneira eficaz. Isso é evidenciado pelo fato de que a taxa de incidência de sífilis congênita no mesmo ano foi de 9,9 casos por 1.000 nascidos vivos, representando um aumento significativo de 14,6% em comparação com o ano anterior (2020).<sup>1</sup>

Apesar do amplo conhecimento sobre a transmissão vertical da sífilis, suas consequências e a eficácia das medidas preventivas, a SC permanece como um problema de saúde pública significativo no Brasil e no mundo. Quando ocorre falha na única medida eficaz de prevenção, que consiste na identificação e tratamento adequado da gestante com sífilis, resta apenas manejar clinicamente o RN exposto. Isto, porém, é um desafio, pois a maioria dos RNs são assintomáticos ao nascimento e não se dispõe de um exame complementar específico, que determine com precisão o diagnóstico de uma criança infectada. Atualmente, a decisão quanto à conduta para com o neonato requer a análise de algoritmos que envolvam a história materna de sífilis (tratamento, resposta terapêutica, risco de reinfecção), a comparação entre os títulos de VDRL da mãe no momento do parto com os RNs, o exame clínico da criança e alteração de exames complementares não específicos para SC (hemograma, radiografia de ossos longos e análise de líquido cefalorraquidiano). Além desses aspectos, destaca-se que, no momento da decisão de tratar, ou não, o RN, é importante que seja garantido o seguimento clínico ambulatorial do lactente exposto à sífilis. Existem variáveis associadas à maior chance de SC, porém, estas não estão explicitamente descritas nas diretrizes nacionais e internacionais. Torna-se necessário, portanto, identificar os fatores maternos, obstétricos e neonatais associados ao risco de SC para a definição epidemiológica de caso de SC e, assim, auxiliar a tomada de decisão na maternidade pela equipe assistencial.

Diante do exposto, o presente estudo teve como objetivo identificar os determinantes da assistência obstétrica e neonatal associados ao diagnóstico de SC, bem como avaliar se os critérios utilizados nos algoritmos, para guiar o manejo, na maternidade, do RN exposto à sífilis, são preditores de SC.

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## **4. OBJETIVO**

### **4.1 Objetivo geral**

Identificar e analisar os fatores associados à assistência obstétrica e ao recém-nascido que possam ser preditores de SC.

### **4.2 Objetivos específicos**

4.2.1 Descrever as variáveis clínicas e obstétricas das mães, bem como as variáveis clínicas das crianças participantes do estudo, para compreensão do perfil dos participantes;

4.2.2 Analisar a associação entre variáveis maternas específicas, como histórico médico, comportamentos de risco e tratamentos durante a gestação, e a ocorrência de SC;

4.2.3 Avaliar a associação entre as características clínicas das crianças, incluindo as manifestações clínicas e os resultados de exames laboratoriais, e o diagnóstico confirmado ou descartado de SC;

4.2.4 Identificar e quantificar os fatores de risco significativamente associados ao diagnóstico confirmado de SC;

4.2.5 Avaliar se os critérios utilizados para guiar o manejo do recém-nascido exposto à sífilis na maternidade são, de fato, preditores de SC.

## 5. MATERIAIS E MÉTODOS

### 5.1 Delineamento, local e período de estudo

Trata-se de um estudo de coorte retrospectivo, realizado no Centro de Referência e Treinamento em Doenças Infecciosas e Parasitárias (CTR) Orestes Diniz, compreendendo as crianças atendidas no período de 2017 a 2022. O CTR Orestes Diniz é um ambulatório cogerenciado pela Universidade Federal de Minas Gerais e pela Prefeitura de Belo Horizonte, atuando como referência no atendimento ambulatorial a crianças expostas verticalmente a agravos infecciosos, sendo a SC a principal demanda dos encaminhamentos.<sup>1</sup> Diante do exposto, esse serviço foi o local de escolha para a realização deste estudo.

### 5.2 Critérios de inclusão

Foram incluídos todos os lactentes encaminhados ao CTR Orestes Diniz, devido à exposição vertical à sífilis.

### 5.3 Critérios de exclusão

Foram excluídos pacientes:

- 5.3.1 cujo diagnóstico de SC não foi possível de ser descartado, ou confirmado;
- 5.3.2 cuja mãe teve o diagnóstico de sífilis descartado;
- 5.3.3 sobre os quais não foi possível obter o registro de testes maternos para sífilis;
- 5.3.4 que não tiveram, durante o seguimento, VDRL (*Venereal Disease Research Laboratory*) registrado em dois momentos diferentes até o 6º mês de vida.

### 5.4 Definições

As definições adotadas neste trabalho foram adaptadas a partir de diretrizes do Ministério da Saúde do Brasil<sup>2</sup> e do Centro para o Controle e Prevenção de Doenças (CDC) dos Estados Unidos:<sup>3</sup>

- 5.4.1 Sífilis confirmada na gestante: mulher que apresentou teste treponêmico e teste não treponêmico (VDRL) positivos durante o pré-natal ou parto. Dentre os testes treponêmicos utilizados estão os testes imunocromatográfico, de imunofluorescência indireta (FTA-ABs), quimioluminescência e hemaglutinação para *T. pallidum*.

- 5.4.2 Sífilis descartada na gestante: mulher que apresentou teste treponêmico e teste não treponêmico negativos durante o pré-natal, parto ou pós-parto.
- 5.4.3 Diagnóstico indefinido de sífilis na gestante: mulher que apresentou registro de apenas um teste positivo, treponêmico ou não treponêmico, durante o pré-natal ou parto.
- 5.4.4 Sífilis congênita confirmada: criança que apresentou teste treponêmico positivo após 18 meses de vida. Dentre os testes treponêmicos utilizados estão os testes imunocromatográfico, de imunofluorescência indireta (FTA-ABs), quimioluminescência e hemaglutinação para *T. pallidum*.
- 5.4.5 Sífilis congênita descartada: um dos seguintes critérios: (a) criança sem tratamento prévio para sífilis e que não finalizou o seguimento com teste treponêmico, porém, apresentou dois VDRL negativos, durante o acompanhamento ambulatorial; (b) criança com teste treponêmico negativo, coletado aos 12 meses, e repetido aos 18 meses, no caso de o primeiro exame ter apresentado resultado positivo.
- 5.4.6 Tratamento materno adequado: deve cumprir todos os seguintes critérios:<sup>2</sup> (a) uso de penicilina benzatina; (b) esquema adequado para o estágio clínico da sífilis;<sup>4</sup> (c) tratamento finalizado até 30 dias antes do parto; (d) dose(s) adequadamente registrada(s), (e) queda adequada de títulos do VDRL após o tratamento (queda de VDRL em pelo menos duas titulações em 3 meses, ou de 4 diluições em 6 meses), ou estabilidade dos títulos de VDRL em gestantes com VDRL  $\leq 1:4$ .
- 5.4.7 Tratamento adequado do parceiro sexual: uso de esquema adequado para o estágio clínico da sífilis, semelhantemente ao esquema proposto para a gestante, ou dose única de 2,4 milhões de unidades de penicilina benzatina, se assintomático com teste negativo.

## 5.5 Coleta de dados

As informações foram coletadas por acadêmicas treinadas do curso de Medicina e supervisionadas pelos médicos especialistas assistentes, ou pelos pesquisadores. A coleta de dados foi realizada durante o atendimento às crianças, a partir das informações fornecidas pela mãe, ou por meio da análise dos registros do prontuário, sumário de alta da mãe e da criança, e relatório de encaminhamento.

Para estruturar e padronizar a coleta de dados, utilizou-se um formulário desenvolvido em conformidade com o protocolo de pesquisa, o qual está detalhadamente apresentado no APÊNDICE 1.

Para a análise descritiva e comparativa foram coletadas as seguintes informações:

- características relacionadas à mãe e à assistência obstétrica: número de gestação, parto e aborto, uso de drogas ilícitas durante a gestação, história pregressa de sífilis, coinfeção com HIV, manifestações clínicas, realização de pré-natal, titulação de VDRL (pré-natal e parto), realização de teste treponêmico, tratamento materno e do parceiro sexual para sífilis.
- características relacionadas ao recém-nascido: idade gestacional, Apgar, antropometria ao nascimento, manifestações clínicas, tratamento para SC.
- propedêutica complementar realizada no período neonatal: hemograma, titulação de VDRL no sangue periférico, rotina (bioquímica e celularidade) e VDRL no líquido cefalorraquidiano (LCR), radiografia de ossos longos, fundoscopia, estudo de imagem do encéfalo (ultrassonografia transfontanela, ressonância nuclear magnética, tomografia computadorizada).
- títulos de VDRL coletado durante o seguimento clínico e teste treponêmico, coletado aos 12 meses, e repetido aos 18 meses, no caso de o primeiro exame ter apresentado resultado positivo.

## 5.6 Amostra

Foi utilizada amostragem não probabilística pela possibilidade de aumentar o poder estatístico por meio do tamanho amostral, já que o local do estudo é um centro de referência em atendimento a crianças com SC.

## 5.7 Análise estatística

Para a análise estatística dos dados, foi utilizado o *software Statistical Package for Social Sciences* (SPSS) 21.0 (IBM, Armonk, NY).

Na análise descritiva, variáveis contínuas foram expressas como média e desvio-padrão, ou mediana e intervalo interquartil, dependendo da sua distribuição. Variáveis categóricas foram apresentadas como frequência e percentual.

A análise comparativa das variáveis entre os grupos de crianças com diagnóstico de SC confirmado e descartado incluiu o teste de Mann-Whitney para variáveis contínuas e o teste

exato de Fisher para as variáveis categóricas. A significância estatística foi considerada quando  $p < 0,05$  e a medida da magnitude da associação foi avaliada pelo *odds ratio* (OR) e intervalo de confiança (IC) de 95%.

Para a análise multivariada, foi utilizado um modelo de regressão logística, que incluiu inicialmente as variáveis de relevância clínica com  $p < 0,20$ , permanecendo no modelo final apenas as variáveis com  $p < 0,05$ .

### 5.8 Considerações éticas

O estudo trata-se de um braço do Projeto de Pesquisa aprovado no Comitê de Ética e Pesquisa (COEP) da UFMG, em 03 de abril de 2017, intitulado “Diagnóstico de infecções congênitas e correlação com o acometimento fetal e evolução clínica de crianças infectadas por transmissão vertical”, CAAE 65339716.0.0000.5149 (ANEXO 1), com Termo de Consentimento Livre e Esclarecido (APÊNDICE 2).

Este estudo foi de natureza observacional e não influenciou ou determinou qualquer intervenção na condução clínica dos pacientes acompanhados no ambulatório. Todas as condutas clínicas, incluindo coletas de sangue e outros procedimentos, foram definidas e realizadas conforme os protocolos estabelecidos pelo Ministério da Saúde, ou segundo os critérios definidos pelos médicos assistentes, independentemente da participação no estudo. Portanto, o estudo não apresentou riscos adicionais aos participantes, além daqueles inerentes à sua assistência clínica rotineira.

### 5.9 Financiamento

O trabalho foi realizado com auxílio de recurso de Bolsa Institucional de Iniciação Científica UFMG/FAPEMIG e UFMG/CNPq.

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## 6. RESULTADOS E DISCUSSÃO

Apresentação do artigo original.

### **Determinants of obstetric and neonatal care for congenital syphilis confirmed by treponemal test in clinical follow-up at a reference outpatient clinic**

#### **ABSTRACT**

Introduction – Despite being an ancient and treatable disease, syphilis remains a public health issue in Brazil and worldwide. Congenital syphilis, which results from the transmission of the spirochete *Treponema pallidum* (T. *pallidum*) from the infected pregnant woman to the fetus, is a major complication. The sole prevention for congenital syphilis is the timely diagnosis and treatment of the infected pregnant woman. Thus, identifying variables associated with vertical transmission of syphilis is essential for developing targeted policies and addressing care deficiencies.

Objective – To identify and analyze factors related to obstetric care and the evaluation of the newborn that are predictors of congenital syphilis.

Methods – A retrospective cohort study was conducted at a reference center for infectious disease attendance in Belo Horizonte, Brazil, from 2017 to 2022. Children exposed to vertical transmission of syphilis were included. Confirmed congenital syphilis was defined based on reactive treponemal test results after 18 months of life, and congenital syphilis was ruled out following non-reactive results. A descriptive analysis of demographic, clinical, and laboratory characteristics of mothers and newborns was performed. Subsequently, a comparative analysis of variables between groups with confirmed and excluded congenital syphilis diagnoses was conducted. Statistical significance was considered at  $p < 0.05$ , and the magnitude of association was assessed by odds ratio (OR) with a 95% confidence interval (CI). The study was approved by the Ethics Committee.

Results – Out of 867 eligible patients, 377 children were included in the comparative analysis, with ten (2.7%) diagnosed with confirmed congenital syphilis and 367 (97.3%) discarded. Three variables were independently associated with congenital syphilis: absence of maternal treatment with benzathine penicillin (OR=4.29; CI 95% 1.13-18.96), presence of clinical manifestations during the neonatal period or at the first consultation (OR=4.97; CI 95% 1.30-18.96), and VDRL titration of the newborn collected at the maternity > 1:2 (OR=11.28; CI 95% 1.42-94.44).

Conclusion – The high percentage of mothers considered inadequately treated reflects challenges in managing infected pregnant women, significantly increasing the risk of congenital syphilis. The altered VDRL result in the newborn, identified as an independent variable associated with the final congenital syphilis diagnosis, underscores the importance of considering the VDRL level in decisions to treat the newborn at the maternity. On the other hand, although clinical manifestations during the neonatal period have been identified as factors associated with congenital syphilis, the nonspecific nature of these findings contributes to the complexity of properly managing newborns vertically exposed to syphilis.

## INTRODUCTION

Despite being an ancient and treatable disease, syphilis remains a significant public health issue worldwide for over a century. An epidemiological model adjusted for sentinel surveillance indicated that the estimated global prevalence of syphilis in pregnant women was 0.69% (95% CI=0.57–0.81%) in 2016, with a global congenital syphilis rate of 473 (385–561) cases per 100,000 live births and a total of 661,000 congenital syphilis cases, including 355,000 cases of adverse pregnancy or birth outcomes<sup>1</sup>.

In Brazil, despite universal screening of women during prenatal care and childbirth and the wide availability of standard syphilis treatment as recommended by national protocols, the

detection rate of syphilis in pregnant women was 32.4 cases per 1,000 live births, and the incidence rate of congenital syphilis was 10.3 cases per 1,000 live births in 2022<sup>2</sup>.

Risk factors for maternal syphilis cited in the literature include inadequate prenatal care, young women, low socioeconomic status, prostitution, and illicit drug use<sup>3</sup>. Other documented factors include having another sexually transmitted infection (STI) and having sexual relations with more than one partner in the past 12 months<sup>4</sup>. In Brazil, a study showed higher prevalence of syphilis in pregnant women with less than eight years of education, those who identified as black or mixed race, women without prenatal care, and those treated in public or mixed services<sup>5</sup>. A systematic review, which included studies on risk factors for congenital syphilis over more than four decades, revealed that socioeconomic factors and inadequate prenatal care remain predictors of congenital syphilis<sup>6</sup>.

Untreated syphilitic pregnant women may experience adverse gestational outcomes such as fetal loss, stillbirth, neonatal death, prematurity, low birth weight, and clinical manifestations in the newborn indicating congenital syphilis<sup>7</sup>. However, about two-thirds of infected live births are asymptomatic at birth, and among symptomatic children, most clinical manifestations are nonspecific, such as hepatomegaly, splenomegaly, jaundice, and rash<sup>8</sup>.

The only effective measure to prevent congenital syphilis is the treatment of infected women with penicillin. A recently published meta-analysis showed that treating pregnant women with syphilis reduced the risk of premature birth by 52% (95% CI=42–61%), stillbirths by 79% (95% CI=65–88%), and low birth weight by 50% (95% CI=41–58%)<sup>9</sup>.

In the absence of a serological test that confirms the diagnosis of congenital syphilis, diagnosis and management rely on a combination of factors, including information about maternal treatment during pregnancy, clinical evaluation of the child, radiological exams, cerebrospinal fluid analysis, and comparison of VDRL titers between the mother and child<sup>10</sup>.

This situation often leads to the need for invasive testing and, in some cases, prolonged hospitalization for treatment of the newborn.

Considering the challenges mentioned, the aim of this study was to identify and analyze maternal factors and obstetric care, as well as newborn characteristics, associated with the occurrence of congenital syphilis.

## METHODS

This retrospective cohort study included patients attended at a reference outpatient clinic for infectious and parasitic diseases in Belo Horizonte, Minas Gerais, Brazil, from 2017 to 2022. Eligibility included all infants referred to the center due to vertical exposure to syphilis. Exclusion criteria included: (a) mothers with a negative syphilis diagnosis; (b) unavailable maternal syphilis test records; (c) infants without two recorded VDRL titers by 6 months of age or without a treponemal test by the end of follow-up.

Syphilis status was classified using adapted guidelines from the Brazilian Ministry of Health<sup>10</sup> and the U.S. Centers for Disease Control and Prevention<sup>11</sup>. Definitions included: 1) Confirmed maternal syphilis: Positive treponemal and non-treponemal tests during prenatal care or at delivery; 2) Uncertain maternal syphilis: Only one positive test, either treponemal or non-treponemal, during prenatal care or delivery; 3) Confirmed congenital syphilis: Positive treponemal test after 18 months of life; 4) Excluded congenital syphilis: Negative treponemal test at 12 or 18 months, or untreated children without a final treponemal test but with two negative outpatient VDRL tests.

Mothers were considered adequately treated if they met all the following criteria: use of benzathine penicillin regimen according to the clinical stage, treatment completed over 30 days before delivery, properly recorded doses, and an adequate decrease in VDRL titers after treatment (a decrease of at least two dilutions in 3 months or four dilutions in 6 months) or

stable VDRL titers in mothers with  $\text{VDRL} \leq 1:4$ . Methods used to detect treponemal antibodies for both maternal and child diagnoses included immunochromatography, indirect immunofluorescence (FTA-ABs), chemiluminescence, or hemagglutination.

Partner treatment was considered adequate when the appropriate regimen for the clinical stage of syphilis was used, or when a single dose of benzathine penicillin was administered if asymptomatic with a negative test.

Data were collected based on information provided by the mother during consultations, maternity discharge summaries for both the mother and child, referral reports, and medical records. This included details on the number of pregnancies, deliveries, and abortions, illicit drug use during pregnancy, history of syphilis, HIV coinfection, clinical manifestations, prenatal care, VDRL titers, treponemal tests, maternal and partner treatment for syphilis, and infant characteristics such as gestational age, Apgar scores, birth anthropometry, clinical manifestations, congenital syphilis treatment, and complementary diagnostics performed during the neonatal period.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM, Armonk, NY). Continuous variables were described using medians and interquartile ranges, while categorical variables were expressed as frequencies and percentages. Comparative analyses employed the Mann-Whitney and Fisher's exact tests. Statistical significance was set at  $p < 0.05$ , and the magnitude of the association was assessed using odds ratios (OR) with a 95% confidence interval (CI). A logistic regression model was used to identify significant predictors of congenital syphilis, initially including variables with  $p < 0.20$  and retaining those with  $p < 0.05$  in the final model.

The study was approved by the Institutional Ethics and Research Committee, with informed consent obtained from all participating mothers.

## RESULTS

### Study Population characteristics

From 2017 to 2022, 867 children attended at the reference center due to vertical exposure to syphilis were identified. The formation of the cohort is depicted in Flowchart 1. Of these children, 40 mothers (4.6%) had records of coinfections, including toxoplasmosis (n=13), HIV (n=9), viral hepatitis (n=5), genital herpes simplex (n=7), HTLV (n=2), cytomegalovirus (n=1), trichomoniasis (n=3), Zika (n=1), and Chagas disease (n=1). Additionally, five of these mothers (12,5%) had dual infections concurrent with syphilis.

Maternal symptoms during the prenatal period were observed in 28 cases (3.2%), and skin rash was the most commonly reported manifestation.

Following the application of exclusion criteria, 377 children (43.5%) were included in the comparative analysis. Of these, 10 (2.7%) had a confirmed serological diagnosis of congenital syphilis, while 367 (97.3%) were excluded based on negative treponemal tests. Descriptive analysis of this population is detailed in Tables 1 and 2.

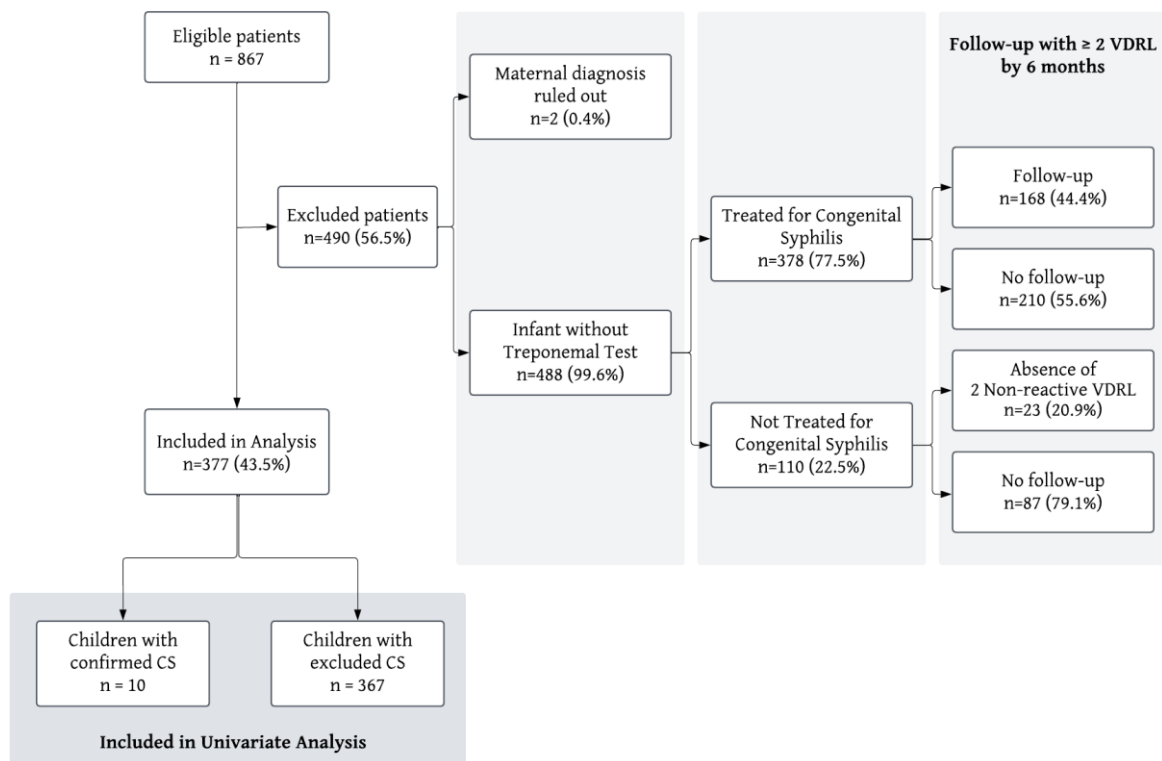


Figure 1: Flowchart of the cohort formation for the retrospective study of children referred to CTR Orestes Diniz due to vertical exposure to syphilis from 2017 to 2022.

### Characteristics of Mothers of Children Completing Follow-up with a Treponemal Test

Among the 377 children included in the univariate analysis (Table 1), syphilis was confirmed in 221 mothers (58.6%), while 154 (40.8%) had only one positive test recorded. VDRL titers at delivery greater than 1:4 was not statistically associated to serological confirmed syphilis of the newborn ( $p=0,051$ ).

Regarding maternal syphilis treatment, 300 mothers (79.6%) received at least one dose of benzathine penicillin during pregnancy. Among them, 264 (88.0%) had their treatment well-documented, and 211 (70.3%) completed their treatment more than 30 days before childbirth. There were no statistical differences between children with confirmed or excluded congenital syphilis concerning these treatment variables.

Information on partners treatment was available for only 297 cases, with 101 (34.0%) considered adequately treated. Among mothers with sufficient data to assess syphilis treatment,

only 17.7% (58/327) were considered adequately treated, including criteria for assessing both maternal therapy and partners treatment. When excluding partners treatment from the criteria, the proportion of mothers who met the criteria increased to 36.6% (129/346). No statistical difference was observed between groups of children with confirmed or excluded congenital syphilis regardless of partners treatment status. However, the absence of maternal treatment with benzathine penicillin was associated with a confirmed diagnosis of congenital syphilis (OR 4.10; CI 95% 1.15-14.53).

Table 1: Profile of mothers of children exposed to syphilis attended at the reference center in Belo Horizonte, Minas Gerais, Brazil, between 2017 and 2022

| Variable                                              | Population n=867 (%) |                                     | Analyzed population (n=377)         |                         |
|-------------------------------------------------------|----------------------|-------------------------------------|-------------------------------------|-------------------------|
|                                                       |                      | Children with confirmed CS n=10 (%) | Children with excluded CS n=367 (%) | OR (95% CI)** p         |
| Syphilis diagnosis prior to pregnancy                 | 40 (4.6)             | 0 (0.0)                             | 15 (4.1)                            | 1.000                   |
| Maternal coinfection <sup>&amp;</sup>                 | 40 (4.6)             | 0 (0.0)                             | 14 (3.8)                            |                         |
| HIV coinfection                                       | 9 (1.0)              | 0 (0.0)                             | 2 (0.5)                             | 1.000                   |
| Illicit drug use                                      | 58 (6.7)             | 1 (10.0)                            | 20 (5.4)                            | 0.440                   |
| Clinical manifestations during gestation <sup>§</sup> | 28 (3.2)             | 0 (0.0)                             | 13 (1.5)                            | 1.000                   |
| 1st VDRL titer > 1:16*                                | 548/830 (66.0)       | 3/8 (37.5)                          | 222/358 (62.0)                      | 2.72 (0.64-11.56) 0.175 |
| VDRL titer at time of birth > 1:4*                    | 463/835 (55.4)       | 1/8 (12.5)                          | 193/359 (53.8)                      | 8.14 (0.99-66.83) 0.051 |
| Maternal syphilis diagnosis                           |                      |                                     |                                     |                         |
| Confirmed                                             | 465 (53.6)           | 7 (70.0)                            | 214 (58.3)                          |                         |
| Uncertain <sup>#</sup>                                | 384 (44.4)           | 1 (10.0)                            | 153 (41.7)                          |                         |
| Excluded                                              | 2 (0.2)              | NA                                  | NA                                  |                         |
| No serological tests                                  | 16 (1.8)             | 2 (20.0)                            | 0 (0)                               |                         |
| <b>continue</b>                                       |                      |                                     |                                     |                         |

|                                                          |                |             |                |                   |       |
|----------------------------------------------------------|----------------|-------------|----------------|-------------------|-------|
| No penicillin treatment                                  | 191 (22.0)     | 5 (50.0)    | 72 (19.6)      | 4.10 (1.15-14.53) | 0.029 |
| Treatment with three doses of benzathine                 | 537 (61.9)     | 4 (40.0)    | 232 (63.3)     |                   | 0.182 |
| Treatment completed more than 30 days before birth       | 456 (52.6)     | 5 (50.0)    | 206 (56.1)     |                   | 0.320 |
| Sexual partner untreated or not treated with benzathine* | 398/680 (58.8) | 7/8 (87.5)  | 179/298 (60.1) | 4,65 (0,56-38,31) | 0.153 |
| Adequate treatment of sexual partner*                    | 240/656 (36.6) | 2/8 (25.0)  | 99/289 (34.3)  | 1.56 (0.30-7.89)  | 0.589 |
| Adequate maternal treatment *                            |                |             |                |                   |       |
| Including partner treatment                              | 132/751 (17.6) | 2/9 (22.2)  | 56/318 (17.6)  |                   | 0.663 |
| Regardless of partner treatment                          | 266/797 (33.4) | 4/10 (40.0) | 125/336 (37.2) |                   | 1.000 |

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OR odds ratio; CI confidence interval; NA not applicable; NR non-reactive

\*Data not available for all children

\*\*OR calculated through univariate logistic regression

&HIV, toxoplasmosis, viral hepatitis, genital herpes, HTLV, cytomegalovirus, trichomoniasis, Chagas disease.

§Fever, rash, headache, myalgia, genital lesions.

# Cases where only one type of test was positive.

### **Characteristics of children who completed treponemal test follow-up**

Among the children included in the univariate analysis (Table 2), 91.6% (306/334) were born in Belo Horizonte. The North region recorded the highest number of births at 36.9% (113/306), followed by Centro-Sul with 35.6% (109/306). The Northwest, Barreiro, and West regions accounted for 15.7%, 10.5%, and 1.3% of births, respectively. Most of these children, representing 97.4% (298/306), were born in public maternity hospitals.

Clinical manifestations at the maternity or during the initial consultation at the reference service were recorded in 77 children (20.4%), being more prevalent in the group with confirmed congenital syphilis (OR 6.25; CI 95% 1.72–22.75).

The first VDRL test was recorded for 376 children (99.7%), showing a significant association between titers above 1:2 and the diagnosis of congenital syphilis (OR 12.96; CI 95% 1.62–103.37).

Blood tests performed at birth in 267 children identified abnormalities in 22 (8.2%), with no statistical differences between groups. These included anemia, thrombocytopenia, leukopenia, leukocytosis, and eosinophilia. Thrombocytopenia was the only abnormality observed in the confirmed congenital syphilis group, affecting one child.

Hyperproteinorrachia and/or pleocytosis were found in the cerebrospinal fluid of 16.0% of the children (45/281), with no statistical difference between groups ( $p=0.21$ ). Cerebrospinal fluid alterations were observed in only two children with confirmed congenital syphilis, both showing hyperproteinorrachia. The cerebrospinal fluid VDRL was reactive in 1.8% of infants (5/282), including one from the confirmed congenital syphilis group and four from the excluded congenital syphilis group. In the excluded group, one child had a traumatic lumbar puncture, and the others had incomplete cerebrospinal fluid analysis records, making it impossible to evaluate the occurrence of bleeding.

Radiographic abnormalities in long bones were noted in 9.4% of children (27/287), exclusively in the group with excluded congenital syphilis diagnosis.

Parenteral penicillin antibiotic therapy was administered to 306 patients (81.2%). All children with confirmed congenital syphilis received one of the prescribed treatments: benzathine penicillin in a single dose for three children, crystalline penicillin for 10 days for four children, and procaine penicillin for 10 days for three children (Table 3).

Table 2: Profile of children exposed to syphilis attended at the reference center in Belo Horizonte, Minas Gerais, Brazil, between 2017 and 2022.

| Variable                                            | Population<br>(n=867) | Analyzed population (n=377)          |                                      |                  | P     |
|-----------------------------------------------------|-----------------------|--------------------------------------|--------------------------------------|------------------|-------|
|                                                     |                       | Children with confirmed<br>CS (n=10) | Children with excluded<br>CS (n=367) | OR (IC<br>95%)** |       |
| Children characteristics                            |                       |                                      |                                      |                  |       |
| GA at birth (weeks) *                               | 39 (26-42)            | 38 (35-41)                           | 39 (28-41)                           |                  | 0.117 |
| Median (range)                                      |                       |                                      |                                      |                  |       |
| Prematurity *                                       | 103/758               | 1/8 (12.5)                           | 48/327 (14.7)                        |                  | 1.000 |
| Frequency (%)                                       | (13.6)                |                                      |                                      |                  |       |
| Apgar score at 5 minutes < 7 *                      |                       | 1/8 (12.5)                           | 5/313 (1.6)                          |                  | 0.142 |
| Frequency (%)                                       |                       |                                      |                                      |                  |       |
| Birth weight *(grams)                               |                       |                                      |                                      |                  |       |
| Median (range)                                      | 3035 (860-4774)       | 2735 (2495-3450)                     | 3052 (940-4774)                      |                  | 0.085 |
| Percentile < 10                                     | 124/729               | 1/9 (11.1)                           | 55/313 (17.6)                        |                  | 1.000 |
| Median (range)                                      | (17.0)                |                                      |                                      |                  |       |
| Weight < 2500g                                      | 122/807               | 1/9 (11.1)                           | 50/340 (14.7)                        |                  | 1.000 |
| Frequency (%)                                       | (15.1)                |                                      |                                      |                  |       |
| Head circumference at birth (cm) *                  | 34 (21-38)            | 33 (31-35)                           | 34 (21/38)                           |                  | 0.343 |
| Median (range)                                      |                       |                                      |                                      |                  |       |
| Length at birth (cm) *                              | 48 (34-59)            | 46.5 (44-49)                         | 48 (34/59)                           |                  | 0.206 |
| Median (range)                                      |                       |                                      |                                      |                  |       |
| continue.                                           |                       |                                      |                                      |                  |       |
| Newborn VDRL titers ≥ 4 times those of the mother * | 25/733 (3.4)          | 0/6 (0.0)                            | 12/317 (3.8)                         |                  | 1.000 |

|                                                                             |                 |                 |                 |                     |       |
|-----------------------------------------------------------------------------|-----------------|-----------------|-----------------|---------------------|-------|
| Frequency (%)                                                               |                 |                 |                 |                     |       |
| First newborn VDRL titer *                                                  | 1:2 (1:1-1:512) | 1:8 (1:1-1:128) | 1:2 (1:1-1:256) |                     | 0.002 |
| Median (range)                                                              |                 |                 |                 |                     |       |
| First newborn VDRL titer > 1:2 *                                            | 502/855         | 9/10 (90.0)     | 150/366 (41.0)  | 12.96 (1.62-103.37) | 0.016 |
| Frequency (%)                                                               | (58.7)          |                 |                 |                     |       |
| Clinical manifestations in the neonatal period or at the first consultation | 187 (21.6)      | 6 (60.0)        | 71 (19.3)       | 6.25 (1.72-22.75)   | 0.005 |
| Frequency (%) <sup>#</sup>                                                  |                 |                 |                 |                     |       |
| Splenomegaly                                                                | 10 (5.3)        | 1 (16.7)        | 2 (2.8)         |                     |       |
| Hepatomegaly                                                                | 15 (8.0)        | 2 (33.3)        | 4 (5.6)         |                     |       |
| Rash                                                                        | 7 (3.7)         | 1 (16.7)        | 1 (1.4)         |                     |       |
| Jaundice &                                                                  | 136 (72.7)      | 2 (33.3)        | 59 (83.1)       |                     |       |
| Petechiae                                                                   | 4 (2.1)         | 1 (16.7)        | 1 (1.4)         |                     |       |
| Microcephaly                                                                | 7 (3.7)         | 2 (33.3)        | 2 (2.8)         |                     |       |
| Axial hipotonia                                                             | 15 (8.0)        | 0 (0.0)         | 3 (4.2)         |                     |       |
| Abnormal neurodevelopment                                                   | 5 (2.7)         | 2 (33.3)        | 1 (1.4)         |                     |       |
| Abnormal blood count*                                                       | 56/612 (9.2)    | 1/6 (16.7)      | 21/261 (8.0)    |                     | 0.406 |
| Frequency (%)                                                               |                 |                 |                 |                     |       |
| Abnormal CSF ¶*                                                             | 102/610         | 2/10 (20.0)     | 43/271 (15.9)   |                     | 0.214 |
| Frequency (%)                                                               | (16.7)          |                 |                 |                     |       |
| Reactive CSF VDRL*                                                          | 11/604 (1.8)    | 1/9 (11.1)      | 4/273 (1.5)     |                     | 0.151 |
| Frequency (%)                                                               |                 |                 |                 |                     |       |
| Abnormal long bone radiography*                                             | 53/629 (8.4)    | 0/8 (0.0)       | 27/279 (9.7)    |                     | 1.000 |
| Frequency (%)                                                               |                 |                 |                 |                     |       |

|                          |         |                |                |       |
|--------------------------|---------|----------------|----------------|-------|
| Newborn treatment for CS | 679/867 | 10 /10 (100.0) | 296/367 (80.6) | 0.219 |
| Frequency (%)            | (78.3)  |                |                |       |

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OR odds ratio; CI confidence interval; GA gestational age; NB newborn; CSF cerebrospinal fluid; NA not applicable; NR non-reactive; CS congenital syphilis.

\*Data not available for all children.

\*\* OR calculated through univariate logistic regression.

# Percentages considered for symptomatic patients.

&Unable to determine which patients had cholestatic jaundice due to missing data on serum bilirubin levels.

¶Altered cell count and/or biochemistry.

Table 3 – Data of the ten children with confirmed congenital syphilis diagnosis and their respective mothers attended at the reference center in Belo Horizonte, Minas Gerais, Brazil, between 2017 and 2022

| Variables                                 | Cases                    |      |    |    |          |                          |                         |                        |          |                          |
|-------------------------------------------|--------------------------|------|----|----|----------|--------------------------|-------------------------|------------------------|----------|--------------------------|
| Maternal VDRL titer during pregnancy      | 1                        | 2    | 3  | 4  | 5        | 6                        | 7                       | 8                      | 9        | 10                       |
| First test (trimester)                    | 1:64 (1 <sup>st</sup> )  | NA   | SI | SI | NA       | 1:64 (2 <sup>nd</sup> )  | 1:32 (2 <sup>nd</sup> ) | NR (1 <sup>st</sup> )  | NA       | 1:512 (2 <sup>nd</sup> ) |
| Second test (trimester)                   | 1:128 (2 <sup>nd</sup> ) | NA   | NA | NA | NA       | 1:128 (3 <sup>rd</sup> ) | 1:64 (3 <sup>rd</sup> ) | NR (2 <sup>nd</sup> )  | NA       | 1:128 (3 <sup>rd</sup> ) |
| Third test (trimester)                    | 1:32 (3 <sup>rd</sup> )  | NA   | NA | NA | NA       | SI                       | SI                      | 1:8 (3 <sup>rd</sup> ) | NA       | SI                       |
| VDRL at delivery                          | 1:16                     | 1:64 | SI | SI | 1:8      | 1:4                      | 1:8                     | 1:8                    | 1:8      | 1:32                     |
| Treponemal test                           | Positive                 | SI   | SI | SI | Positive | Positive                 | Positive                | Positive               | Positive | Positive                 |
| Penicillin treatment during prenatal care | Yes                      | No   | SI | No | No       | Yes                      | Yes                     | Yes                    | No       | Yes                      |
| Partner treated with penicillin           | No                       | No   | No | No | No       | SI                       | Yes                     | SI                     | No       | No                       |
| Adequate maternal treatment               | No                       | No   | No | No | No       | No                       | Sim                     | No                     | No       | No                       |
| GA at birth (weeks)                       | 41                       | 38   | SI | 35 | 38       | SI                       | 40                      | 39                     | 38       | 40                       |
| Birth weight percentile                   | 2                        | 11   | SI | 58 | 81       | SI                       | 4                       | 91                     | 7        | 40                       |

continue

|                                                          |                                 |                                      |                                   |                                   |                                   |                                 |                                |                                 |                                   |                                |
|----------------------------------------------------------|---------------------------------|--------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|---------------------------------|--------------------------------|---------------------------------|-----------------------------------|--------------------------------|
| First VDRL titer                                         | 1:8                             | 1:32                                 | 1:128                             | 1:16                              | 1:8                               | 1:4                             | 1:8                            | NR                              | 1:16                              | 1:8                            |
| Clinical manifestation at birth or at first consultation | Jaundice<br>ADNPM               | Hepatomegaly,<br>petechiae,<br>ADNPM | Rash                              | Hepatosplenomegaly                | Jaundice                          | No                              | No                             | No                              | No                                | ADNPM                          |
| Newborn treatment                                        | Benzathine penicillin<br>1 dose | Procaine penicillin<br>10 days       | Crystalline Penicillin<br>10 days | Crystalline Penicillin<br>14 days | Crystalline Penicillin<br>10 days | Benzathine penicillin<br>1 dose | Procaine penicillin<br>10 days | Benzathine penicillin<br>1 dose | Crystalline Penicillin<br>10 days | Procaine penicillin<br>10 days |
| Age at which VDRL became non-reactive                    | 5 months                        | 4 months                             | SI                                | 6 months                          | 4 months                          | 5 months                        | 5 months                       | 1 months                        | 9 months                          | 7 months                       |

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SI: no information; NA: not applicable; NR: non-reactive; GA: gestational age; ADNPM: delayed neuropsychomotor development.

In the multivariate analysis (Table 4), three independent risk factors were associated with the confirmation of congenital syphilis: absence of maternal treatment with benzathine penicillin, clinical manifestations in the neonatal period or at the first consultation, and newborn VDRL titers greater than 1:2 at birth.

Table 4 – Multivariate analysis of risk factors for positive treponemal test at 18 months of age in children exposed to syphilis during gestation and attended at the reference center in Belo Horizonte, Minas Gerais, Brazil, between 2017 and 2022.

| Variable                                                   | p-Value | OR (95% CI)        |
|------------------------------------------------------------|---------|--------------------|
| Absence of maternal treatment with benzathine penicillin   | 0.032   | 4.29 (1.13–18.96)  |
| Presence of clinical manifestations in the neonatal period | 0.019   | 4.97 (1.30–18.96)  |
| Newborn VDRL titers greater than 1:2 at birth              | 0.022   | 11.28 (1.42–94.44) |

## DISCUSSION

The prevalence of congenital syphilis in this study, conducted at a reference center for infectious diseases in the capital of Minas Gerais, Brazil, was 2.6% (10/377). This rate aligns closely with findings from two maternity hospitals in Salvador, which reported a prevalence of 3.7%<sup>12</sup>, and another hospital in Belo Horizonte, which observed a rate of 4.3%<sup>13</sup>. However, the prevalence noted in our study is lower than those reported in some international contexts, such as 6.2% at a hospital in Italy<sup>14</sup> and 9.4% in a comprehensive Chinese study<sup>15</sup>. Moreover, it contrasts significantly with other Brazilian studies, which reported prevalences of 41.1% in Basic Health Units in Teresina<sup>16</sup> and 69.5% in a hospital in Sobradinho in the Federal District<sup>17</sup>. The variations in prevalence rates across studies can be attributed to differences in the diagnostic criteria for congenital syphilis and the timing of their implementation.

In line with the goals of this study, a strict criterion for defining congenital syphilis was employed, despite evidence from observational studies with certain methodological constraints

that have reported cases of children with confirmed congenital syphilis experiencing seroreversion of the treponemal test<sup>18,19</sup>.

The probability of vertical transmission of syphilis is higher in women coinfecting with HIV, as observed in two studies included in a recent systematic review, which suggest that these women are 4 to 16 times more likely to transmit syphilis vertically<sup>6</sup>. Despite this, the prevalence of syphilis-HIV coinfection in this cohort was notably low, observed in the mothers of only two children (0.5%), both in the group where congenital syphilis was ruled out. This low incidence can be attributed to the specific inclusion criteria of the study, which focused on children referred to the reference service due to vertical exposure to syphilis. In contrast, studies assessing the prevalence of syphilis coinfection among cohorts of HIV-positive mothers report higher prevalence rates. For instance, a study conducted by Yeganeh et al.<sup>20</sup> found that 10% of women (n=171) showed serological evidence of syphilis and 1.4% of infants (n=24) were coinfecting with both syphilis and HIV. The absence of a significant association between HIV coinfection and confirmed congenital syphilis diagnosis in this study is likely due to the small number of coinfecting women in the sample.

When analyzing the presence of a history of syphilis, this study did not find a statistically significant difference between the groups. This contrasts with both the study by Qin et al.<sup>21</sup>, which indicated that a history of syphilis is a protective factor (OR 0.24; 95% CI 0.11-0.53), and the study by Hong et al.<sup>22</sup>, which presented syphilis prior to pregnancy as a risk factor (OR 1.65; 95% CI 1.36-2.02). Discrepancies in results may be attributed to variations in the studied populations, diagnostic criteria for syphilis, or the influence of unmeasured confounding factors in this study. In any case, these findings highlight the importance of careful analysis of the history of syphilis and its impact on the risk of congenital syphilis in different contexts.

Illicit drug use during pregnancy was not associated with a statistically significant difference in the occurrence of congenital syphilis, contrasting with studies that suggest an

increased prevalence<sup>3,23-26</sup>. In a U.S. cohort study, which included only pregnant women with syphilis who reported using some type of illicit or licit drug (alcohol, cigarettes, prescribed opioids), it was observed that the use of any of these substances nearly doubled the prevalence of congenital syphilis (95% CI 1.6-2.38), with even higher rates among those who used prescribed opioids (OR 6.09; 95% CI 3.50-10.58)<sup>27</sup>. Conversely, the findings of this study align with other research that did not find an association between drug use and congenital syphilis<sup>28-32</sup>. The absence of this association in some studies may be due to the reluctance of mothers to report such use or the omission of questioning by the attending physician during the medical history, thus underestimating the frequency of this variable.

Active maternal syphilis is defined by the presence of non-treponemal test titers greater than 1:8, which is a recognized risk factor for congenital syphilis<sup>11</sup>. Using this value as a reference, some studies have also demonstrated an association between higher titers and congenital syphilis<sup>21,22,33</sup>. In this study, VDRL titers at the time of delivery greater than or equal to 1:8 showed borderline significance (OR 8.14; 95% CI 0.99-66.82). These findings highlight the critical importance of rigorous monitoring and appropriate treatment of mothers with titers above 1:8 to effectively prevent the vertical transmission of syphilis.

As part of the follow-up for pregnant women with syphilis, evaluating the sexual partner is essential, given that syphilis is a sexually transmitted infection. Testing and treatment of the sexual partner are recommended in the main protocols for managing syphilis in pregnant women<sup>10,11,34</sup>, as the absence of these measures increases the risk of therapeutic failure due to the possibility of reinfection. The risk of reinfection should be considered one of the criteria for inadequate treatment of the pregnant woman<sup>10</sup>. However, this study did not demonstrate an association between congenital syphilis and the absence of partner treatment, which should be interpreted with caution, given that information about partner treatment was missing for 51% of the mothers of the analyzed patients.

It is widely accepted in the literature that parenteral penicillin G is effective in treating syphilis in pregnant women and preventing congenital syphilis, although this recommendation is based on studies with low-quality evidence and has limitations in defining the ideal therapeutic regimen<sup>9,35</sup>. This study did not find an association between adequate maternal treatment and confirmed diagnosis of congenital syphilis, which may be attributed to the stringent criteria adopted for defining adequate maternal treatment and the frequent lack of recorded information. However, in agreement with other authors<sup>22,36</sup>, an association was observed between pregnant women who were not treated with benzathine penicillin and the diagnosis of congenital syphilis in the univariate analysis, an association that remained significant in the multivariate analysis (OR 3.99; 95% CI 1.06–5.08).

Unlike what is described in the literature<sup>8</sup>, this study did not observe an association between congenital syphilis and prematurity or low birth weight, which can be partially explained by the substantial loss of information on gestational age and birth weight, limiting the power of the analysis.

One of the established criteria for managing congenital syphilis is the presence of symptoms at birth<sup>10,11</sup>. This is corroborated by the present study, which demonstrated an independent association between the presence of clinical manifestations in the neonatal period or at the first consultation and the diagnosis of congenital syphilis (OR 4.71; 95% CI 1.23–17.96). It is important to note that the symptoms suggesting congenital syphilis are nonspecific and common to other congenital diseases, both infectious and non-infectious.

Despite guidelines diagnosing congenital syphilis when the newborn non-treponemal test titers are four times higher than the maternal titers<sup>10,11</sup>, a WHO review in 2004 noted that only 30% of infected children have higher titers than their mothers. This is because early treated children may not develop high titers<sup>37</sup>. In this study, no significant association was found between this variable and congenital syphilis. However, newborns with VDRL titers greater

than 1:2 had a higher risk (OR 11.28; 95% CI 1.38–91.96), highlighting the importance of considering any reactive VDRL titer.

Neurosyphilis can be present even in asymptomatic children, and the diagnosis can be suggested through cerebrospinal fluid abnormalities such as elevated protein levels, pleocytosis, and reactive non-treponemal tests<sup>8,36</sup>. However, the comparative analysis of cerebrospinal fluid abnormalities is limited because these changes can also occur in other infectious conditions, such as bacterial sepsis, and reference values vary according to gestational age at birth and chronological age at the time of collection. In this study, normal reference values were based on clinical management protocols for congenital syphilis<sup>10,11</sup>, but no association was found with the diagnosis of congenital syphilis. Another limitation of this study was the lack of information on trauma during the procedure or the number of red blood cells in the cerebrospinal fluid of many children, making it impossible to assess the true presence of abnormalities. This limitation might also explain the presence of reactive VDRL in the cerebrospinal fluid of four children in the congenital syphilis excluded group. Additionally, in the absence of other evidence of congenital syphilis, a reactive VDRL test in the cerebrospinal fluid is controversial, as IgG antibodies can cross both the placental and blood-brain barriers<sup>38</sup>.

Bone abnormalities are common manifestations of early congenital syphilis, primarily resulting from periostitis and cortical demineralization. Radiological findings are nonspecific and can range from radiopaque bands to apparent bone destruction<sup>8</sup>. In this study, all records of long bone radiographic abnormalities were in the group of children with excluded congenital syphilis. This finding may be influenced by the inexperience of the attending physician in radiographic evaluation, potentially leading to misinterpretation of findings, especially considering the variable quality of radiological exams. Additionally, the lack of access to the

radiological images and the poorly detailed notes in discharge reports or medical records of these children posed further challenges in accurately assessing these abnormalities.

One of the main limitations of this study was the high rate of patients excluded from the analysis, partly due to the stringent exclusion criteria and partly due to insufficient data available for statistical analysis. Additionally, the loss of long-term follow-up may have been influenced by the data collection period, which coincided with the COVID-19 pandemic<sup>39</sup>.

The proper management of pregnant women with syphilis requires a set of measures that include the appropriate prescription of recommended antibiotic therapy, shared responsibility of the patient, treatment of the sexual partner, and detailed recording of all actions in the prenatal card<sup>10</sup>. Some of the limitations presented in this study are directly related to failures in medical records at all levels of care, from prenatal to maternity. This should prompt reflection among health managers, as the lack of information makes it difficult to identify gaps in care.

Another noteworthy observation in this study is the high rate of absenteeism in follow-up appointments for the children, which justifies treating the newborn based on epidemiological criteria for defining congenital syphilis. This deserves attention, as managing the newborn in the maternity ward often involves evaluating the likelihood of outpatient follow-up for the infant exposed to syphilis, according to recommendations from the Ministry of Health<sup>10</sup>.

The absence of information regarding some variables in this study may have hindered the recognition of the association between congenital syphilis and well-established risk factors in the literature<sup>6</sup>. Another factor to consider is the small number of children with congenital syphilis confirmed by the treponemal test, which may have limited the study power to detect variables with statistically significant differences demonstrated in previously published studies<sup>6</sup>.

In conclusion, despite a high rate of prenatal syphilis screening, only a small proportion of seropositive patients in this study were adequately diagnosed and treated. Additionally, mothers with syphilis who did not receive benzathine penicillin during prenatal care had a higher risk of having a child diagnosed with congenital syphilis. This study highlights two important factors in managing newborns exposed to syphilis. First, VDRL titers greater than 1:2, even if not four times higher than the maternal titers, should be considered significant. Second, the presence of clinical manifestations, even if nonspecific and common to other neonatal conditions, must be considered. These factors should be considered in healthcare to ensure the effective implementation of public health policies for the timely prevention and treatment of congenital syphilis.

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## 7. CONSIDERAÇÕES FINAIS

1. Neste estudo, os fatores associados ao diagnóstico de sífilis congênita (SC) foram investigados em uma amostra de crianças expostas verticalmente à sífilis e as suas respectivas mães, em um centro de referência em doenças infecciosas. Os resultados encontrados destacam a importância do tratamento materno com penicilina benzatina, como uma medida eficaz na redução do diagnóstico de SC. Mães que não receberam esse tratamento durante o pré-natal apresentaram um risco significativamente maior de terem uma criança com diagnóstico de SC. Isso ressalta a necessidade de fortalecer os protocolos

de prevenção e manejo da sífilis durante a gestação, com foco na identificação e tratamento adequado das gestantes infectadas.

2. Outro aspecto evidenciado no estudo foi o baixo percentual de mulheres classificadas como tendo sido adequadamente tratadas, sugerindo dificuldades em se executar o protocolo que define as ações preventivas para impedir a transmissão da sífilis da mãe para o concepto.
3. Apesar dos resultados promissores, relacionados ao tratamento materno com penicilina benzatina, o presente estudo enfrentou algumas limitações. A alta taxa de exclusão de pacientes, devido a critérios rigorosos, e à falta de dados completos em algumas variáveis foram desafios que afetaram a amplitude de nossa análise. Além disso, a ausência de associação significativa com outros fatores de risco, já estabelecidos na literatura, como história pregressa de sífilis e uso de drogas ilícitas durante a gestação, sugere a necessidade de investigações adicionais para compreender melhor essas complexas relações.
4. Apesar das diretrizes estabelecerem, como critério diagnóstico de SC, a titulação do teste treponêmico do RN quatro vezes ou mais que os títulos da mãe na maternidade, é importante observar que apenas uma minoria das crianças infectadas apresenta títulos mais altos do que suas mães. Os resultados desse estudo demonstraram que os títulos de VDRL do RN maiores que 1:2 na maternidade estiveram associados com o diagnóstico final de SC, reforçando a importância de se valorizar a reatividade do VDRL como um indicador relevante.
5. Observou-se que a presença de manifestações clínicas no período neonatal, ou na primeira consulta, foi um fator de risco independente para o diagnóstico de SC. Essas manifestações, embora inespecíficas e compartilhadas por outras afecções do período neonatal, devem ser valorizadas como indicadores da possibilidade de SC.
6. Os achados desse estudo ressaltam que os algoritmos propostos por diretrizes nacionais e internacionais, para o manejo do RN exposto à sífilis, permanecem adequados. Esses algoritmos se valem de investigação detalhada da história materna de sífilis e a avaliação clínico-laboratorial do lactente. As variáveis associadas ao diagnóstico de SC, nesse estudo, alertam os profissionais que prestam assistência na maternidade ao RN de mãe com sífilis, para que apliquem com rigor os critérios estabelecidos nos protocolos.
7. No contexto atual de saúde pública, a erradicação da SC permanece sendo um desafio significativo, apesar de ser uma doença prevenível. O compromisso contínuo com a melhoria da conscientização, rastreamento e tratamento da sífilis durante a gravidez é fundamental para reduzir a transmissão vertical da doença.

8. Esse estudo representa mais um passo na compreensão dos fatores relacionados à SC e serve como motivador para que novos trabalhos e pesquisas possam ser realizados.
9. Perspectivas futuras incluem a realização de estudos prospectivos que possam avaliar com maior precisão as estratégias de saúde pública direcionadas à redução da sífilis em gestantes e à prevenção da transmissão vertical.

## APÊNDICE 1 – Formulário para coleta de dados

| <b>Formulário para Coleta de Dados do Projeto de Iniciação Científica Referente à Sífilis Congênita</b><br><b>Centro de Referência de Treinamento – Orestes Diniz</b> |         |                                                                                  |                            |                                                 |           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------------------------------------------------------------------------|----------------------------|-------------------------------------------------|-----------|
| Nome:                                                                                                                                                                 |         |                                                                                  |                            |                                                 |           |
| Prontuário HC-UFG:                                                                                                                                                    |         | Prontuário PBH:                                                                  |                            | Data de nascimento:                             |           |
| Data 1ª consulta:                                                                                                                                                     |         | Idade 1ª consulta:                                                               |                            | Maternidade:                                    |           |
| Observações quanto à coleta de dados:                                                                                                                                 |         |                                                                                  |                            | Controle referente à digitação deste formulário |           |
|                                                                                                                                                                       |         |                                                                                  |                            | Formulário completamente preenchido?            | Sim   Não |
|                                                                                                                                                                       |         |                                                                                  |                            | Informações lançadas no banco de dados?         | Sim   Não |
| INFORMAÇÕES RELATIVAS À MÃE NO PRÉ-NATAL                                                                                                                              |         |                                                                                  |                            |                                                 |           |
| DUM: ( ) sem informação - 09.09.09                                                                                                                                    |         | G   P   A ( ) sem informação - 99                                                |                            |                                                 |           |
| Idade gestacional da criança ao nascimento:                                                                                                                           |         | Classificação da idade gestacional:                                              |                            |                                                 |           |
| semanas   dias   ( ) sem informação - 99                                                                                                                              |         | ( ) pré-termo - 1   ( ) termo - 2<br>( ) pós-termo - 3   ( ) sem informação - 99 |                            |                                                 |           |
| Co-infecção materna pelo HIV? ( ) sim - 1   ( ) não - 2   ( ) outras coinfeção - 3                                                                                    |         |                                                                                  |                            |                                                 |           |
| Descrever se outra infecção materna:                                                                                                                                  |         |                                                                                  |                            |                                                 |           |
|                                                                                                                                                                       |         |                                                                                  |                            |                                                 |           |
| Sintomatologia materna no período pré-natal                                                                                                                           |         |                                                                                  |                            |                                                 |           |
|                                                                                                                                                                       | Sim (1) | Não (2)                                                                          |                            | Sim (1)                                         | Não (2)   |
| Assintomático                                                                                                                                                         |         |                                                                                  | Hepato e/ou esplenomegalia |                                                 |           |
| Febre                                                                                                                                                                 |         |                                                                                  | Exantema                   |                                                 |           |
| Linfadenomegalia                                                                                                                                                      |         |                                                                                  | Mialgia                    |                                                 |           |
| Redução da acuidade visual                                                                                                                                            |         |                                                                                  |                            |                                                 |           |
| Descrever outros sintomas:                                                                                                                                            |         |                                                                                  |                            |                                                 |           |
|                                                                                                                                                                       |         |                                                                                  |                            |                                                 |           |
| Idade gestacional da ocorrência do sintoma:                                                                                                                           |         |                                                                                  |                            |                                                 |           |
| ( ) 1º trimestre   ( ) 2º trimestre   ( ) 3º trimestre   ( ) não se aplica - 88   ( ) sem informação - 99                                                             |         |                                                                                  |                            |                                                 |           |
|                                                                                                                                                                       |         |                                                                                  |                            |                                                 |           |
| Formulário para Coleta de Dados do Projeto de Iniciação Científica Referente à Doenças Congênicas — Validação em 06/08/20                                             |         |                                                                                  |                            |                                                 |           |

| PROPEDEÚTICA MATERNA - SÍFILIS                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|-------------|--------------------------|-------------------|-----------------------|---------------------------|------------------------------------------|
| VDRL (teste de rastreio)                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Data<br>não se aplica<br>(08.08.08)<br>sem informação<br>(09.09.09) | Momento do exame                                                                                                                                                 |             |             |             |                          |                   |                       |                           | Titulação:<br>*ver codificação<br>abaixo |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                     | Antes da<br>gestação<br>(0)                                                                                                                                      | 1ª T<br>(1) | 2ª T<br>(2) | 3ª T<br>(3) | Imediato<br>ao parto (4) | Pós-<br>parto (5) | Não se<br>aplica (88) | Sem<br>informação<br>(99) |                                          |
| Exame 01                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 02                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 03                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 04                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 05                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 06                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 07                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 08                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 09                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 10                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 11                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| Exame 12                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| <b>*Codificação da variável titulação:</b><br>1 - 1:1      2 - 1:2      4 - 1:4      8 - 1:8      16 - 1:16      32 - 1:32      64 - 1:64<br>128 - 1:128      256 - 1:256      512 - 1:512      1024 - 1:1024      2048 - 1:2048      4096 - 1:4096<br>0 - Reagente (não sabe título)      7777 - não reagente      8888 - não se aplica      9999 - sem informação                                                                                             |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |
| <b>Titulação do último VDRL:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                     | Considerar o VDRL colhido na maternidade (antes do parto ou logo após o parto). Caso não tenha um exame imediato ao parto, registrar o último VDRL do pré-natal. |             |             |             |                          |                   |                       |                           |                                          |
| <b>Queda adequada de VDRL?</b> ( ) sim - 1      ( ) não - 2      ( ) não se aplica - 88<br><br>Queda adequada do VDRL consiste em queda de pelo menos duas diluições em até três meses <u>ou</u> negatificação do VDRL em até seis meses. Se houve queda inicial do VDRL e posterior ascensão, <b>não</b> consideramos que houve queda adequada.<br>- VDRL 1:64 → 1:32 (queda de uma diluição) → 1:16 (queda de duas diluições) → 1:8 (queda de três diluições) |                                                                     |                                                                                                                                                                  |             |             |             |                          |                   |                       |                           |                                          |

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|                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Testes treponêmicos (confirmatórios)</b>                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>FTA-Abs ou hemaglutinação</b>                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Realizado? <input type="checkbox"/> sim - 1 <input type="checkbox"/> não - 2                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Data da realização do exame:</b><br><input type="checkbox"/> sem informação - 08.08.08<br><input type="checkbox"/> não se aplica - 09.09.09                                                                                                                                                                                                             | <b>Correlacionar a seguir a data de realização do exame:</b><br><input type="checkbox"/> Anterior à gestação - 0 <input type="checkbox"/> 1º trimestre - 1 <input type="checkbox"/> 2º trimestre - 2<br><input type="checkbox"/> 3º trimestre - 3 <input type="checkbox"/> Imediato ao parto - 4 <input type="checkbox"/> Pós-parto - 5<br><input type="checkbox"/> não informado - 99 <input type="checkbox"/> não se aplica - 88 |
| <b>Resultado do exame:</b><br><input type="checkbox"/> positivo - 1 <input type="checkbox"/> negativo - 2 <input type="checkbox"/> indeterminado - 3 <input type="checkbox"/> não se aplica - 88                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Teste rápido</b>                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Realizado? <input type="checkbox"/> sim - 1 <input type="checkbox"/> não - 2                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Data da realização do exame:</b><br><input type="checkbox"/> sem informação - 08.08.08<br><input type="checkbox"/> não se aplica - 09.09.09                                                                                                                                                                                                             | <b>Correlacionar a seguir a data de realização do exame:</b><br><input type="checkbox"/> Anterior à gestação - 0 <input type="checkbox"/> 1º trimestre - 1 <input type="checkbox"/> 2º trimestre - 2<br><input type="checkbox"/> 3º trimestre - 3 <input type="checkbox"/> Imediato ao parto - 4 <input type="checkbox"/> Pós-parto - 5<br><input type="checkbox"/> não informado - 99 <input type="checkbox"/> não se aplica - 88 |
| <b>Resultado do exame:</b><br><input type="checkbox"/> positivo - 1 <input type="checkbox"/> negativo - 2 <input type="checkbox"/> indeterminado - 3 <input type="checkbox"/> não se aplica - 88                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Conclusão dos testes treponêmicos</b><br><input type="checkbox"/> positivo - 1 <input type="checkbox"/> negativo - 2 <input type="checkbox"/> indeterminado - 3 <input type="checkbox"/> não se aplica - 88<br><br>Interpretar os resultados de ambos os exames e concluir se houve ou não infecção materna pela sífilis com base no teste treponêmico. |                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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| TERAPÊUTICA MATERNA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| <b>Tratamento da mãe</b> → considerar apenas o tratamento <b>durante a gestação</b> (tratamento pós-parto não afeta a transmissão vertical)<br>Se a gestante recebeu vários tratamentos durante a gestação (devido a reinfecções), considerar o último tratamento e anotar os demais no campo observação.                                                                                                                                                                                                                                                                                |                    |
| <b>Penicilina benzatina:</b> ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                    |
| Número de doses: ( ) uma dose ( ) duas doses ( ) três doses ( ) não se aplica ( ) sem informação                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |
| Data de início:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>Observação:</b> |
| Data de término:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |
| <b>Penicilina procaína:</b> ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                    |
| <b>Observação:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                    |
| <b>Penicilina cristalina:</b> ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                    |
| <b>Observação:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                    |
| <b>Tratamento do parceiro com penicilina benzatina:</b> ( ) sim - 1 ( ) não - 2 ( ) sem informação                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                    |
| Número de doses: ( ) uma dose ( ) duas doses ( ) três doses ( ) não se aplica ( ) sem informação                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |
| <b>Observação:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                    |
| <b>Adequação do tratamento materno:</b> ( ) sim - 1 ( ) não - 2<br>É considerado adequado se preencher <u>todos os critérios</u> abaixo                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                    |
| <b>Esquema terapêutico adequado para o estágio da infecção pela sífilis?</b> ( ) sim - 1 ( ) não - 2<br>Considera-se adequada 1 dose para sífilis primária ou secundária; e 3 doses para sífilis terciária ou latente → no geral, consideramos a gestante como portadora de sífilis latente e realizamos o tratamento com três doses de penicilina benzatina. Apenas podemos tratar como primária ou secundária se houver evidência de lesão típica durante a gestação. Se a gestante reinfetou durante a gestação e foi tratada mais de uma vez, considerar o último esquema realizado. |                    |
| <b>Início do tratamento pelo menos 30 dias antes do parto?</b> ( ) sim - 1 ( ) não - 2 ( ) sem informação - 99<br>Se a gestante reinfetou durante a gestação e foi tratada mais de uma vez, considerar o último tratamento realizado.                                                                                                                                                                                                                                                                                                                                                    |                    |
| <b>Queda adequada do VDRL?</b> ( ) sim - 1 ( ) não - 2 ( ) não se aplica - 88<br>Queda adequada do VDRL consiste em queda de pelo menos duas diluições em até três meses <u>ou</u> negatificação do VDRL em até seis meses. Se houve queda inicial do VDRL e posterior ascensão, <u>não</u> consideramos que houve queda adequada.<br>- VDRL 1:64 → 1:32 (queda de uma diluição) → 1:16 (queda de duas diluições) → 1:8 (queda de três diluições)                                                                                                                                        |                    |
| <b>Tratamento do parceiro adequado?</b> ( ) sim - 1 ( ) não - 2<br>Considera-se tratamento do parceiro adequado se uso de esquema correto conforme o estágio da sífilis (em geral, consideramos latente e usamos três doses de penicilina benzatina). Lembrando que o parceiro deve ser tratado mesmo se possuir VDRL não reagente, já que ele pode estar na janela imunológica.                                                                                                                                                                                                         |                    |
| <b>Tratamento registrado?</b> ( ) sim - 1 ( ) não - 2<br>Registro adequado de todo o tratamento na caderneta da gestante, bem como do controle do VDRL pós-tratamento.                                                                                                                                                                                                                                                                                                                                                                                                                   |                    |

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| DADOS RELATIVOS AO NASCIMENTO |       |           |                                                                    |                    |  |
|-------------------------------|-------|-----------|--------------------------------------------------------------------|--------------------|--|
|                               | Valor | Percentil | APGAR - 1º minuto:                                                 | APGAR - 5º minuto: |  |
| Peso (g)                      |       |           |                                                                    |                    |  |
| Comprimento (cm)              |       |           | Via de nascimento:                                                 |                    |  |
| Perímetro cefálico (cm)       |       |           | ( ) vaginal - 1      ( ) cesariana - 2      ( ) não informado - 99 |                    |  |

| INFORMAÇÕES RELATIVAS À PRIMEIRA CONSULTA                                                           |         |         |                                |         |         |
|-----------------------------------------------------------------------------------------------------|---------|---------|--------------------------------|---------|---------|
| Dados antropométricos                                                                               |         |         |                                |         |         |
|                                                                                                     | Valor   | Z-score | Observações:                   |         |         |
| Peso                                                                                                |         |         |                                |         |         |
| Estatura                                                                                            |         |         |                                |         |         |
| Perímetro cefálico                                                                                  |         |         |                                |         |         |
| Sintomas presentes no período neonatal ou durante a primeira consulta? ( ) sim - 1      ( ) não - 2 |         |         |                                |         |         |
|                                                                                                     | Sim (1) | Não (2) |                                | Sim (1) | Não (2) |
| Linfonomegalia?                                                                                     |         |         | Macrocrania?                   |         |         |
| Esplenomegalia?                                                                                     |         |         | Convulsões?                    |         |         |
| Hepatomegalia?                                                                                      |         |         | Microftalmia?                  |         |         |
| Icterícia?                                                                                          |         |         | Estrabismo?                    |         |         |
| Exantema?                                                                                           |         |         | Alteração no tônus ou postura? |         |         |
| Petéquias?                                                                                          |         |         | Alteração de DNPM?             |         |         |
| Microcrania?                                                                                        |         |         |                                |         |         |
| Descrever outras alterações:                                                                        |         |         |                                |         |         |
|                                                                                                     |         |         |                                |         |         |

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| PROPEDEÚTICA NA CRIANÇA - SÍFILIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| VDRL (teste de rastreio)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Realizado?<br>Sim (1) Não (2)                                                                                                      | Data<br>não se aplica (08.08.08)<br>sem informação (09.09.09)          | Titulação:<br>*ver codificação ao lado                                                                                                                                    |
| Exame 01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>Sobre o exame 01</b><br>Comparação com VDRL materno pareado:<br>( ) maior - 1 ( ) menor ou igual - 2<br>( ) sem comparação - 99 |                                                                        | <b>Sobre o exame 01</b><br>Número de vezes que VDRL da criança foi maior que o materno:<br>( ) uma - 1 ( ) duas - 2 ( ) três - 3<br>( ) quatro - 4 ( ) não se aplica - 88 |
| Exame 02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
| Exame 03                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
| Exame 04                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
| Exame 05                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
| Exame 06                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
| Exame 07                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
| Exame 08                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
| <b>*Codificação da variável titulação:</b><br>1 - 1:1      2 - 1:2      4 - 1:4      8 - 1:8      16 - 1:16      32 - 1:32      64 - 1:64<br>128 - 1:128      256 - 1:256      512 - 1:512      1024 - 1:1024      2048 - 1:2048      4096 - 1:4096<br>0 - Reagente (não sabe título)      7777 - não reagente      8888 - não se aplica      9999 - sem informação                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
| Testes treponêmicos (confirmatórios) - FTA-Abs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
| Exame 01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Realizado?<br>( ) sim - 1<br>( ) não - 2                                                                                           | Data:<br>( ) não se aplica - 08.08.08<br>( ) sem informação - 09.09.09 | Resultado do exame:<br>( ) positivo - 1 ( ) negativo - 2<br>( ) indeterminado - 3 ( ) não se aplica - 88                                                                  |
| Exame 02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Realizado?<br>( ) sim - 1<br>( ) não - 2                                                                                           | Data:<br>( ) não se aplica - 08.08.08<br>( ) sem informação - 09.09.09 | Resultado do exame:<br>( ) positivo - 1 ( ) negativo - 2<br>( ) indeterminado - 3 ( ) não se aplica - 88                                                                  |
| <b>Status da criança codificado baseado em teste treponêmico:</b><br>( ) positivo - 1 ( ) negativo - 2 ( ) indeterminado - 3 ( ) não se aplica - 88<br>O teste treponêmico na criança pode permanecer positivo até 18 meses sem representar que a criança se infectou. Dessa forma, para avaliar o status codificado da criança, é importante interpretar a data do teste treponêmico e o seu resultado.<br>De um modo geral, tem-se realizado o teste a partir de 1 ano de idade:<br>- Resultado negativo → status codificado da criança: negativo → exclui a infecção pela sífilis<br>- Resultado positivo → repetir o teste treponêmico após os 18 meses<br>- Novo teste positivo (> 18 meses) → status codificado da criança: positivo → confirma a infecção pela sífilis<br>- Novo teste negativo (> 18 meses) → status codificado da criança: negativo → exclui a infecção pela sífilis<br>Caso haja perda de seguimento da criança antes da confirmação ou da exclusão do diagnóstico, consideramos o status codificado da criança como indeterminado. |                                                                                                                                    |                                                                        |                                                                                                                                                                           |
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| PROPEDEÚTICA COMPLEMENTAR DA CRIANÇA                                                                                                                                                                                                                                                               |                                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| Hemograma realizado? ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                                       |                                                                   |
| Exame alterado?<br>( ) sim - 1 ( ) não - 2 ( ) não se aplica - 88                                                                                                                                                                                                                                  | SOMA das alterações =                                             |
| <b>Assinalar abaixo se alteração apontada pelo exame:</b><br>( ) Anemia - 1 ( ) Leucopenia - 2 ( ) Leucocitose - 4 ( ) Plaquetopenia - 8 ( ) Plaquetose - 16<br>( ) Reticulocitose - 32 ( ) Outras - 64 ( ) Não se aplica - 888 ( ) Sem informação - 999<br>Outras alterações:                     |                                                                   |
| Triagem auditiva realizada? ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                                |                                                                   |
| <b>Tipo de exame:</b><br>( ) TANE - 1 ( ) BERA - 2<br>( ) não informado - 99 ( ) não se aplica - 88                                                                                                                                                                                                | Exame alterado?<br>( ) sim - 1 ( ) não - 2 ( ) não se aplica - 88 |
| Fundoscopia realizada? ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                                     |                                                                   |
| <b>Exame alterado?</b><br>( ) sim - 1 ( ) não - 2 ( ) não se aplica - 88<br><b>DESCREVER a alteração se esta foi identificada no exame:</b>                                                                                                                                                        |                                                                   |
| Ultrassonografia transfontanelar realizada? ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                |                                                                   |
| Exame alterado?<br>( ) sim - 1 ( ) não - 2 ( ) não se aplica - 88                                                                                                                                                                                                                                  | SOMA das alterações =                                             |
| <b>Assinalar a seguir a alteração se esta foi identificada no exame:</b><br>( ) Calcificações cranianas - 1 ( ) Dilatação ventricular - 2 ( ) Atrofia cortical - 4 ( ) Vasculite - 8<br>( ) Microcefalia - 16 ( ) Outras - 32 ( ) Sem informação - 99 ( ) Não se aplica - 88<br>Outras alterações: |                                                                   |
| Tomografia computadorizada de Encéfalo realizada? ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                          |                                                                   |
| Exame alterado?<br>( ) sim - 1 ( ) não - 2 ( ) não se aplica - 88                                                                                                                                                                                                                                  | SOMA das alterações =                                             |
| <b>Assinalar a seguir a alteração se esta foi identificada no exame:</b><br>( ) Calcificações cranianas - 1 ( ) Dilatação ventricular - 2 ( ) Atrofia cortical - 4 ( ) Vasculite - 8<br>( ) Microcefalia - 16 ( ) Outras - 32 ( ) Sem informação - 99 ( ) Não se aplica - 88<br>Outras alterações: |                                                                   |

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|                                                                                                                                                                                                                                                                                                                                                                                        |                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| <b>Ressonância Magnética de Encéfalo realizada?</b> ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                                                                                            |                              |
| <b>Exame alterado?</b><br>( ) sim - 1 ( ) não - 2 ( ) não se aplica - 88                                                                                                                                                                                                                                                                                                               | <b>SOMA das alterações =</b> |
| <b>Assinalar a seguir a alteração se esta foi identificada no exame:</b><br>( ) Calcificações cranianas - 1 ( ) Dilatação ventricular - 2 ( ) Atrofia cortical - 4 ( ) Vasculite - 8<br>( ) Microcefalia - 16 ( ) Outras - 32 ( ) Sem informação - 99 ( ) Não se aplica - 88<br>Outras alterações:                                                                                     |                              |
| <b>Radiografia de Ossos Longos realizada?</b> ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                                                                                                  |                              |
| <b>Exame alterado?</b><br>( ) sim - 1 ( ) não - 2 ( ) não se aplica - 88                                                                                                                                                                                                                                                                                                               | <b>SOMA das alterações =</b> |
| ( ) Alteração de periósteo (duplo contorno) - 1 ( ) Alteração de epífise (lesões osteolíticas) - 2<br>( ) Alteração de metáfise - 4 ( ) Alteração de diáfise (reforço periósteo) - 8<br>( ) Alteração de diáfise (lesões osteolíticas) - 16 ( ) Calo ósseo - 32<br>( ) Outras - 64 ( ) Sem informação - 999 ( ) Não se aplica - 888<br><b>Descrever OUTRAS alterações encontradas:</b> |                              |
| <b>Líquor realizado?</b> ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                                                                                                                       |                              |
| <b>Exame alterado?</b><br>( ) sim - 1 ( ) não - 2 ( ) não se aplica - 88                                                                                                                                                                                                                                                                                                               | <b>SOMA das alterações =</b> |
| <b>Assinalar abaixo se alteração apontada pelo exame:</b><br>( ) Pleiocitose - 1 ( ) Elevação de proteínas - 2 ( ) Diminuição da glicose - 4 ( ) outras - 8<br>( ) não informado - 99 ( ) não se aplica - 88<br><b>Descrever OUTRAS alterações encontradas:</b>                                                                                                                        |                              |
| <b>VDRL realizado?</b> ( ) sim - 1 ( ) não - 2                                                                                                                                                                                                                                                                                                                                         |                              |
| <b>Resultado:</b> ( ) reagente - 1 ( ) não reagente - 2 ( ) não se aplica - 88                                                                                                                                                                                                                                                                                                         |                              |
| <b>Propedêutica alterada?</b> ( ) sim - 1 ( ) não - 2 ( ) não realizada - 9                                                                                                                                                                                                                                                                                                            |                              |
| <b>Desfecho composto da propedêutica</b><br>( ) LCR - 1 ( ) óssea - 2 ( ) hemograma - 4 ( ) fundoscopia - 8 ( ) imagem cerebral - 16<br>( ) Outras 32 ( ) não se aplica - 88<br><b>SOMA das alterações =</b>                                                                                                                                                                           |                              |

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| DIAGNÓSTICO DA CRIANÇA                                                                                                                                                                                                                                                                                                          |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <b>Sífilis</b>                                                                                                                                                                                                                                                                                                                  |  |
| <b>Status do diagnóstico:</b><br><input type="checkbox"/> confirmado - 1 <input type="checkbox"/> provável - 2 <input type="checkbox"/> suspeito - 4 <input type="checkbox"/> descartado - 8                                                                                                                                    |  |
| <b>Momento da infecção:</b> <input type="checkbox"/> congênito - 1 <input type="checkbox"/> adquirido - 2 <input type="checkbox"/> não definido - 3                                                                                                                                                                             |  |
| <b>Descrever outra coinfeção se presente:</b><br><br>                                                                                                                                                                                                                                                                           |  |
| <b>Proposta de seguimento da criança</b><br><input type="checkbox"/> Perda de seguimento - 1 <input type="checkbox"/> Internação hospitalar - 2 <input type="checkbox"/> Alta - 4 <input type="checkbox"/> Transferência para outro serviço - 8<br><input type="checkbox"/> Seguimento - 16 <input type="checkbox"/> Outro - 32 |  |
| <b>Descrever outro:</b><br><br>                                                                                                                                                                                                                                                                                                 |  |

| TERAPÊUTICA DA CRIANÇA                                                                                                                                                                                                                  |                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| <b>Penicilina benzatina utilizada?</b> <input type="checkbox"/> sim - 1 <input type="checkbox"/> não - 2                                                                                                                                |                                                                           |
| <b>Número de doses administradas</b><br><input type="checkbox"/> uma - 1 <input type="checkbox"/> duas - 2 <input type="checkbox"/> três - 3<br><input type="checkbox"/> não informado - 99 <input type="checkbox"/> não se aplica - 88 | <b>Início do tratamento:</b><br><br><b>Término do tratamento:</b><br><br> |
| <b>Observações:</b><br><br>                                                                                                                                                                                                             |                                                                           |
| <b>Penicilina procaína utilizada?</b> <input type="checkbox"/> sim - 1 <input type="checkbox"/> não - 2                                                                                                                                 |                                                                           |
| <b>Observações:</b><br><br>                                                                                                                                                                                                             |                                                                           |
| <b>Penicilina cristalina utilizada?</b> <input type="checkbox"/> sim - 1 <input type="checkbox"/> não - 2                                                                                                                               |                                                                           |
| <b>Observações:</b><br><br>                                                                                                                                                                                                             |                                                                           |

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## APÊNDICE 2 – Termo de Consentimento Livre e Esclarecido

### TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO – INFECÇÕES CONGÊNITAS: PREVENÇÃO, DIAGNÓSTICO E TRATAMENTO

#### CONSENTIMENTO LIVRE E ESCLARECIDO

##### Título do Projeto: INFECÇÕES CONGÊNITAS: PREVENÇÃO, DIAGNÓSTICO E TRATAMENTO

Antes de você aceitar participar desta pesquisa é importante que você leia e entenda esta explicação.

O diagnóstico de infecções maternas com risco de transmissão para o recém-nascido é importante para prevenção e tratamento precoce das crianças acometidas. Vários exames podem ser realizados para descobrir essas infecções, como exames de sorologia (sangue), ultrassons fetais, exames específicos no líquido amniótico das placentas e no líquido (líquido da espinha), quando indicados, em busca dos microorganismos responsáveis. Muitas dessas infecções podem ser tratadas para melhorar a qualidade de vida dessas crianças, desde que o tratamento seja iniciado precocemente.

O objetivo desta pesquisa é avaliar como tem sido feito o diagnóstico e como tem sido a evolução clínica das crianças acometidas durante o acompanhamento. Todos os procedimentos são rotinas e já são realizados normalmente na maternidade onde seu filho nasceu e no ambulatório de doenças infecciosas onde será feito o seguimento. Não serão colhidos exames ou nem será feito nenhum procedimento além dos exames de rotina necessários para avaliar se a criança encontra-se com alguma manifestação da doença. Não haverá nenhum risco, a não ser os relacionados aos procedimentos indicados pelos médicos assistentes.

As informações sobre sua doença e de seu filho serão confidenciais e não será usado nome de vocês. Apenas os pesquisadores poderão ter acesso a essas informações e identificá-los.

Você não será prejudicado em nenhum momento da assistência e o atendimento de seu filho continuará a ser realizado normalmente, caso você não queira participar ou caso desista de participar em qualquer momento do estudo. Além disso, não está previsto qualquer benefício ou pagamento pela sua participação.

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Rúbrica do responsável

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Rúbrica do pesquisador

Se tiver alguma dúvida quanto a este estudo e seus direitos, poderá contatar Dra. Roberta Maia de Castro Romanelli, Dra Fabiana Maria Kakehasi, Dra Lilian Oliveira Diniz, Dra Ericka Viana Machado Carellos pelo telefone (XX-31) 34099772. Se você tiver alguma dúvida sobre a condução ética dessa pesquisa, você pode contactar o Comitê de Ética da UFMG (3409-4592) localizado Av. Antônio Carlos, 6627, Pampulha - Belo Horizonte - MG - CEP 31270-901-Unidade Administrativa II - 2º Andar - Sala: 2005 - Campus UFMG (E-mail: coep@prpq.ufmg.br), ou o Comitê de Ética da Secretaria Municipal de Saúde (3277-5309), localizado a Avenida Afonso Pena, 2336, 9o andar. Funcionários - Belo Horizonte.

Se, por algum motivo você desistir de participar do estudo, você e seu filho não serão prejudicados em nenhum aspecto da assistência e continuarão a receber os mesmos procedimentos rotineiros.

#### Consentimento

Li e entendi as informações acima. Tive a oportunidade de fazer perguntas e esclarecer minhas dúvidas. Este formulário esta sendo assinado voluntariamente por mim. Concordo em participar do estudo até que eu decida o contrário. Receberei uma via assinada deste consentimento.

\_\_\_\_\_  
Nome do responsável

\_\_\_\_\_  
Assinatura do responsável

\_\_\_\_/\_\_\_\_/\_\_\_\_\_  
Data

\_\_\_\_\_  
Nome do pesquisador

\_\_\_\_\_  
Assinatura do pesquisador

\_\_\_\_/\_\_\_\_/\_\_\_\_\_  
Data

# Maternal and perinatal risk factors associated with congenital syphilis

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## Abstract

**Objective:** Mother-to-child transmission of syphilis remains an important global public health problem. Untreated intrauterine infection may result in adverse events for the fetus or newborn (NB). Maternal risk factors, such as prenatal care, early diagnosis, and appropriate treatment, significantly impact the likelihood of vertical transmission of syphilis. The purpose of this review is to evaluate maternal risk factors for congenital syphilis and the characteristics of exposed NB.

**Methods:** A total of 14 studies were evaluated, including 8 cohort studies, 4 cross-sectional and 2 control cases. A total of 12,230 women were included, with confirmed or highly probable congenital syphilis outcome, and 2285 NB. The studies evaluated risk factors for congenital syphilis, which were maternal, demographic, obstetric factors and characteristics of the exposed NB.

**Results:** Included in the risk factors studied, inadequate prenatal care and late onset, as well as inadequate or late treatment of maternal syphilis were significant risk factors for the outcome of congenital syphilis. When the time set of maternal diagnosis was correlated with neonatal infection, there was a tendency to worsen prognosis (more infected NB) in women diagnosed later in pregnancy, as well as in women who underwent few prenatal consultations and inadequate treatment. Women with recent syphilis with high VDRL titres had a higher rate of vertical transmission. The prior history of syphilis with adequate treatment was identified as a protective factor, resulting in lower rates of congenital syphilis. Among the epidemiological and demographic aspects surveyed, it was observed that young age, lower schooling, unemployment, low family income and no fixed residence were associated with higher risk of congenital syphilis.

**Conclusions:** The association of syphilis with adverse socio-economic conditions and inadequate prenatal care suggests that the improvement of the population's living conditions and equitable access to quality health services may have an impact on the reduction of congenital syphilis.

## KEYWORDS

congenital, pregnant woman, prenatal care, syphilis

## INTRODUCTION

Congenital syphilis (CS) is the result of the transplacental transmission of the spirochete *Treponema pallidum* from

the infected pregnant woman to the conceptus, during any time of pregnancy, and, rarely, during childbirth. Untreated intrauterine infection may result in abortion, stillbirth, Hydrops fetalis, premature delivery, perinatal death, in addition to clinical manifestations in the postnatal period [1, 2]. Prenatal care programs that include testing and treatment of

Sustainable Development Goals: Good Health and Wellbeing, Reduced Inequalities.

pregnant women have been shown to be effective in reducing adverse pregnancy outcomes [1]. Early screening for maternal syphilis during pregnancy associated with immediate treatment with benzathine penicillin of infected mothers leads to mother and baby healing and prevents the main complications associated with vertical transmission of syphilis [3].

Despite being an ancient and preventable disease, CS remains a public health problem in several countries. In 2016, the worldwide estimated prevalence of syphilis in pregnant women was 0.69% (95% CI 0.57%–0.81%) resulting in an overall congenital syphilis rate of 473 (385–561) to 100,000 live births and a total of 661,000 cases of CS, including 355,000 cases of adverse outcomes related to pregnancy or birth [4].

In Brazil, the 2020 detection rate of syphilis in pregnant women was 21.6/1000 live births. The incidence rate of congenital syphilis was 7.7/1000 live births and the mortality rate due to CS was 6.5/100,000 live births [5].

Vertical transmission of syphilis has been well-documented for several decades, but the diagnosis of CS remains demanding. Most newborns (NB) are asymptomatic at birth and gold standard tests for diagnosis, such as dark field *Treponema* research and polymerase chain reaction (CRP), are not available in clinical practice. The detection of IgG antibodies against *Treponema* in newborns does not allow the diagnosis of congenital infection due to the maternal-fetal transfer of these antibodies, and it is not possible to distinguish maternal antibodies from endogenous antibodies produced by the offspring. The detection of specific IgM treponemal antibodies, which do not cross the placental barrier, would confirm fetal infection, however, these laboratory tests have low sensitivity, so they are not validated for commercial use [6].

There is no further evaluation that could accurately determine the infection in the newborn. Non-treponemal tests are generally used in the evaluation of neonates with suspected CS because they provide quantitative results that can be compared with maternal results. They are also recommended to monitor diseases after treatment. These tests, however, are not specific and are not automated, and differences in the results in testing at alternate times can be observed [6, 7].

Hence, for the management of newborns exposed vertically to syphilis and the consequent decision to treat or not the baby, the CS case definition should follow validated criteria defined by WHO or official protocols from Health Ministry of several countries. These criteria consider the combination of clinical, laboratory and epidemiological evaluation, including the presence of known risk factors for CS. In this sense, several studies evaluating maternal and neonatal factors associated with CS have been published. This systematic review was accomplished to critically compile and analyse the results published to date with the aim of improving the health care of pregnant women and newborns.

## METHODS

The PECO question was defined as: Population = infants exposed to syphilis during pregnancy and their mothers; Exposure = risk factors in prenatal and perinatal time; Control = infants without risk factors; Outcome = congenital syphilis (confirmed or probable).

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol was used to construct this systematic review, which was registered in PROSPERO (CRD42021279652).

## Search strategy

A systematic search was conducted in the main electronic online databases (Medline, EMBASE, ScELO and Cochrane Library) of all articles registered until February 2021, without language restriction. The search terms used were 'Syphilis Serodiagnosis', 'treponemal infections', 'pregnant women', 'prenatal care', 'risk factors' and 'congenital syphilis'.

The search performed in each of the bases with the boolean descriptors and operators are described below:

- Pubmed: ((Syphilis Serodiagnosis) OR (Treponemal Infections)) AND ((Pregnant Women) OR (Prenatal Care) OR (risk factors)) AND (Syphilis, Congenital)
- EMBASE: ('syphilis serology' OR treponematoses OR 'treponemal infection') AND ('pregnant woman' OR 'prenatal care' OR 'risk factor') AND 'congenital syphilis'.
- Cochrane: ((Syphilis Serodiagnosis) OR (Treponemal Infections)) AND ((Pregnant Women) OR (Prenatal Care)) AND (Syphilis, Congenital).
- ScELO ('Syphilis Serodiagnosis' OR 'Treponemal Infections') AND ('Pregnant Women' OR 'Prenatal Care' OR 'risk factors') AND 'Syphilis Congenital'

In addition, we manually reviewed the bibliographic citations of the included studies to verify possible articles identified in the initial research.

## Selection criteria

Observational studies (cross-sectional, case-control and prospective and retrospective cohort) that investigated risk factors for congenital syphilis in children exposed to syphilis were included. The presence of a treponemal and a non-treponemal positive test during pregnancy or delivery were considered a diagnosis of maternal syphilis, or if the criteria for congenital syphilis were met for the neonates of the mothers in the study. Congenital syphilis was defined according to CDC/USA surveillance criteria [8] for confirmed and highly probable congenital syphilis or use of IgM treponemal test at birth and/or IgG at 18 months.

Exclusion criteria included studies in which the population was not pregnant, or studies that had unclear statistical analysis methods, or that did not present data possible to be extracted for analysis, in addition to duplicates and studies presenting overlapped data. Articles whose population studied was specific as pregnant women with HIV or deprived of liberty were also removed, since the variable considered in this review was to evaluate exposure or not to certain risk factors. In addition, studies that used possible or unlikely definitions of congenital syphilis according to the CDC criteria [9], or that were not clear regarding the inclusion criteria of children were excluded.

Two researchers (LBP, BSFS) performed the selection and extraction of the data independently. Discrepancies were resolved by a consensus among all authors.

### Data extraction and quality analysis

Each author conducted the individual reading of the articles, followed by a detailed review of all studies that met the inclusion criteria for data extraction, such as author name, year of publication, study design, sample size, main characteristics of the population, as well as location, period and limitations of the studies. These characteristics were grouped for analysis and shown in Table 1.

The risk of bias was assessed using the Newcastle-Ottawa scale [24] for control and cohort case studies and an adapted form of this scale for cross-sectional studies [25]. Stars are considered to evaluate study quality, with nine to ten stars indicating 'very good' quality, seven to eight stars indicating 'good' quality, five to six stars indicating 'satisfactory' quality, and zero to four stars indicating 'unsatisfactory' quality. A maximum of nine stars are

considered for case-control studies and cohorts and a maximum of seven stars are considered for cross-sectional studies.

The quality of the studies was evaluated by two reviewers (LBP, BSF) severally using the described scale and any disagreement was consensually resolved with two other reviewers (MRR, EC). Study practicalities have also been described.

### Statistical analysis

The information was synthesized in Table 3 with descriptive variables including the sample size and the comparative analysis that register measures of association (relative risk and odds ratio) with respective confidence intervals at 95% and *p*-value.

## RESULTS

### Studies selection

Our search identified 775 publications in the databases. Four articles cited in the references of the included studies were added. After removing duplicates (190) and excluding others after reading the title and abstract (415), 174 articles were considered potentially relevant and independently reviewed. Of these, 14 studies met the eligibility criteria: 8 cohort studies, 4 cross-sectional and 2 control cases (Figure 1).

Six studies were from the United States, four from China and four from other countries. A total of 12,230 women who were diagnosed with syphilis in the current pregnancy were added, resulting in 2285 children diagnosed with

TABLE 1 Main features of the studies included in the review.

| Reference                  | Design of experiment | Study location | Study duration | Number of pregnant women diagnosed with syphilis | Number of newborns with presumed or confirmed syphilis |
|----------------------------|----------------------|----------------|----------------|--------------------------------------------------|--------------------------------------------------------|
| Rawstron et al. [10]       | Cohort               | USA            | 1988–1989      | 397                                              | 75                                                     |
| McFarlin et al. [11]       | Cohort               | USA            | 1991–1992      | 190                                              | 72                                                     |
| Risser and Hwang [12]      | Cross-sectional      | USA            | 1990–1992      | 1070                                             | 694                                                    |
| Mobley et al. [13]         | Cohort               | USA            | 1991–1993      | 673                                              | 186                                                    |
| Tikhonova et al. [14]      | Cohort               | Russia         | 1995–1999      | 715                                              | 544                                                    |
| Lago et al. [15]           | Case-control         | Brazil         | 1998–1999      | 118                                              | 77                                                     |
| Liu et al. [16]            | Cohort               | China          | 2002–2007      | 554                                              | 29                                                     |
| Kirkcaldy et al. [17]      | Cross-sectional      | USA            | 2004–2008      | 242                                              | 78                                                     |
| Tridapalli et al. [18]     | Cohort               | Italy          | 2006–2007      | 203                                              | 51                                                     |
| Qin et al. [19]            | Cohort               | China          | 2007–2012      | 2,671                                            | 96                                                     |
| Hong et al. [20]           | Cohort               | China          | 2003–2014      | 4746                                             | 162                                                    |
| Biswas et al. [21]         | Cross-sectional      | USA            | 2012–2014      | 427                                              | 164                                                    |
| Wang et al. [22]           | Case-control         | China          | 2011–2014      | 155                                              | 27                                                     |
| Amgulruengkitt et al. [23] | Cross-sectional      | Thailand       | 2013–2017      | 69                                               | 30                                                     |

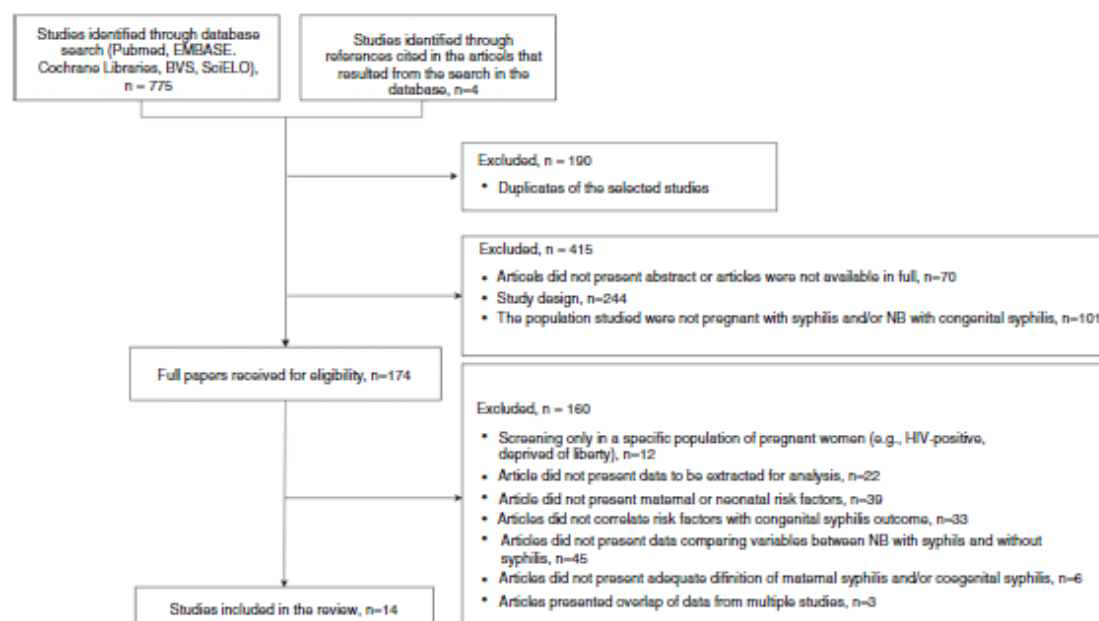


FIGURE 1 Flowchart of the study selection process.

TABLE 2 Quality analysis of studies that evaluated maternal, obstetric, and neonatal risk factors associated with congenital syphilis according to the Newcastle-Ottawa scale.

| Reference                   | Design of experiment         | Selection | Comparability | Exposure <sup>a</sup> | Outcome <sup>b</sup> | Quality        |
|-----------------------------|------------------------------|-----------|---------------|-----------------------|----------------------|----------------|
| Lago et al. [15]            | Case-control                 | ★★★       | ★             | ★                     | -                    | Satisfactory   |
| Wang et al. [22]            | Case-control                 | ★★★       | ★★            | ★★★                   | -                    | Good           |
| Rawstron et al. [10]        | Cohort                       | ★★★       | ★             | -                     | ★★                   | Satisfactory   |
| McFarlin et al. [11]        | Cohort                       | ★★        | ★             | -                     | ★                    | Unsatisfactory |
| Mobley et al. [13]          | Cohort                       | ★★★★      | ★             | -                     | ★★                   | Good           |
| Tikhonova et al. [14]       | Cohort                       | ★★★       | ★             | -                     | ★★                   | Satisfactory   |
| Liu et al. [16]             | Cohort                       | ★★★★      | ★             | -                     | ★★★                  | Good           |
| Tridapalli et al. [18]      | Cohort                       | ★         | -             | -                     | ★★                   | Unsatisfactory |
| Qin et al. [19]             | Cohort                       | ★★★★      | ★★            | -                     | ★★★                  | Very good      |
| Hong et al. [20]            | Cohort                       | ★★★★      | ★             | -                     | ★★★                  | Good           |
| Risser and Hwang [12]       | Cross-sectional <sup>c</sup> | ★★        | ★★            | -                     | ★★                   | Satisfactory   |
| Kirkcaldy et al. [17]       | Cross-sectional <sup>c</sup> | ★★        | ★             | -                     | ★★                   | Satisfactory   |
| Biswas et al. [21]          | Cross-sectional <sup>c</sup> | ★★        | ★             | -                     | ★★                   | Satisfactory   |
| Anugulruengkitt et al. [23] | Cross-sectional <sup>c</sup> | ★★        | ★             | -                     | ★★                   | Satisfactory   |

<sup>a</sup>Exposure: cohort studies do not have 'exposure' according to study design and scoring criteria in Newcastle-Ottawa scale.<sup>b</sup>Outcome: case-control studies do not present 'outcome' according to and scoring criteria in Newcastle-Ottawa scale.<sup>c</sup>For analysis of cross-sectional studies, an adaptation of Newcastle-Ottawa was used [25].

confirmed or presumed syphilis. The main characteristics of the included studies are presented in Table 1.

Of the 14 selected studies, one was classified as very good, four as good, six as satisfactory and four as unsatisfactory (Table 2).

In women diagnosed with syphilis during pregnancy or childbirth with the outcome of confirmed or probable congenital syphilis the variables identified were:

- Demographics and maternal history (residence, education, income, occupation, immigration; age, race, marital status, history of other sexually transmitted infection (STIs), number of sexual partners, treatment for syphilis prior to pregnancy, HIV co-infection);
- Obstetrics (previous pregnancy, history of pregnancy with adverse outcome, previous abortion, prenatal abortion, treatment during pregnancy, gestational age at the time of

TABLE 3 Maternal and obstetric factors related to congenital syphilis.

| Maternal variables                |                        |                                                                                                                                                                                    |                  |                                                                                                                                                            |
|-----------------------------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Socio-demographic                 | Reference              | Variables                                                                                                                                                                          | <i>p</i>         | RR or OR (IC95%)                                                                                                                                           |
| Age                               | Qin et al. [19]        | Mother's age                                                                                                                                                                       | -                | OR non adjusted:<br>0.62 (0.49–0.78)                                                                                                                       |
|                                   |                        | <ul style="list-style-type: none"> <li>• &lt;25 years</li> <li>• 25–30 years</li> <li>• 30–35 years</li> <li>• &gt;35 years</li> </ul>                                             |                  | <ul style="list-style-type: none"> <li>• 1</li> <li>• 0.44 (0.27–0.70)</li> <li>• 0.27 (0.14–0.49)</li> <li>• 0.34 (0.17–0.69)</li> </ul>                  |
| Ethnicity                         | Tridapalli et al. [18] | Mother's age <20 years                                                                                                                                                             | -                | RR: 3.44 (1.63–7.27)                                                                                                                                       |
|                                   | Mobley et al. [13]     | Black ethnicity                                                                                                                                                                    | -                | OR adjusted: 4.5 (1.3–15.5)                                                                                                                                |
|                                   | Risser and Hwang [12]  | Hispanic ethnicity                                                                                                                                                                 | -                | OR 1.8 (1.3–2.5)                                                                                                                                           |
|                                   | Qin et al. [19]        | Chinese minority ethnicity ('non Han')                                                                                                                                             | -                | OR non adjusted: 1.13 (1.01–1.25)                                                                                                                          |
| Income                            | Lago et al. [15]       | Income < US\$ 30/per month                                                                                                                                                         | -                | OR adjusted: 2.8 (1.1–7.4)                                                                                                                                 |
| Location                          | Hong et al. [20]       | Antenatal clinic in less developed area                                                                                                                                            | <i>p</i> < 0.001 | OR adjusted: 1.62 (1.38–1.91)                                                                                                                              |
|                                   | Mobley et al. [13]     | Rural area resident                                                                                                                                                                | -                | OR adjusted: 2.0 (1.4–2.9)                                                                                                                                 |
| Marital status                    | Qin et al. [19]        | Marital status: single                                                                                                                                                             | -                | OR non adjusted: 2.88 (1.64–5.05)                                                                                                                          |
|                                   | Lago et al. [15]       |                                                                                                                                                                                    | -                | OR adjusted: 2.8 (1.1–7.8)                                                                                                                                 |
| Migration                         | Wang et al. [22]       | Immigrant                                                                                                                                                                          | -                | OR non adjusted: 4.9 (1.7–17.7)                                                                                                                            |
|                                   | Tikhonova et al. [14]  |                                                                                                                                                                                    | <i>p</i> < 0.001 | -                                                                                                                                                          |
| Education                         | Hong et al. [20]       | Education: primary education or no schooling                                                                                                                                       | <i>p</i> < 0.001 | OR adjusted 1.5 (1.17–1.92)                                                                                                                                |
|                                   | Biswas et al. [21]     | Any level of higher education or more as a protective factor                                                                                                                       | <i>p</i> = 0.006 | -                                                                                                                                                          |
|                                   | Lago et al. [15]       | 10 years of education or more as a protective factor                                                                                                                               | -                | OR adjusted: 0.2 (0.1–0.7)                                                                                                                                 |
|                                   | Qin et al. [19]        | Education: <ul style="list-style-type: none"> <li>• Complete and incomplete primary</li> <li>• Middle school</li> <li>• Technical education</li> <li>• Higher education</li> </ul> | -                | OR non adjusted: <ul style="list-style-type: none"> <li>• 1</li> <li>• 0.27 (0.17–0.45)</li> <li>• 0.23 (0.12–0.42)</li> <li>• 0.40 (0.19–0.83)</li> </ul> |
| Drug                              | Mobley et al. [13]     | Use of cocaine                                                                                                                                                                     | -                | OR non adjusted 9.3 (2.6–33.1)                                                                                                                             |
| Sex partners                      | Qin et al. [19]        | Number of sexual partners in the 6 months prior to pregnancy                                                                                                                       | -                | 1.50 (1.01–2.22)                                                                                                                                           |
|                                   |                        | <ul style="list-style-type: none"> <li>• 1</li> <li>• ≥ 3</li> </ul>                                                                                                               |                  | <ul style="list-style-type: none"> <li>• 1</li> <li>• 3.82 (1.11–13.18)</li> </ul>                                                                         |
| Previous syphilis                 | Hong et al. [20]       | Treatment for pre-pregnancy syphilis                                                                                                                                               | <i>p</i> < 0.001 | OR adjusted: 1.65 (1.36–2.02)                                                                                                                              |
|                                   | Rawstron et al. [10]   |                                                                                                                                                                                    | <i>p</i> < 0.026 | -                                                                                                                                                          |
| Pregnancy loss                    | Qin et al. [19]        | Past history of syphilis                                                                                                                                                           | -                | OR non adjusted: 0.24 (0.11–0.53)                                                                                                                          |
|                                   | Lago et al. [15]       | Stillborn prior to current pregnancy                                                                                                                                               | -                | OR non adjusted: 4.6 (1.2–17.8)                                                                                                                            |
| HIV positivity                    | Mobley et al. [13]     | ≥1 gestational loss                                                                                                                                                                | -                | OR adjusted 0.3 (0.2–0.6)                                                                                                                                  |
|                                   | Hong et al. [20]       | HIV co-infection                                                                                                                                                                   | <i>p</i> = 0.039 | OR adjusted: 4.01 (1.08–14.93)                                                                                                                             |
|                                   | Lago et al. [15]       |                                                                                                                                                                                    | -                | OR non adjusted: 16.0 (3.1–109.5)                                                                                                                          |
| Variable related to prenatal care | Reference              | Variables                                                                                                                                                                          | <i>p</i>         | RR or OR (IC95%)                                                                                                                                           |
| Prenatal care service             | Biswas et al. [21]     | Service where prenatal care was held: <ul style="list-style-type: none"> <li>• Private</li> <li>• No health insurance</li> </ul>                                                   | <i>p</i> < 0.001 | -                                                                                                                                                          |

TABLE 3 (Continued)

| Variable related to prenatal care         | Reference                   | Variables                                                                                                              | <i>p</i>                   | RR or OR (IC95%)                                                                                                                        |
|-------------------------------------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| GA at the first prenatal consultation     | Biswas et al. [21]          | Prenatal care as a protective factor<br>• Any time<br>• $\geq 40$ days before delivery                                 | $p < 0.001$<br>$p < 0.001$ | -                                                                                                                                       |
|                                           | Biswas et al. [21]          | GA at the first prenatal consultation<br>• 1st trimester as a risk factor<br>• 3rd trimester as a risk factor          | $p < 0.001$                | -                                                                                                                                       |
|                                           | Tikhonova et al. [14]       | GA at the first prenatal consultation $\leq 20$ weeks                                                                  | $p < 0.001$                | -                                                                                                                                       |
|                                           | Hong et al. [20]            | GA at the first prenatal consultation $\geq 28$ weeks                                                                  | $p < 0.001$                | OR adjusted: 21.47 (18.07–25.50)                                                                                                        |
| Prenatal care                             | Biswas et al. [21]          | Prenatal care as a protective factor                                                                                   | $p < 0.001$                | -                                                                                                                                       |
|                                           | Risser and Hwang [12]       |                                                                                                                        | $p < 0.001$                | -                                                                                                                                       |
|                                           | Mohley et al. [13]          | Absence of prenatal care                                                                                               | -                          | OR adjusted: 2.7 (1.3–5.5)                                                                                                              |
|                                           | Qin et al. [19]             |                                                                                                                        | -                          | OR non adjusted: 4.00 (2.64–6.05)                                                                                                       |
|                                           | Tikhonova et al. [14]       |                                                                                                                        | $p < 0.001$                | OR adjusted: 2.8 (1.7–4.7)                                                                                                              |
|                                           | Risser and Hwang [12]       |                                                                                                                        | -                          | OR: 6.0 (3.9–9.2)                                                                                                                       |
| Prenatal visit                            | Rawstron et al. [10]        |                                                                                                                        | $p < 0.001$                | -                                                                                                                                       |
|                                           | Lago et al. [15]            | $< 6$ prenatal consultations                                                                                           | -                          | OR adjusted: 3.2 (1.3–8.1)                                                                                                              |
|                                           | Tikhonova et al. [14]       | $\leq 3$ prenatal consultations                                                                                        | $p < 0.001$                | -                                                                                                                                       |
| Screening for syphilis in prenatal care   | Tridapalli et al. [18]      | Absence of screening for syphilis in prenatal care                                                                     | -                          | RR: 3.1 (1.47–6.21)                                                                                                                     |
|                                           | Biswas et al. [21]          |                                                                                                                        | $p < 0.001$                | -                                                                                                                                       |
|                                           | Biswas et al. [21]          | 1st test for syphilis $< 40$ days before delivery                                                                      | $p < 0.001$                | -                                                                                                                                       |
|                                           | Kirkcaldy et al. [17]       | First test for syphilis performed in the 1st or 2nd trimester as a protective factor                                   | $p < 0.001$                | -                                                                                                                                       |
| Maternal treatment for syphilis           | McFarlin et al. [11]        | Maternal treatment for syphilis before pregnancy or early in pregnancy (14 weeks GA) as a protective factor            | $p = 0.005$                | -                                                                                                                                       |
| Syphilis diagnosis                        | Reference                   | Variables                                                                                                              | <i>p</i>                   | RR or OR (IC95%)                                                                                                                        |
| GA at diagnosis                           | Wang et al. [22]            | GA at diagnosis $> 36$ weeks                                                                                           | -                          | OR non adjusted: 24.1 (3.6–1000)                                                                                                        |
| Screening for syphilis                    | Tikhonova et al. [14]       | Screening for syphilis $\geq 28$ weeks                                                                                 | $p < 0.001$                | OR adjusted: 4.0 (2.6–6.0)                                                                                                              |
|                                           | Tikhonova et al. [14]       | Screening for syphilis $\leq 27$ weeks                                                                                 | $p < 0.001$                | -                                                                                                                                       |
|                                           | Anugulruengkitt et al. [23] | Positive serology for syphilis in the 3rd trimester                                                                    | $p < 0.001$                | -                                                                                                                                       |
| Titers of non-treponemal antibodies tests | Liu et al. [16]             | Logarithm (1/titer of non-treponemal antibodies)<br>*Values have been transformed using the reciprocal TRUST title log | $p < 0.001$                | OR non adjusted: 11.18 (5.16–24.24)                                                                                                     |
|                                           | Qin et al. [19]             | Titers of non-treponemal antibodies tests<br>• 1:1<br>• 1:8<br>• 1:16<br>• 1:32<br>• $\geq 1:64$                       | -                          | OR non adjusted: 2.07 (1.83–2.34)<br>• 1<br>• 2.66 (1.06–6.63)<br>• 10.38 (4.66–23.12)<br>• 13.56 (5.93–31.02)<br>• 38.75 (16.08–93.39) |
|                                           | Qin et al. [19]             | Titers of non-treponemal antibodies test<br>• $< 1:8$<br>• $\geq 1:8$                                                  | -                          | OR non adjusted:<br>• 1<br>• 10.62 (6.69–16.85)                                                                                         |

(Continues)

TABLE 3 (Continued)

| Syphilis diagnosis                        | Reference                   | Variables                                                                                               | <i>p</i>          | RR or OR (IC95%)                                                                                                     |
|-------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------|
| Stage of syphilis                         | McFarlin et al. [11]        | High VDRL titer in diagnosis                                                                            | <i>p</i> < 0.001  | -                                                                                                                    |
|                                           | McFarlin et al. [11]        | High VDRL titer in delivery                                                                             | <i>p</i> < 0.001  | -                                                                                                                    |
|                                           | Rawstron et al. [10]        | RPR titers:<br>• Geometric mean: 1:4.5<br>• Mean: 1:182                                                 | <i>p</i> < 0.001  | -                                                                                                                    |
|                                           | Qin et al. [19]             | Primary syphilis                                                                                        | -                 | OR non adjusted: 65.90 (38.29–113.44)                                                                                |
|                                           | Kirkcaldy et al. [17]       |                                                                                                         | <i>p</i> = 0.001  | -                                                                                                                    |
|                                           | Liu et al. [16]             | Early syphilis (<2 years)                                                                               | <i>p</i> = 0.001  | OR non adjusted: 5.01 (2.15–11.69)                                                                                   |
|                                           | Tikhonova et al. [14]       | Primary or secondary syphilis versus latent syphilis                                                    | <i>p</i> < 0.001  | OR adjusted: 3.7 (2.4–5.7)                                                                                           |
|                                           | Risser and Hwang. [12]      | Clinical stage of syphilis:<br>• Primary or secondary<br>• Early latent<br>• Late latent<br>Reinfection |                   | OR (multivariate analysis):<br>• 1.0<br>• 1.9 (1.3–2.9)<br>• 3.4 (1.9–5.9)<br>OR (análise univariada): 2.4 (1.5–3.8) |
| Maternal treatment                        | Reference                   | Variables                                                                                               | <i>p</i>          | RR or OR (IC95%)                                                                                                     |
| Inadequate maternal treatment             | Hong et al. [20]            | No treatment for syphilis                                                                               | <i>p</i> < 0.001  | OR adjusted: 68.28 (29.64–157.28)                                                                                    |
|                                           | Biswas et al. [21]          |                                                                                                         | <i>p</i> < 0.001  | -                                                                                                                    |
|                                           | Biswas et al. [21]          | Inadequate maternal treatment (latent syphilis only)                                                    | <i>p</i> < 0.001  | -                                                                                                                    |
|                                           | Qin et al. [19]             | Treatment<br>• Incomplete<br>• Non-penicillin                                                           | -                 | OR non adjusted:<br>• 11.00 (6.46–18.72)<br>• 3.24 (1.50–6.97)                                                       |
| Maternal treatment as a protective factor | Tridapalli et al. [18]      | Inadequate maternal treatment                                                                           | <i>p</i> = 0.0001 | RR: 15.32 (5.22–47.31)                                                                                               |
|                                           | Rawstron et al. [10]        | Any maternal treatment as a protective factor                                                           | <i>p</i> < 0.001  | -                                                                                                                    |
|                                           | Anugulruengkitt et al. [23] | Adequate maternal treatment as a protective factor                                                      | <i>p</i> < 0.001  | -                                                                                                                    |
| Time of treatment                         | Kirkcaldy et al. [17]       | Median GA week of maternal treatment: 36 weeks (6–42 week interval)                                     | <i>p</i> < 0.001  | -                                                                                                                    |
|                                           | Liu et al. [16]             | GA at the time of maternal treatment for syphilis                                                       | <i>p</i> < 0.001  | OR non adjusted: 1.1 (1.06–1.15)                                                                                     |
|                                           | McFarlin et al. [11]        |                                                                                                         | <i>p</i> = 0.005  | -                                                                                                                    |
|                                           | Qin et al. [19]             | GA in the 1st treatment<br>• <12 weeks<br>• >29 weeks                                                   | -                 | OR non adjusted: 2.67 (1.99–3.59)<br>• 1<br>• 6.50 (2.36–17.86)                                                      |
|                                           | Hong et al. [20]            | Benzathine penicillin started after 28 weeks of gestation                                               | -                 | OR adjusted: 8.06 (2.93–22.21)                                                                                       |
|                                           | Biswas et al. [21]          | Initiation of treatment <30 days before delivery                                                        | <i>p</i> < 0.001  | -                                                                                                                    |
|                                           | Qin et al. [19]             | Time between the end of the 1st treatment and delivery<br>• >4 weeks<br>• <4 weeks                      | -                 | OR non adjusted:<br>• 1<br>• 16.89 (8.46–33.73)                                                                      |
| Outcome                                   | McFarlin et al. [11]        | Outcome in current pregnancy: stillborn                                                                 | <i>p</i> < 0.001  | -                                                                                                                    |
| Perinatal and neonatal variables          |                             |                                                                                                         |                   |                                                                                                                      |
| Perinatal and neonatal variables          | Referència                  | Variables                                                                                               | <i>p</i>          | RR or OR (IC95%)                                                                                                     |
| GA at birth                               | Mobley et al. [13]          | 32–37 GA weeks                                                                                          | -                 | OR non adjusted: 2.0 (1.2–3.2)                                                                                       |
|                                           | Tridapalli et al. [18]      | Prematurity                                                                                             | <i>p</i> = 0.0001 | RR: 5.72 (2.93–11.18)                                                                                                |
|                                           | Anugulruengkitt et al. [23] |                                                                                                         | <i>p</i> = 0.004  | -                                                                                                                    |
|                                           | Rawstron et al. [10]        | <34 GA weeks                                                                                            | <i>p</i> = 0.0004 | -                                                                                                                    |

TABLE 3 (Continued)

| Perinatal and neonatal variables |                             |                                                     |                   |                                |
|----------------------------------|-----------------------------|-----------------------------------------------------|-------------------|--------------------------------|
| Perinatal and neonatal variables | Referência                  | Variables                                           | <i>p</i>          | RR or OR (IC95%)               |
| Birth weight                     | Mohley et al. [13]          | Birth weight: 1500–2499 g                           | -                 | OR non adjusted: 2.1 (1.3–3.2) |
|                                  | Tridapalli et al. [18]      | Birth weight < 2000 g                               | <i>p</i> = 0.0001 | RR: 7.85 (4.37–14.11)          |
|                                  | Anugulruengkitt et al. [23] | Low Birth weight                                    | <i>p</i> = 0.009  | -                              |
|                                  | Rawstron et al. [10]        | Small newborns for gestational age ( <i>p</i> < 10) | <i>p</i> = 0.0001 | -                              |
| Complementary exam               | Tridapalli et al. [18]      | Change in cerebrospinal fluid                       | -                 | RR: 11.05 (4.71–17.55)         |
|                                  | Tridapalli et al. [18]      | Changes in radiography of long bones                | -                 | RR: 3.51 (1.72–6.88)           |

Abbreviation: GA, gestational age.

treatment, gestational age at the time of diagnosis, non-treponemal test result, syphilis stage, and information on prenatal funding);

- Neonatal: sex, birth weight, gestational age, Apgar, intensive care unit stay (ICU), head circumference, cerebrospinal fluid, blood count and long bones radiographs.

Table 3 presents the studies according to the significant variables evaluated and the magnitude of risk found.

The most studied maternal risk factors were age, race/colour, marital status, history of another sexually transmitted infection, number of sexual partners, treatment for syphilis prior to pregnancy; co-infection with HIV, educational level, residence, income, occupation, and evaluation on immigration. Other factors such as menarche age, age at sexual debut, condom use before pregnancy and whether the woman was deprived of freedom or was a sex worker were less studied factors and did not obtain significance in any study.

Seven studies evaluated the level of education [13, 15, 16, 19–22], one of them with statistical significance, demonstrating that the lower the level of education, the higher the risk of congenital syphilis [20]. In three of these studies [15, 19, 21], having more than 10 years of schooling was a protective factor (OR 0.2 [0.1–0.7]). The variable occupation was evaluated by four studies [15, 18, 19, 22], but none of them with statistical significance. The income variable was evaluated only by one study showing higher risk (OR 2.8–1.1–7.4) [15]. The variable ‘immigration’ was evaluated by three studies [17, 18, 22] conducted in three different countries, China, United States, and Italy. Only in the Chinese study [22], there was an association with higher risk for CS.

The history/treatment of syphilis prior to pregnancy was identified in two studies and it was associated to lower incidence of congenital syphilis. Qin et al. evaluated maternal history of syphilis as a protective factor (OR = 0.24, 0.11–0.53), probably due to previous treatment [19]. In the study by Hong et al., the incidence was 0.22% (95% CI, 0.05–0.66%), with OR 1.6 (1.36–2.02) among babies born to women seropositive for syphilis and who were adequately treated before pregnancy, demonstrating that previous treatment may be inadequate or that reinfection may occur [20].

The obstetric factors assessed were previous pregnancy, history of pregnancy with adverse outcome, previous abortion, prenatal care, treatment during pregnancy, gestational age at diagnosis and treatment, results of non-treponemal tests, stages of syphilis and type of prenatal funding. The non-performance or late onset of prenatal care were risk factors for the outcome of CS in eight studies, all of them presenting statistical significance [10, 12–15, 19–21]. Risser et al. [12] evaluated the incidence of CS in the absence of prenatal care with OR 6.0 (3.9–9.2) and Hong et al. [20] that evaluated this incidence with the beginning of prenatal care after 28 weeks of gestation with OR 21.47 (18.07–25.50). Another factor widely studied and with statistical significance was both incomplete or late treatment of maternal syphilis, as demonstrated by Qin et al. who evaluated incomplete treatment during pregnancy with OR 11.00 (6.46–18.72) and its onset after 29 weeks of gestation with OR 6.50 (2.36–17.86) [19].

The clinical characteristics of newborns with a confirmed diagnosis or with a probable infection of congenital syphilis have been described in five studies [10, 11, 13, 18, 23], and prematurity and low birth weight have been shown to be related to the chance of vertical transmission. As Tridapalli et al. compared infected children and all other cases born to HIV-positive mothers for syphilis, prematurity (RR 5.72, 95% CI 2.93–11.18) and birth weight less than 2000 g (RR 7.85, 95% CI 4.37–14.11) are presented as risk factors for CS [18]. Rawstron et al. studied the same variables and demonstrated that newborns with congenital syphilis had significantly lower average birth weight (*p* = 0.001) and were more likely to be small for gestational age (*p* = 0.0001). The mean gestational age of infected infants was lower, with more than 34 weeks of gestation (*p* = 0.0004) [10]. Other characteristics such as gender, Apgar, history of hospitalization, other clinical manifestations, and alterations of complementary tests of the NB were less evaluated.

## DISCUSSION

The proper management of maternal syphilis during prenatal care and at the time of delivery is essential for the prevention of congenital syphilis and clinical attention of

newborns exposed vertically to syphilis. In this systematic review, it was observed that, among the demographic, maternal, obstetric, and neonatal risk factors, the variables of greatest relevance for the outcome of CS were mainly factors related to prenatal care and adequate maternal treatment.

Therefore, prenatal care as well as its early onset are important factors for implementing measures in the control of CS [26, 27]. Among the 458 cases of CS reported to the Centres for Disease Control and Prevention in 2014, almost a quarter were born to mothers who did not receive prenatal care [28]. In this systematic review, six studies demonstrated an association between absence of prenatal care and CS [10, 12–14, 19], and in the work of Risser and Hwang, the risk of CS was six times higher when the mother did not have this kind of assistance [12].

In this systematic review, six studies showed that the late onset of prenatal care was associated with congenital syphilis [13–15, 19–21].

The importance of adequate prenatal care in CS prevention is the early detection of syphilis and treatment in pregnant women [29], with a higher risk of adverse outcome in pregnancy when the woman is screened in the third trimester compared to the first and second trimester [27]. Wang et al. demonstrated that mothers with syphilis diagnosed with gestational age over 36 weeks were approximately 25 times more likely to have a newborn with CS than women who were diagnosed with syphilis with gestational age below or equal to 12 weeks [22].

In addition to early diagnosis, some studies in this systematic review have demonstrated statistical significance among high titers of non-treponemal tests of the mother and CS [10, 11, 19]. In the study by Qin et al, almost three quarters of children with CS were born to mothers with elevated titres ( $\geq 1:8$ ) of non-treponemal antibodies. The authors demonstrated that the risk increased as the titres also increased, reaching the risk magnitude of 38 times when they were  $\geq 1:64$ . Despite the wide amplitude of the CI values, the minimum limit was 16, indicating that it is a high-risk variable for CS. By dividing the population into two, putting the cut-off point at 1:8, this same study demonstrated a risk almost 11 times higher when maternal titres were  $\geq 1:8$  [19]. Although this factor cannot be analysed in isolation in maternal history, attention should be taken to the risk of CS in children born to mothers with high non-treponemal test titres.

## Treatment

Adequate treatment for syphilis during pregnancy is the only measure that leads to the prevention of vertical transmission in infected women [26]. This is well established and was demonstrated in the study by Hong et al, who observed a 68 times higher risk of CS when the mother did not receive treatment during pregnancy, despite presenting a wide CI [20]. With this data, it is noteworthy that all newborns of

untreated mothers should be considered as having probable CS and they should be submitted to evaluation and treatment.

The antimicrobial for the treatment of syphilis during pregnancy recommended by the Centres for Disease Control and Prevention (CDC) is benzathine G penicillin, being considered 98% effective in the prevention of CS [26]. Qin et al. demonstrated a three-fold higher risk of CS when the pregnant woman received treatment with an antimicrobial other than penicillin [19]. Moreover, it is known that, although penicillin applied at any time during pregnancy treats the woman, this may not occur with the fetus as demonstrated in the study by Rawstron et al, in which nine mothers who had a history of treatment during pregnancy had children with CS and five mothers with a history of treatment before pregnancy had stillborn [10]. This may have occurred not due to therapeutic failure, but to the possibility that treatment was inadequate or that the woman had become reinfected. For this reason, the main global protocols recommend evaluation of information on the treatment of sexual partners to assess the risk of reinfection in treated women [26, 30].

In the study by Rawstron et al, any treatment before and during pregnancy showed statistical significance among children with and without CS [10]. However, although the study gave the definitions of adequate treatment during pregnancy, it did not evaluate the association between the adequacy of maternal treatment and the diagnosis of CS. Adequate treatment during pregnancy is crucial for the prevention of syphilis transmission, being one of the factors considered in the protocols to evaluate the indication of treatment of the child. The data published that evaluated whether the treatment of pregnancy was adequate, following the criteria of international protocols, corroborated the statement in literature. In the study by Tridapalli et al, the risk of CS reached 15 times when the mother received inadequate treatment, even with a CI with wide variation (CI 5.22–47.31) [18]. This systematic review endorses, therefore, that the child of a mother with treatment considered inadequate should be evaluated as presenting suspected CS.

Another factor considered relevant to evaluate the quality of maternal treatment is gestational age at the beginning of treatment, considering that physiological changes at the end of pregnancy lead to increased creatinine clearance and reduced protein concentration in the plasma, thus altering the pharmacokinetics of penicillin. For that, the guidelines consider that the treatment that ends up to 30 days before delivery could be considered adequate [9]. One study found that the initiation of treatment less than 30 days before delivery was significantly associated with CS ( $p < 0.001$ ) [21], but the authors did not present the measures of magnitude of effect and confidence interval, which limits our conclusions. On the other hand, Qin et al. observed that the completion of treatment up to four weeks before delivery was significantly associated with the CS outcome, demonstrating a 16-fold risk of CS when treatment was completed less than four weeks (CI 8.46–33.73) before delivery [19].

Hong et al. evaluated the risk of congenital syphilis by comparing different moments of treatment of pregnant women [20]. The study used 28 weeks of GA as a cut-off point of treatment and presented lower incidence of CS among women who received treatment before this period. CS was 8 times more common in women treated after 28 weeks and 68 times more in untreated women compared to those treated before that date. This association was also observed in the study by Qin et al, demonstrating that treatment started from 29 weeks of gestation was associated with a 6.5-fold risk of CS [19], with a broad CI, but with a considerably significant minimum limit (CI 2.36–17.86). Moreover, according to the results of the univariate logistic analysis published in the study by Liu et al, each week of delay in the treatment of pregnant women would increase the risk of CS by about 10% [16].

### Adverse pregnancy outcome

Maternal syphilis is associated with adverse gestational outcomes, such as miscarriage, stillbirth, premature delivery, neonatal death, and low birth weight [31]. Five studies of this systematic review found an association between the variable's prematurity and birth weight with CS [11, 13, 18, 23]. This information may contribute to the decision of the clinical management of NB, considering that in some cases the only alteration presented may be low birth weight or prematurity.

Although CS may be related to prematurity and restriction of intrauterine growth, these manifestations are nonspecific and may be related to other maternal factors, such as the use of illicit drugs.

### Clinical signs in the newborn

The presence of cerebrospinal fluid (CSF) alterations is associated with CS with high magnitude in the study by Tridapalli et al, although it is not mentioned what alterations were found [18]. The absence of changes in cerebrospinal fluid, however, does not exclude the diagnosis of neurosyphilis in NB, according to a study conducted by Michelow et al. A total of 148 neonates were evaluated for the presence of infection in the central nervous system. The authors found that the alteration of only one parameter (VDRL reagent or high protein levels or pleocytosis) presented maximum sensitivity of 56% and, when more than one alteration was present, sensitivity reached 82% [32]. The low sensitivity demonstrated in the study reveals the difficulties inherent in the evaluation of CSF in NB. Therefore, given the presence of changes in cerebrospinal fluid analysis, the NB should be treated for neurosyphilis. In addition, findings in CSF analysis may be present in approximately 8% of asymptomatic infants born to mothers with untreated early syphilis [33], showing the importance of subjecting this group of patients to lumbar puncture (spinal tap).

Another important consideration related to complementary tests refers to long bone radiography, which is important for the evaluation of CS in symptomatic or non-symptomatic neonates [33]. Tridapalli et al. found an increased risk of CS in infants with alteration in this imaging exam [18]. However, the authors do not specify what these features were.

McFarlin et al. compared NB with CS and NB without CS evidence and demonstrated that newborns with CS were more likely to be admitted to the neonatal intensive care unit or progressive care unit with longer length of stay (11 vs. 5.5 days), besides presenting higher morbidity [11]. The study makes it clear that maternal treatment during pregnancy can reduce the severity of the disease for the newborn without eradicating adverse outcomes, since in the group of mothers adequately treated for syphilis during pregnancy, 28% had deliveries before 37 weeks of gestation.

### Limitations and bias

This systematic review is based on the analysis of observational studies, some of them with unsatisfactory methodological quality, as presented in Newcastle evaluation. The design of the studies may result in potential selection bias.

While demographic factors are well defined in the literature, there is still a gap in relation to the diagnosis of syphilis in the vertically exposed infant, which impacts the conduction of studies since the diagnosis of CS is often presumptive.

A limitation of the analysis was that most of the selected studies did not include stillbirths attributable to maternal syphilis, potentially resulting in underestimation of the risk of developing CS, particularly among women who did not receive treatment for syphilis.

### CONCLUSION

The association of syphilis with adverse socio-economic conditions and inadequate prenatal care suggests that the improvement of the population's living conditions and equitable access to quality health services may have an impact on the reduction of congenital syphilis. Interventions directed to pregnant women and their sexual partners, such as health education, preventive measures of syphilis and other STIs, monitoring and management of prenatal follow-up should be maintained as a focus of health care for the timely management and treatment of these pregnant women and their offspring.

### ACKNOWLEDGEMENTS

The authors would like to thank all participants and health professionals who made this study possible.

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**ANEXO 2 – Termos de aprovação do projeto de pesquisa**

UNIVERSIDADE FEDERAL DE MINAS GERAIS  
COMITÊ DE ÉTICA EM PESQUISA - COEP

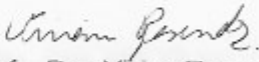
**Projeto: CAAE – 65339716.0.0000.5149**

**Interessado(a): Profa. Roberta Maia de Castro Romanelli**  
Departamento de Pediatria  
Faculdade de Medicina- UFMG

**DECISÃO**

O Comitê de Ética em Pesquisa da UFMG – COEP aprovou, no dia 03 de abril de 2017, o projeto de pesquisa intitulado **“Diagnóstico de infecções congênitas e correlação com o acometimento fetal e evolução clínica de crianças infectadas por transmissão vertical”** bem como o Termo de Consentimento Livre e Esclarecido.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto através da Plataforma Brasil.

  
Profa. Dra. Vivian Resende  
Coordenadora do COEP-UFMG

Av. Pres. Antonio Carlos, 6627 – Unidade Administrativa II – 2º andar – Sala 2005 – Cep: 31.270-901 – BH-MG  
Telefax: (031) 3409-4592 - e-mail: coep@ppq.ufmg.br

UNIVERSIDADE FEDERAL DE  
MINAS GERAIS



## PARECER CONSUBSTANCIADO DO CEP

### DADOS DO PROJETO DE PESQUISA

**Título da Pesquisa:** Diagnóstico de Infecções Congênitas e Correlação com o Acometimento Fetal e Evolução Clínica de Crianças Infectadas por Transmissão Vertical

**Pesquisador:** Roberta Maia de Castro Romanelli

**Área Temática:**

**Versão:** 2

**CAAE:** 65339716.0.0000.5149

**Instituição Proponente:** UNIVERSIDADE FEDERAL DE MINAS GERAIS

**Patrocinador Principal:** Financiamento Próprio

### DADOS DO PARECER

**Número do Parecer:** 2.007.160

#### Apresentação do Projeto:

Projeto já em andamento com solicitação de prorrogação com a alteração de se poder acompanhar os casos prospectivamente. Trata-se de um projeto que visa estudar infecções congênitas e sua evolução em pacientes atendidas no ambulatório de Doenças Infecciosas Orestes Diniz. Serão alvo de estudo mulheres e seus recém-nascidos com suspeita ou confirmação de doenças infecciosas transmissíveis verticalmente, como sífilis, toxoplasmose, CMV, Zika, dentre outras. Tais casos já são atendidos no serviço ambulatorial do Orestes Diniz e são submetidos a uma série de exames por indicação clínico-assistencial do próprio serviço de referência. O projeto visa o estudo sistemático das informações laboratoriais e clínicas dos indivíduos para o entendimento da dinâmica das doenças estudadas com vistas a melhorias nos protocolos de atendimento, diagnóstico e tratamento.

#### Critérios de inclusão:

1-Filhos de mulheres que apresentarem soroconversão durante a gestação. A soroconversão será definida por:

a. Surgimento de IgG durante a gestação, desde que a sorologia tenha sido realizada com o mesmo método e em mesmo laboratório.

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Continuação do Parecer: 2.007.160

- b. Aumento dos títulos de IgG em quatro vezes (ou duas diluições), desde que tenha sorologias realizadas com mesmo método e em mesmo laboratório.
  - c. Surgimento de IgM, desde que tenha sorologias realizadas com mesmo método e em mesmo laboratório.
  - d. Altos títulos de IgG, com testes de avididade com baixos valores (segundo os valores de referência do laboratório)
  - e. Outros exames laboratoriais positivos como Reação em Cadeia de Polimerase
- 2- Púperas com diagnóstico de doenças infecciosas com possibilidade de transmissão vertical durante o pré-natal através de outros exames realizados como propedêutica para investigação de acordo com sintomatologia apresentada e seus recém-nascidos
- 3- RN ou lactente com suspeita clínica de infecção congênita.

### Critérios de exclusão:

- 1- Mulheres que não consentirem com sua participação e de seu RN.

### Objetivo da Pesquisa:

#### Objetivo Primário:

Avaliar as infecções congênitas encaminhadas ao Centro de Referência e Treinamento em Doenças Infecciosas e Parasitárias Orestes Diniz (CTR/DIP Orestes Diniz) e avaliar os métodos laboratoriais usados para o diagnóstico.

#### Objetivo Secundário:

- 1- Identificar os métodos diagnósticos das infecções durante a gestação e definir os casos de infecção suspeita, provável ou confirmada.
- 2- Diagnosticar e investigar precocemente os casos de infecções congênitas
- 3- Avaliar e tratar adequadamente as crianças acometidas para evitar ou reduzir a morbi-mortalidade decorrentes dessas infecções.

### Avaliação dos Riscos e Benefícios:

#### Riscos

Os autores afirmam que "a pesquisa não possui risco à integridade psíquica ou física, por se tratar de coleta de dados durante as consultas e em prontuários. Serão solicitados apenas exames que já

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fazem parte da rotina de avaliação pós-natal dos casos de suspeita de infecção congênita e seus resultados serão discutidos individualmente com os pacientes através do médico assistente. Será mantido sigilo e a não divulgação de dados pessoais, além de continuidade do acompanhamento e do tratamento, independente da participação na pesquisa."

### Benefícios:

Não haverá benefícios diretos aos participantes porque todos os exames que serão feitos já fazem parte da assistência médica naturalmente oferecido pelo serviço de referência. O acompanhamento fornecerá dados que permitirão reavaliar a rotina já implementada para diagnóstico e condutas terapêuticas nas infecções congênitas, propiciando também nova análise do custo-benefício dos exames e tratamentos utilizados.

### Comentários e Considerações sobre a Pesquisa:

Trata-se de projeto relevante e de importância para melhorias no atendimento à saúde. Não trás riscos ao sujeito de pesquisa pois não alterará sua rotina de atendimento, mas propõem o uso dos seus dados clínico-laboratoriais para uma análise sistemática da evolução da doença e do atendimento.

### Considerações sobre os Termos de apresentação obrigatória:

Foram apresentados:

Folha de Rosto - adequada

Parecer consubstanciado do Departamento - adequado

Projeto de pesquisa - adequado

TCLE - Foi ajustado conforme solicitação da diligência

### Conclusões ou Pendências e Lista de Inadequações:

Diante da correção do TCLE conforme solicitado, sou a favor smj da aprovação do projeto de pesquisa.

### Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o COEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o

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Continuação do Parecer: 2.007.160

desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

| Tipo Documento                                            | Arquivo                                      | Postagem               | Autor                            | Situação |
|-----------------------------------------------------------|----------------------------------------------|------------------------|----------------------------------|----------|
| Informações Básicas do Projeto                            | PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_827956.pdf | 28/03/2017<br>13:48:55 |                                  | Aceito   |
| Outros                                                    | CartaRespostaCOEP280317.pdf                  | 28/03/2017<br>13:48:29 | Roberta Maia de Castro Romanelli | Aceito   |
| TCLE / Termos de Assentimento / Justificativa de Ausência | TCLECongenitas280317.pdf                     | 28/03/2017<br>13:48:02 | Roberta Maia de Castro Romanelli | Aceito   |
| Projeto Detalhado / Brochura Investigador                 | CongenitasPlataformaBrasil230317.pdf         | 23/03/2017<br>14:33:04 | Roberta Maia de Castro Romanelli | Aceito   |
| Folha de Rosto                                            | FolhadeRostoCongenitas.pdf                   | 24/11/2016<br>16:08:52 | Roberta Maia de Castro Romanelli | Aceito   |
| Outros                                                    | AprovacaoDepartamentoCongenitas.pdf          | 17/11/2016<br>18:19:53 | Roberta Maia de Castro Romanelli | Aceito   |
| Outros                                                    | SolicitacaoRenovacaoCongenitas.pdf           | 17/11/2016<br>18:12:53 | Roberta Maia de Castro Romanelli | Aceito   |
| Outros                                                    | APROVACAORELATORIOANTERIORCONGENITAS.pdf     | 17/11/2016<br>18:04:46 | Roberta Maia de Castro Romanelli | Aceito   |
| Parecer Anterior                                          | PARECERANTERIORCONGENITAS.pdf                | 17/11/2016<br>17:52:55 | Roberta Maia de Castro Romanelli | Aceito   |
| Outros                                                    | 653397160parecerassinado.pdf                 | 07/04/2017<br>15:54:38 | Vivian Resende                   | Aceito   |
| Outros                                                    | 65339716aprovacao.pdf                        | 07/04/2017<br>15:54:48 | Vivian Resende                   | Aceito   |

Situação do Parecer:

Aprovado

Necessita apreciação da CONEP:

Não

Endereço: Av. Presidente Antônio Carlos, 6627 2º Ad SI 2005

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UNIVERSIDADE FEDERAL DE  
MINAS GERAIS



Continuação do Parecer: 2.007.160

BELO HORIZONTE, 07 de Abril de 2017

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Assinado por:  
Vivian Resende  
(Coordenador)

Endereço: Av. Presidente Antônio Carlos, 6627 2º Ad Si 2005  
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