Complications, clinical manifestations of congenital syphilis, and aspects related to its prevention: an integrative review

ABSTRACT
Objectives: to identify the scientific evidence about the clinical complications and manifestations of congenital syphilis and aspects related to its prevention. Methods: integrative review after a search in the databases LILACS and MEDLINE, carried out in March 2018, using the descriptors "syphilis, congenital", "complications", and "signs and symptoms", leading to the selection of 27 researches. Results: the publications found were published from 1966 to 2017, and most of them were from Latin America and Africa. Negative outcomes, laboratory changes, and the clinical manifestations in congenital syphilis, whether early or delayed, were, respectively: low weight at birth, anemia, hepatosplenomegaly, and dental alterations. The lack of treatment of the pregnant women in the prenatal was the most common occasion in which the opportunity to prevent the complications of congenital syphilis was lost. Conclusions: the scientific evidences analyzed showed serious complications of congenital syphilis that could be avoided if early opportunities of diagnosing and treating the pregnant women are not lost during the prenatal.

Descriptors: Congenital Syphilis; Sings and Symptoms; Complications; Syphilis; Prenatal Care.

RESUMEN
Objetivos: identificar las evidencias científicas acerca de las complicaciones y manifestaciones clínicas de la sífilis congénita e aspectos relacionados a la prevención. Métodos: revisión integrativa, mediante búsqueda en bases de datos LILACS e MEDLINE, realizada en marzo de 2018, utilizando los descritores “sífilis, congénita”, “complicaciones”, “síntomas y signos”, resultando en 27 investigaciones seleccionadas. Resultados: encontraron-se publicações entre os anos de 1966 e 2017, na maioria oriundas da América Latina e África. Desfecho desfavorável, a alteração laboratorial e as manifestações clínicas da sífilis congênita precoce e tardia mais evidenciados foram, respectivamente, baixo peso ao nascer, anemia, hepatosplenomegalia e alterações odontológicas. Observou-se que a falta de tratamento da gestante no pré-natal foi a principal oportunidade perdida de prevenção das complicações da sífilis congênita. Conclusões: as evidências científicas analisadas apresentam graves complicações da sífilis congênita que seriam evitadas desde que oportunidades precoces de diagnóstico e tratamento da gestante não fossem perdidas durante o pré-natal.

Descritores: Sífilis Congênita; Sinais e Sintomas; Complicações; Sífilis; Atendimento Pré-Natal.

How to cite this article:
Rocha AF, Araújo MAL, Barros VL, Américo CF, Silva Jr GB. Complications, clinical manifestations of congenital syphilis, and aspects related to its prevention: an integrative review. Rev Bras Enferm. 2021;74(4):e20190318. https://doi.org/10.1590/0034-7167-2019-0318

EDITOR IN CHIEF: Dulce Barbosa
ASSOCIATE EDITOR: Elucir Gir

Submission: 07-17-2019 Approval: 04-18-2021
INTRODUCTION

Despite all attempts to eliminate congenital syphilis (CS) as a public health problem, estimates show that the disease affects a million pregnant women every year throughout the world. When it is not adequately treated, it can cause more than 300 thousand fetal and neonate deaths, putting nearly 200 thousand children under the risk of an untimely death\textsuperscript{1-3}.

The morbidity and mortality by CS are avoidable and sensible to the health care conditions of women and children. An in-depth investigation about the aspects involved in the transmission of syphilis from mother to child is useful to identify the facts that determine and put children under the risk of sequelae and death, not to mention that an investigation of the kind could aid in the development of strategies to prevent and control the disease.

Brazil is a subscriber of the United Nations Sustainable Development Goals (SDG)\textsuperscript{4}, which include controlling CS and eliminating the avoidable deaths of newborns and children below 5 years old. In countries where the prevalence of CS is high, the eradication of such a public health problem would have a positive impact, helping to achieve these goals.

The importance of controlling CS is especially related to the complications that this infection can cause in babies\textsuperscript{5-7}. Although most children are asymptomatic at the time of birth\textsuperscript{8}, CS can manifest early, up to their second year of age, or late, after this period. The symptoms usually can be dermatological, osseous, ophthalmic, auricular, neurological, or dental, in addition to alterations that can be found by laboratory exams\textsuperscript{9}.

Considering the problem posed to the world by the current CS epidemic, it is extremely important to divulge the clinical complications and manifestations that this infection can cause in babies, including identifying factors that can help avoiding them.

OBJECTIVES

To identify the scientific evidence about the complications and clinical manifestations of CS and the aspects related to prevention.

METHODS

This is an integrative literature review, designed with the following steps: definition of a research question, search or sampling in literature (after defining inclusion and exclusion criteria), categorization of the information extracted, evaluation of the studies selected, interpretation of the results, and, finally, presentation of a review/synthesis of the knowledge provided\textsuperscript{10-11}.

The problem addressed by the review (the research question) was determined using the PICO strategy: \textit{P (population): pregnant women and children; I (interest): congenital syphilis; O (outcome): clinical complications and manifestations.} The letter C, representing “comparison”, does not apply to this research. As a result, the following guiding question was formed: What are the scientific evidences about complications and clinical CS manifestations, and what other studies have found about aspects related to prevention?

The online search was carried out in the Virtual Health Library (VHL), in the databases Latin American and Caribbean Health Sciences Literature (LILACS) and Medical Literature Analysis and Retrieval System Online (MEDLINE). Studies were selected in March 2018, using two crossed pairings of the three health descriptors (DeCS/MeSH: 1) “syphilis, congenital” AND “complications”; 2) “syphilis, congenital” AND “signs and symptoms”. The limiting boolean operator “AND” was used to restrict the search only to findings about CS complications and clinical manifestations.

The inclusion criteria considered the following characteristics: original articles, available in full, and published in Portuguese, English, or Spanish. The systematic review and meta-analysis articles were also included, since some journals consider these to be original articles. Since syphilis has existed for millennia, with repercussions all around the globe, the year of publication of the investigations was not restricted, allowing for a broad survey of literature. Abstracts, editorials, letters to the editors, technical information, previous notes, repeated articles, and those that were not in accordance with the objective of this study were excluded.

The initial search for articles found 1,982 results. From these, 1,390 were excluded because they were not available in-full or were not in Portuguese, English, nor Spanish. Furthermore, 77 were duplicates, and as a result, were discarded. The titles and abstracts were read and, when the article seemed to be a potential inclusion, its results were skimmed. This allowed for the selection of 27 articles to be read in full and categorized for an analysis. The results were interpreted, and the final presentation of the review took place (Figure 1).

![Flowchart of article selection, according to the search for descriptors and for the inclusion criteria proposed](image-url)

Note: VHL - Virtual Health Library.

Figure 1 - Flowchart of article selection, according to the search for descriptors and for the inclusion criteria proposed.
To diminish potential biases, two researchers selected, independently, studies for the analysis. A third researcher was also participating, to help deciding on the inclusion or inclusion of articles whenever there were disagreements.

The studies were presented using tables that included identification data, methodological characteristics, evidence levels, results, and conclusions. Considering the variety of complications and clinical manifestations that were identified, the description of the results, as well as the descriptive analysis carried out to present the findings of this analysis were compiled, based on the following findings: negative outcomes, laboratory changes and radiological changes, and early and late CS manifestations.

RESULTS

Data from the studies selected for analysis show a diversity of negative outcomes, laboratory and/or radiological alterations, and early and late CS manifestations. Publications from 1966 to 2017 were found, but the interval between the earlier publications was of approximately 10 years; from 2013 on, their frequency was higher, and their number increased. Most publications originated from Latin-American (n = 11) and African countries (n = 5). It stands out that the most recent studies were carried out in Brazil (E1, E2, E3, E4, E6).

Most studies were descriptive and cross-sectional (n = 21). From the studies analyzed, only four showed some type of follow up with the children (E9, E12, E17, and E19). Two (E8 and E14) were systematic reviews, and, as a result, their level of evidence was I (Chart 1).

From the 27 studies analyzed, 18 focused on the negative outcomes of CS, such as low weight at birth (n = 11), stillbirths (n = 9), or neonate death (n = 9). With the exception of E8, all others had more than one outcome, including miscarriage (n = 7), prematurity (n = 8), or post-neonate death (n = 3). Only E14 had, in the scope of its investigation, all outcomes observed in this review (miscarriage, stillbirth, death, prematurity, and low weight at birth) (Chart 2).

### Chart 1 - Characterization of articles according to authorship, year of publication, title, country, journal, level of evidence and type of study

| Code | Author/Year | Title | Country | Journal | Level of evidence | Type of study |
|------|-------------|-------|---------|---------|------------------|--------------|
| E1   | Souza et al., 2017[13] | Analysis of congenital syphilis cases notification in a reference hospital of Niterói, Rio de Janeiro State, from 2008 to 2015 | Brazil | J Bras Doenças Sex Transm. | VI | Descriptive |
| E2   | Cardoso et al., 2016[14] | Underreporting of Congenital Syphilis as a Cause of Fetal and Infant Deaths in Northeastern Brazil | Brazil | PLoS ONE | VI | Cross-sectional |
| E3   | Feliz et al., 2016[15] | Aderência ao seguimento no cuidado ao recém-nascido exposto a sífilis e características associadas à interrupção do acompanhamento | Brazil | Rev. Bras. Epidemiol. | VI | Descriptive |
| E4   | Domingues; Leal, 2016[16] | Incidência de sífilis congênita e fatores associados à transmissão vertical da sífilis: dados do estudo Nascer no Brasil | Brazil | Cad. Saúde Pública | VI | Cross-sectional |
| E5   | Ferreira et al., 2016[17] | Skin rash: a manifestation of early congenital syphilis | Portugal | BMJ Case Reports | VI | Case report |
| E6   | Lafetá et al., 2016[18] | Sífilis materna e congênita, subnotificação e difícil controle | Brazil | Rev. Bras. Epidemiol. | VI | Descriptive |
| E7   | Dou et al., 2016[19] | Epidemic Profile of Maternal Syphilis in China in 2013 | China | BioMed Research International | VI | Cross-sectional |
| E8   | Arnesen; Serruya; Duran, 2015[20] | Gestational syphilis and stillbirth in the Americas: a systematic review and meta-analysis | - | Rev Panam Salud Publica | I | Systematic review and meta-analysis |
| E9   | Rac et al., 2014[21] | Progression of ultrasound findings of fetal syphilis after maternal treatment | United States | Am J Obstet Gynecol. | IV | Retrospective cohort |
| E10  | Chowdhary et al., 2014[22] | Early detection of congenital syphilis | India | J Indian Soc Pedod Prev Dent. | VI | Case report |
| E11  | Cavagnaro et al., 2014[23] | Sífilis congênita precoz: a propósito de 2 casos clínicos | Chile | Rev Chil Pediatr. | VI | Case report |
| E12  | Lage; Vaccari; Fiori, 2013[24] | Clinical features and follow-up of congenital syphilis | Brazil | Sex Transm Dis. | IV | Cohort |
| E13  | Newman et al., 2013[25] | Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data | Worldwide research | PLoS Med | VI | Descriptive |
| E14  | Gomez et al., 2013[26] | Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis | - | Bull World Health Organ. | I | Systematic review and meta-analysis |
| E15  | Arriagada et al., 2012[27] | Sífilis congénita: presentación como shock séptico después del periodo neonatal | Chile | Rev Chilena Infectol. | VI | Case report |
| E16  | Pessoa; Galvão, 2011[28] | Clinical aspects of congenital syphilis with Hutchinson's triad | Brazil | BMJ Case Rep. | VI | Case report |

To be continued
Fourteen articles found children with laboratory and/or radiological alterations related to CS. The most common alteration was anemia, which was detected in 11 studies, followed by thrombocytopenia (n = 8), and leukocytosis (n = 7). It stands out that, in half of these articles, there were high levels of proteins and/or leukocytes in the newborns' liquor, and the Venereal Disease Research Laboratory (VDRL) was reactive. Regarding radiological findings, ten publications found changes in long bones, such as periostitis, osteochondritis, osteomyelitis, or Wimberger's sign (Chart 2).

Clinical CS manifestations were the focus of 18 studies. It stands out that the CS manifested early in 15 cases and late in 3. In this context, data relative to the early infection symptoms were predominant (n = 16), such as hepatomegaly and/or splenomegaly (n = 14), in addition to skin lesions with desquamation, consistent with palmoplantar pemphigus (n = 12). Other traits that stand out are the presence of jaundice (n = 9); purulent, serosanguineous and thick nose secretions (n = 7); perioral or perianal fissures/tears (n = 5); and petechia, purpura, and/or rashes (n = 5). Regarding late CS, it manifested in ophthalmic (interstitial keratitis), auricular (neurological deafness/hearing loss), osseous (frontal bossing and saddle nose), and dental (Hutchinson's teeth and mulberry molars) issues. Only E12, a cohort, discussed both types of manifestation (Chart 2).

### Chart 2 - Clinical complications and manifestations of congenital syphilis addressed in the studies analyzed

| Complications and manifestations of congenital syphilis | Analyzed studies (n = 27) |
|--------------------------------------------------------|--------------------------|
| **Negative outcomes** | **Code of the studies with negative outcomes* (n = 18)** |
| Miscarriage/fetal death | E1; E2; E4; E6; E13; E14; E17 |
| Stillbirth | E1; E2; E6; E7; E8; E12; E13; E14; E21 |
| Neonate death | E1; E2; E4; E7; E13; E14; E17; E21; E23 |
| Post-neonate death | E2; E14; E21 |
| Prematurity | E3; E4; E7; E11; E13; E14; E18; E24 |
| Low weight at birth | E3; E4; E7; E11; E13; E14; E18; E20; E23; E24; E27 |
| **Laboratory and radiological changes** | **Code of the studies that presented laboratory and radiological alterations* (n = 14)** |
| Anemia | E1; E5; E11; E12; E15; E20; E22; E23; E24; E26; E27 |
| Thrombocytopenia | E5; E11; E12; E15; E20; E22; E23; E27 |
| Leukocytosis | E11; E12; E15; E20; E22; E25; E27 |
| Leukopenia | E12 |
| VDRL titers twice as high than the mother birth | E11; E12; E15 |

*To be continued*
Complications, clinical manifestations of congenital syphilis, and aspects related to its prevention: an integrative review
Rocha AFB, Araújo MAL, Barros VL, Américo CF, Silva Jr GB.

Chart 2 (concluded)

| Complications and manifestations of congenital syphilis | Analyzed studies (n = 27) |
|--------------------------------------------------------|--------------------------|
| Alterations in liquor puncture                          | 07 E3; E11; E12; E15; E19; E20; E22 |
| Findings in the radiography of long bones              | 10 E1; E3; E12; E15; E19; E20; E22; E24; E26; E27 |

**Early manifestations**

| Number of studies | Codes of the studies that presented early manifestations* (n = 15) |
|-------------------|---------------------------------------------------------------|
| Hepatomegaly      | 14 E5; E9; E11; E12; E15; E18; E19; E20; E22; E23; E24; E25; E26; E27 |
| Splenomegaly      | 14 E1; E5; E11; E12; E15; E18; E20; E22; E23; E24; E25; E26; E27 |
| Jaundice          | 09 E1; E11; E12; E18; E20; E23; E24; E25; E27 |
| Serosanguineous rhinitis | 08 E1; E12; E18; E20; E22; E23; E24; E27 |
| Palomoplantar pemphigus | 12 E5; E11; E12; E15; E18; E19; E20; E22; E23; E25; E26; E27 |
| Perioral or perianal fissures                           | 05 E12; E15; E18; E20; E22 |
| Paleness         | 02 E12; E27 |
| Petechias, purpura, and/or rashes                       | 05 E1; E11; E12; E22; E27 |
| Lymphadenopathy                                          | 02 E12; E22 |
| Respiratory suffering                                    | 02 E12; E23 |
| Pneumonia                                                 | 03 E5; E12; E18 |
| Fever                                                     | 02 E12; E18 |
| Ascites                                                   | 03 E9; E25; E26 |
| Fetal hidropsy                                            | 02 E12; E23 |
| Generalized edema                                         | 02 E25; E26 |
| Pseudoparalysis                                           | 01 E23 |

**Late manifestations**

| Number of studies | Codes of the studies that presented late manifestations* (n = 3) |
|-------------------|---------------------------------------------------------------|
| Hutchinson's teeth | 02 E10; E16 |
| Mulberry molars    | 01 E10 |
| Interstitial keratitis | 01 E16 |
| Neurological deafness | 02 E12; E16 |
| Frontal bossing    | 01 E12 |
| Saddle nose        | 01 E12 |

Note: *The studies may have presented more than one type of outcome; VDRL – Venereal Disease Research Laboratory.

In the 27 articles analyzed, an attempt was made to identify information about the actions that could avoid clinical complications and manifestations of CS in newborns. In 21 studies, it was found that, during prenatal care, many opportunities to prevent against grave outcomes of this infection in the child are not taken advantage off.

The main opportunities for this prevention that were lost were the non-treatment of the pregnant woman during the prenatal (n = 9), the late diagnoses of pregnant women (n = 4), the late start of the prenatal (n = 3), pregnant women that were not properly treated for the disease (n = 3), and women with high titer levels at time of birth, according to the VDRL (n = 3) (Chart 3).

Chart 3 - Avoidability of the clinical complications and manifestations found for congenital syphilis in the studies analyzed

| Lost opportunities related to the avoidability of congenital syphilis consequences for the baby | Number of studies | Codes of the studies that presented lost opportunities* (n = 21) |
|-----------------------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------|
| No prenatal                                                                                   | 2                 | E12, E26 |
| Late prenatal start                                                                          | 3                 | E04, E20, E24 |
| No test during the prenatal                                                                   | 2                 | E13, E18 |
| Late diagnosis                                                                               | 4                 | E01, E07, E11, E12 |
| No treatment during the prenatal                                                              | 9                 | E03, E06, E12, E07, E13, E14, E18, E19, E22 |
| Inadequate treatment                                                                         | 3                 | E03, E12, E17 |
| High titer levels at the moment of birth                                                       | 3                 | E20, E21, E25 |

Note: *The studies may have presented more than one type of lost opportunity.
DISCUSSION

Although syphilis has existed for millennia and there are studies that bring knowledge about CS, this infection is still a serious public health problem, especially in poor and developing countries. Most findings in the babies were related to lost opportunities to provide assistance to the mother.

Even with the high number of published studies, the actual magnitude of the damage this infection brings to Brazil may still be unknown\(^{14}\). Stillbirths and neonatal death are among the most common negative outcomes in the articles found, and the systematic review and meta-analyses included show that this outcome is more likely in pregnant women with syphilis\(^{5-7}\), and in those who were not treated or who were not treated properly\(^{18}\).

Regarding laboratory and radiologic changes in the children, it stands out that all children whose mothers with syphilis were not treated or not treated properly must undergo the VDRL test, a hemogram, a radiography of the long bones, and liquor puncturing, even if they show no symptoms at birth\(^{30}\). A study carried out in Porto Alegre, in Rio Grande do Sul (RS), Brazil, showed that 25\% of the children who were born with no symptoms had an alteration in at least one of these exams\(^{30}\).

Radiographic findings have an important role in the diagnosis of CS. In the Netherlands, a study found radiologic changes in eight out of ten children with CS signs\(^{41}\). These changes varied from a light periosteal reaction through the decalcification of the long bones to characteristics consistent of osteomyelitis. In Brazil, the proportions of changes in radiographies of long bones were of 1.6\% in the state of Paraná (PR)\(^{19}\) and 9.6\% in Rio de Janeiro (RJ)\(^{19}\).

It is important for health professionals to be attentive to other findings that are not typical of children with CS. These findings, despite not being specific of these cases, can indicate complications or associated pathologies. This review found cases of children with CS who showed signs of liver dysfunction\(^{18}\), kidney problems consistent with nephrotic syndrome\(^{40}\), increased creatinine, and histopathological lesions in kidney biopsies\(^{16,33-34}\).

Another important aspect is identifying early clinical manifestations of CS by a minute physical examination of the newborn, aiding in the diagnostic and in providing a timely response. This contributes for a reduction of sequelae from the infection, especially considering that children who are asymptomatic at birth are more likely to die when compared to asymptomatic ones\(^{14}\).

Regarding late CS manifestations, a case study carried out in India with two children showed that the only CS evidences were Hutchinson’s teeth and mulberry molars\(^{21}\). These manifestations present as deformed upper middle incisors, in the form of screwdrivers, little flags, or beveled, generally accompanied by molars that are similar to mulberries due to their multiple cusps. The authors alert that the presence of mulberry molars makes them highly susceptible to cavities and can lead to the early loss of teeth. As a result, these children need dental evaluation and monitoring\(^{21,24}\).

Other findings, such as frontal bossing and saddle nose, in addition to delays in development, were found by a research from Porto Alegre, Rio Grande do Sul, Brazil\(^{40}\). In that study, children who presented laboratory changes at birth were 20 times more likely to develop late CS sequelae. Considering the above, it is noteworthy that there are still late diagnoses for CS. The causes for this may indicate shortcomings in the strategies of prevention and treatment of the different levels of attention\(^{17}\).

Most studies evaluated the newborns during the ten days of hospitalization in the maternity for CS treatment, maybe due to the difficulties in getting to these children after their hospital discharge. Outpatient follow up seems to be challenging, and the few researches on it show that these children often interrupt their follow up. In Merseyside, England, in 1985, 2 out of 7 children with CS, who should be monitored in outpatient clinics up to their 3rd year of age, only came to their evaluation once\(^{12}\). More recently, in Brazil, studies in the cities of Porto Alegre (RS)\(^{8}\) and Curitiba (Paraná - PR)\(^{15}\) showed that the proportion of children who were not present in the health services for their follow up is large.

All studies that analyzed clinical findings in children with early CS showed some shortcoming in the management of care to the pregnant woman, especially when related to tracking, diagnosing, and providing proper treatment to the mothers as soon as possible\(^{8,28,32}\). Researches carried out in Chile, Mexico, and England exposed cases of early CS in which the mothers were only reactive to the second test applied to them or during birth\(^{20,23,27-28,31}\). These women may have been infected during pregnancy and present high titer levels at the moment of birth, corresponding to an early stage of the infection.

Once the opportunities to prevent CS are lost during the prenatal care, its late complications in the newborns can be prevented, as long as these babies are properly managed when they are born.

In the state of Minas Gerais (MG), Brazil, a study showed that the VDRL was not carried out for 25.8\% of babies, while 42.2\% did not undergo a hemogram, radiographies of the long bones, or liquor puncturing\(^{17}\). The health services may present difficulties to the guarantee all exams necessary to diagnose CS, which, in the long term, may lead to the increase in the cases of children with serious sequelae.

The transmission of syphilis to the baby is related to the clinical stage of the mother’s infection, and can reach 100\% when the infection is recent\(^{28-30}\). High titer levels in non-treponemal tests in the mother indicate that the infection is recent and increase the likelihood of negative outcomes. In Shanghai, China, pregnant women whose titer levels were ≥ 1:16 in reacting to the Rapid Plasma Reagin (RPR) exam showed higher levels of CS when compared to those with ≥ 1:8 titer levels\(^{24}\). Furthermore, in Africa, stillbirth is associated with high VDRL titration\(^{26,29}\).

These findings call our attention to how important it is to improve both the prenatal coverage and the early tracking of the pregnant women; in these occasions, the opportunity to test and treat cannot be lost. Diagnosing and starting to treat syphilis as early as possible, preferably in the first trimester of pregnancy, avoids the prolonged exposure of the baby to the treponema. As a result, it should be mentioned that improving prenatal care is essential to prevent negative CS outcomes, considering that a study carried out using the World Health Organization database found that 66\% of adverse effects involved children whose mothers went to prenatal examinations\(^{40}\).

In the United States, a study found how important it is to treat pregnant women with syphilis to prevent complications in the newborn. Through ultrasonography, it was possible to find that...
the number of abnormal findings (hepatomegaly, placentomegaly, polyhydramnios, ascites, and changes in the doppler evaluation of the middle cerebral artery) in fetuses after the mother was treated. It should be noted that, even when there are shortcomings in the attention to the pregnant woman, it is possible to reduce CS complications when the newborn is diagnosed and treated as early as possible. A cohort carried out in SC followed cases of children up to 5 years old and found that some children showed alterations at birth, but did not develop sequelae because they started their treatment in their first seven days of life.

**Study limitations**

A limiting factor of this study is the fact that literature was not exhaustively analyzed, since many researches were not openly available in full. Furthermore, some studies were case reports, which reduces their scope and/or the relevance of the inferences that can be made from these individual findings.

**CONCLUSIONS**

The scientific evidence analyzed here shows severe negative outcomes of CS, such as stillbirths, neonate deaths, and low weight at birth, in addition to radiological and laboratory changes, and a high diversity of early and late clinical manifestations. These outcomes could be avoided, considering that opportunities to diagnose early and treat the pregnant woman were lost during prenatal care.

**REFERENCES**

1. World Health Organization (WHO). The Global elimination of congenital syphilis: rationale and strategy for action [Internet]. Geneva: WHO; 2007 [cited 2019 Apr 8]. Available from: https://apps.who.int/iris/bitstream/handle/10665/43782/9789241595858_eng.pdf?sequence=1
2. World Health Organization (WHO). Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV and syphilis [Internet]. Geneva: WHO; 2014 [cited 2019 Apr 8]. Available from: https://apps.who.int/iris/bitstream/handle/10665/259517/9789241513272-eng.pdf?sequence=1
3. Wijesooriya NS, Rochat RW, Kamb ML, Turlapatı P, Temmerman M, Brouet N, et al. Global burden of maternal and congenital syphilis in 2008 and 2012: a health systems modelling study. Lancet. 2016; 4(8):525-33. https://doi.org/10.1016/S2214-109X(16)30135-8
4. Organização as Nações Unidas (ONU). Centro de Informação Regional das Nações Unidas para a Europa Ocidental. Guia sobre Desenvolvimento Sustentável: 17 objetivos para transformar o nosso mundo [Internet]. UNRIC, 2016 [cited 2019 Apr 8]. Available from: https://www.unric.org/pt/images/stories/2016/ods_2edicao_web_pages.pdf
5. Gomez GB, Kamb ML, Newman LM, Mark J, Brouet N, Hawkes SJ. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. Bull World Health Organ. 2013; 91:217-26. https://doi.org/10.2471/BLT.12.107623
6. Newman L, Kamb M, Hawkes S, Gomez G, Say L, Seuc A, et al. Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data. PLoS Med. 2013;10(2):e1001396. https://doi.org/10.1371/journal.pmed.1001396
7. Domingues RMSM, Leal MC. Incidência de sífilis congênita e fatores associados à transmissão vertical da sífilis: dados do estudo Nascer no Brasil. Cad Saúde Pública. 2016;32(6):e00082415. https://doi.org/10.1590/0102-311X00082415
8. Lago G, Vaccari A, Fiori RM. Clinical features and follow-up of congenital syphilis. Sex Transm Dis. 2013;40(2):85-94. https://doi.org/10.1097/OLQ.0b013e31827bd688
9. World Health Organization (WHO). Guidelines for the treatment of Treponema pallidum (syphilis) [Internet]. Geneva: WHO; 2016 [cited 2019 Apr 8]. Available from: https://apps.who.int/iris/bitstream/handle/10665/249572/9789241549806-eng.pdf
10. Ganong LH. Integrative reviews of nursing research. Res Nurs Health. 1987; 10(1):1-11. 2
11. Whitemore R. Combining evidence in nursing research: methods and implications. Nurs Res. 2005;54(1):56-62.
12. Melnyk BM, Fineout-Overholt E. Evidence-based practice in nursing and health: a guide to best practice. Philadelphia: Wolters Kluwer; 2011.
13. Souza LFM, Monteiro PM, Mota AS, Passos MRL, Pellegrini Jr EM. Analysis of congenital syphilis cases notification in a reference hospital of Niterói, Rio de Janeiro State, from 2008 to 2015. DST J Bras Doenças Sex Transm. 2017;29(1):17-21. https://doi.org/10.5533/DST-2177-8264-201729105
14. Cardoso ARP, Araújo MAL, Andrade RFV, Saraceni V, Miranda AE, Dourado MIC. Underreporting of congenital syphilis as a cause of fetal and infant deaths in Northeastern Brazil. PLoS ONE. 2016;11(12):e0167255. https://doi.org/10.1371/journal.pone.0167255
15. Feliz MC, Medeiros ARP, Rossoni AM, Tahnus T, Pereira AMVB, Rodrigues C. Adherence to the follow-up of the newborn exposed to syphilis and factors associated with loss to follow-up. Rev Bras Epidemiol. 2016;19(4):727-39. https://doi.org/10.1590/1980-5497201600040004
16. Ferreira ST, Correia C, Marçal M, Tuna ML. Skin rash: a manifestation of early congenital syphilis. BMJ Case Reports. 2016; bcr2016216148. https://doi.org/10.1136/bcr-2016-216148
39. Andrade ALMB, Magalhães PVVS, Moraes MM, Tresoldi AT, Pereira RM. Late diagnosis of congenital syphilis: a recurring reality in woman and

38. Nascimento MI, Cunha AA, Guimarães EV, Alvarez FS, Oliveira SRSM, Villas Bôas EL. Gestações complicadas por sífilis materna e óbito fetal.

37. Blencowe H, Cousens S, Kamb M, Berman S, Gramado AE. Lives Saved Tool: supplement detection and treatment of syphilis in pregnancy to

36. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente

35. Freiman I, Super M. Thrombocytopenia and congenital syphilis in South African Bantu infants. Arch Dis Child. 1966;41(215):87-90. https://

33. Aguayo IT, Martínez GD, Munzenmaycr JB, Roscmberg HG, Fuente-Alba JAG. Síndrome Nefrótico Secundario a Lues Congénita. Rev Chile

32. Ewing CI, Roberts C, Davison DC, Arya OP. Early congenital syphilis still occurs. Arch Dis Child. 1985;60(12):1128-33. https://doi.org/10.1136/

31. Chawla V, Pandit PB, Nkrumah FK. Congenital syphilis in the newborn. Arch Dis Child. 1985;60(12):1128-33. https://doi.org/10.1136/adc.60.12.1128

30. Boot JM, Orange AP, Menke HE, Van Eijk RV, Stolz E. Congenital syphilis in The Netherlands: diagnosis and clinical features. Genitourin Med.

29. McDermott J, Steketee R, Larsen S, Wirima J. Syphilis-associated perinatal and infant mortality in rural Malawi. Bull World Health Organ [Internet].

28. Peña A, Cardiel-Marmolejo LE, Matamoros-Márquez M, Iturbide-Cruz LA, Ávalos-Martínez JL, García HJ. Sífilis congénita: presentación
depuerto de un caso y revisión de la literatura. Rev Méd Hosp Gen Méx [Internet]. 2001 [cited 2019 Apr 8];64(4):240-5. Available from: http://www.

27. Reyes JA, Chorbadjian AG, Parada CMA, Turrys CJ, Bravo CN, Araya FCG. Sífilis congénita: optimizando el diagnóstico en 191 neonatos de

26. Krüger C, Malleyeck I. Congenital syphilis: still a serious, under-diagnosed threat for children in resource-poor countries. World J Pediatr.

25. Zhu L, Qin M, Du L, Xie RH, Wong T, Wen SW. Maternal and congenital syphilis in Shanghai, China, 2002 to 2006. Int J Infect Dis.

24. Pessoa L, Galvão V. Clinical aspects of congenital syphilis with Hutchinson’s triad. BMJ Case Rep. 2011:bcr1120115130. https://doi.org/10.1136/

23. Arriagada D, Donoso A, Cruces P, Díaz F. Congenital syphilis: presenting as septic shock alter the neonatal period. Rev Chile Infectol. 2012;29(5):558-63. https://doi.org/10.4067/S0716-10182012000600017

22. Cavagnaro FSM, Pereira TR, Pérez CP, Vargas FDV, Sandoval CC. Sífilis congénita precoz: a propósito de 2 casos clinicos. Rev Chile Pediatri.

21. Chowdhary N, Rani BSK, Mukunda KS, Kiran NK. Early detection of congenital syphilis. J Indian Soc Pedod Prev Dent. 2014;32(4):333-7.

20. Rac MWF, Bryant SN, McIntire DD, Cantey JB, Twickler DM, Wendel Jr GD et al. Progression of ultrasound findings of fetal syphilis after

19. Arnesen L, Martínez G, Mainero L, Serruya S, Durán P. Gestational syphilis and stillbirth in Latin America and the Caribbean. Int J Gynaecol

18. Dou L, Wang X, Wang F, Wang Q, Qiao Y, Su M, et al. Epidemic Profile of Maternal Syphilis in China in 2013. BioMed Research International. 2016;ID9194805. https://doi.org/10.1155/2016/9194805

17. Lafetá KRG, Martelli Jr H, Silveira MF, Paraanaiba LMR. Maternal and congenital syphilis, underreported and difficult to control. Rev Bras

16. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Protocolo Clínico e Diretrizes Terapêuticas para Prevenção da Transmissão Vertical do HIV, Sífilis e Hepatites Virais [Internet]. Brasília, DF (BR): Ministério da Saúde, 2019 [cited 2019 Apr 8];71(6):773-80. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2393540/pdf/bullwho00039-0115.pdf

15. Krüger C, Malleyeck I. Congenital syphilis: still a serious, under-diagnosed threat for children in resource-poor countries. World J Pediatr. 2010;6(2):125-31. https://doi.org/10.1007/s12519-010-0028-2

14. McDermott J, Steketee R, Larsen S, Wirima J. Syphilis-associated perinatal and infant mortality in rural Malawi. Bull World Health Organ [Internet]. 1993 [cited 2019 Apr 8];71(6):773-80. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2393540/pdf/bullwho00039-0115.pdf

13. Boot JM, Orange AP, Menke HE, Van Eijk RV, Stolz E. Congenital syphilis in The Netherlands: diagnosis and clinical features. Genitourin Med. 1989;65(5):300-3. https://doi.org/10.1136/sti.65.5.300

12. Ewing CI, Roberts C, Davison DC, Arya OP. Early congenital syphilis still occurs. Arch Dis Child. 1985;60(12):1128-33. https://doi.org/10.1136/adc.60.12.1128

11. Freiman I, Super M. Thrombocytopenia and congenital syphilis in South African Bantu infants. Arch Dis Child. 1966;41(215):87-90. https://

10. Boot JM, Orange AP, Menke HE, Van Eijk RV, Stolz E. Congenital syphilis in The Netherlands: diagnosis and clinical features. Genitourin Med. 1989;65(5):300-3. https://doi.org/10.1136/sti.65.5.300

9. McDermott J, Steketee R, Larsen S, Wirima J. Syphilis-associated perinatal and infant mortality in rural Malawi. Bull World Health Organ [Internet]. 1993 [cited 2019 Apr 8];71(6):773-80. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2393540/pdf/bullwho00039-0115.pdf

8. Peña A, Cardiel-Marmolejo LE, Matamoros-Márquez M, Iturbide-Cruz LA, Ávalos-Martínez JL, García HJ. Sífilis congénita: presentación de un caso y revisión de la literatura. Rev Méd Hosp Gen Méx [Internet]. 2001 [cited 2019 Apr 8];64(4):240-5. Available from: http://www.medigraphic.com/pdfs/h-gral/hg-2001/hg-20014.pdf

7. Reyes JA, Chorbadjian AG, Parada CMA, Turrys CJ, Bravo CN, Araya FCG. Sífilis congénita: optimizando el diagnóstico en 191 neonatos de

6. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. Protocolo Clínico e Diretrizes Terapêuticas para Prevenção da Transmissão Vertical do HIV, Sífilis e Hepatites Virais [Internet]. Brasília, DF (BR): Ministério da Saúde, 2019 [cited 2019 Apr 8];71(6):773-80. Available from: https://www.aids.gov.br/pt-br/pub/2015/protocolo-clinico-e-diretrizes-terapeuticas-para-prevencao-da-transmissao-vertical-de-hiv

5. Wiggelinkhuizen J, Kaschula ROC, Uys CJ, Kuijten RH, Dale J. Congenital syphilis and glomerulonephritis with evidence for immune

4. Freiman I, Super M. Thrombocytopenia and congenital syphilis in South African Bantu infants. Arch Dis Child. 1966;41(215):87-90. https://

3. Freiman I, Super M. Thrombocytopenia and congenital syphilis in South African Bantu infants. Arch Dis Child. 1966;41(215):87-90. https://

2. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. Protocolo Clínico e Diretrizes Terapêuticas para Prevenção da Transmissão Vertical do HIV, Sífilis e Hepatites Virais [Internet]. Brasília, DF (BR): Ministério da Saúde, 2019 [cited 2019 May 19]. Available from: http://www.aids.gov.br/pt-br/pub/2015/protocolo-clinico-e-diretrizes-terapeuticas-para-prevencao-da-transmissao-vertical-de-hiv

1. Blencowe H, Cousens S, Kamb M, Berman S, Gramado AE. Lives Saved Tool: supplement detection and treatment of syphilis in pregnancy to

Rev Bras Enferm. 2021;74(4):e20190318 8 of