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INTER FACES CIENTÍFICAS

CONGENITAL SYPHILIS EVALUATED FOR SYPHILITIC HEPATITIS - CASE SERIES

SÍFILIS CONGÊNITA AVALIADA PARA HEPATITE SIFILÍTICA – SÉRIE DE CASOS

SÍFILIS CONGÉNITA EVALUADA PARA HEPATITIS SIFILÍTICA – SERIE DE CASOS

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ABSTRACT

This work aimed to report case series evaluated for congenital syphilitic hepatitis. Study conducted at Maternity Santa Isabel in Aracaju SE, northeast Brazil, from December 2021 to May 2022. We evaluated newborns with congenital syphilis using data taken from the pregnant woman's card, the child's card, the anamnesis, and exams performed in the follow-up consultations of these families. Complete medical records of infants who presented the criteria for the diagnosis of congenital syphilis of the Ministry of Health and the Center for Disease Transmission Control were included. The review was 15 of which were selected that fit all the inclusion criteria. The babies were born with good vitality, term, one had low birth weight, six hepatomegaly, all treated with penicillin, nine had altered liver biochemical tests. At ultrasonography, Doppler was normal for all, one case of hepatosplenomegaly and one with splenomegaly. Two mothers who were diagnosed at the time of delivery had fewer than six consultations, their babies had neurosyphilis and presented developmental alertness. The child who had microcephaly and low birth weight also presented altered neurodevelopment. Of the pregnant women, three were over 30 years old, one was white, five had studied less than 8 years, thirteen were not working, family income of 1 minimum wage or less in twelve families. Eight were inadequately treated. Of the parents, eleven had studied less than 8 years and eleven were inadequately treated. The children with syphilis were born vigorous and had adequate treatment. Nine had altered hepatic biochemical exams, two had ultrasonographic alterations, however, without alterations in the Doppler. The children of untreated mothers had neurosyphilis and neurodevelopmental changes.

KEYWORDS

Congenital Syphilis. *Treponema pallidum*. Cholestasis. Hepatitis.

RESUMO

Este trabalho teve por objetivo relatar uma série de casos avaliados para hepatite sifilítica congênita. Estudo realizado na Maternidade Santa Isabel em Aracaju, SE, Nordeste do Brasil, no período de dezembro de 2021 a maio de 2022. Avaliamos recém-nascidos com sífilis congênita por meio de dados retirados do cartão da gestante, do cartão da criança, da anamnese e dos exames realizados nas consultas de acompanhamento dessas famílias. Foram incluídos prontuários completos de lactentes que apresentavam os critérios para diagnóstico de sífilis congênita do Ministério da Saúde e do Centro de Controle de Transmissão de Doenças. Da revisão foram selecionados 15 que se enquadraram em todos os critérios de inclusão. Os bebês nasceram com boa vitalidade, a termo, um tinha baixo peso ao nascer, seis tinham hepatomegalia, todos foram tratados com penicilina, nove tinham exames bioquímicos hepáticos alterados. À ultrassonografia, o Doppler foi normal em todos, um caso de hepatoesplenomegalia e um com esplenomegalia. Duas mães diagnosticadas no momento do parto tiveram menos de seis consultas, seus bebês tinham neurossífilis e apresentavam alerta de desenvolvimento. A criança que teve microcefalia e baixo peso ao nascer também apresentou neurodesenvolvimento alterado. Das gestantes, três tinham mais de 30 anos, uma era branca, cinco estudaram menos de 8 anos, treze não trabalhavam, renda familiar igual ou inferior a 1 salário mínimo em doze famílias. Oito foram tratados inadequadamente. Dos pais, onze estudaram menos de 8 anos e onze foram tratados inadequadamente. As crianças com sífilis nasceram vigorosas e tiveram tratamento adequado. Nove apresentavam exames bioquímicos hepáticos alterados, dois apresentavam alterações ultrassonográficas, porém, sem alterações no Doppler. Os filhos de mães não tratadas apresentaram neurossífilis e alterações no neurodesenvolvimento.

PALAVRAS-CHAVE

Sífilis Congênita. *Treponema pallidum.* Colestase. Hepatite.

RESUMEN

Este trabajo tuvo como objetivo reportar una serie de casos evaluados para hepatitis sifilítica congénita. Estudio realizado en la Maternidad Santa Isabel en Aracaju, SE, noreste de Brasil, de diciembre de 2021 a mayo de 2022. Se evaluaron los recién nacidos con sífilis congénita a través de datos tomados de la tarjeta de la gestante, la tarjeta del niño, la anamnesis y los exámenes realizados en las consultas de seguimiento de estas familias. Se incluyeron las historias clínicas completas de los

lactantes que cumplieron con los criterios para el diagnóstico de sífilis congénita del Ministerio de Salud y el Centro de Control de Transmisión de Enfermedades. De la revisión se seleccionaron 15 que cumplieron con todos los criterios de inclusión. Los bebés nacieron con buena vitalidad, a término, uno con bajo peso al nacer, seis con hepatomegalia, todos en tratamiento con penicilina, nueve con bioquímica hepática anormal. En la ecografía, el Doppler fue normal en todos, un caso de hepatoesplenomegalia y un caso de esplenomegalia. Dos madres diagnosticadas al momento del parto tuvieron menos de seis visitas, sus bebés tenían neurosífilis y su desarrollo estaba alerta. El niño que tenía microcefalia y bajo peso al nacer también tenía un neurodesarrollo alterado. De las gestantes, tres tenían más de 30 años, una era blanca, cinco estudiaban menos de 8 años, trece no trabajaban, ingreso familiar igual o menor a 1 salario mínimo en doce familias. Ocho fueron tratados inadecuadamente. De los padres, once estudiaron menos de 8 años y once fueron tratados inadecuadamente. Los niños con sífilis nacieron vigorosos y tuvieron un tratamiento adecuado. Nueve presentaban bioquímica hepática alterada, dos alteraciones ecográficas, pero sin alteraciones Doppler. Los hijos de madres no tratadas tenían neurosífilis y cambios en el neurodesarrollo.

PALABRAS CLAVE

Sífilis congénita; *Treponema pallidum*; Colestasis; Hepatitis.

1 INTRODUCTION

Syphilis is a bacterial sexually transmitted disease, the etiologic agent is *Treponema pallidum*, the untreated or inadequately treated pregnant woman can transmit it to the fetus by transplacental route, which can cause Congenital Syphilis (CS) (KIMBALL et al., 2020; BRAZIL, 2017). In 2016, 355,000 abortions and dead fetuses occurred in the world: 143,000 involved pregnant women with syphilis. The amount of children with CS symptoms was 109,000, 14,000 cases of neonatal deaths, 41,000 cases of prematurity and low birth weight (LAWN et al., 2016; KORENROMP et. al, 2019). CS is the second most common cause of preventable fetal deaths worldwide (GALVIS; ARRIETA, 2020).

The World Health Organization (WHO) Global Health Sector Strategy has determined that one of the four goals for 2030 will be the elimination of CS, because it is a serious public health problem The goal has been set for 80% of countries with high incidence rates to reduce it to ≤0.5 cases per 1,000 live births (LB) (WHO, 2016). In the United States, from 2013 to 2018, there was an increase in CS rates of 261% with an incidence rate of 33 cases per 100,000 LB (KORENROMP et al., 2019). In the UK between 2010 and 2015, 17 cases of CS were reported (DEALL et al., 2019).

According to the epidemiological bulletin of Brazil (2022a), in the year 2021, 27.019 cases of CS were reported in the Notification Diseases Information System (*Sistema de Informações de Agravos de Notificação* - SINAN), a mortality rate of 7.0 deaths per 100,000 LB. The average incidence rate in Brazil was 9.9 and in Sergipe 16.5 cases for 1,000 LB.

The pathogenesis of syphilis is not well clarified because *Treponema pallidum* does not grow in culture medium, the visualization has to be through electronic microscopy with dark field and needs special dyes such as silver to perform the anatomopathological examination of lesions in contaminated organs (MAGNUSON et al., 1956). It causes a systemic inflammatory response in the fetal circulation with dissemination of the spirochetes to almost all organs. The most affected are the bones, liver, pancreas, intestine, and spleen (CHRISTIAN et al., 1999; BRAZIL, 2017).

Lago and collaborators (2013) reported that hepatomegaly is the most frequent CS manifestation and occurs in virtually all cases of infected children, presenting slow regression, even with proper treatment. The presence of fetal hepatomegaly on the ultrasound of pregnant women with syphilis may signal maternal treatment failure (HOLLIER et al., 2001).

Liver serological changes are related to jaundice and cholestasis with changes in the following tests: CBC, total bilirubin (TB), direct bilirubin (DB) and indirect bilirubin (IB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium, serum albumin, gamma glutamyl--transferase (GGT), activated partial thromboplastin time (APTT), alkaline phosphatase (ALP) (KOLLMANN; DOBSON, 2011; FAWAZ et al., 2017; DUBY, 2019).

Given the above, we aimed to evaluate the epidemiological profile, number of visits, start, father and mother treatment and tests performed prenatal care of pregnant women with syphilis, birth conditions and follow-up of infants diagnosed and treated with congenital syphilis.

2 METHODS

Series with medical records of newborns with congenital syphilis and the pregnant woman's card, the child's card, the anamnesis, and examinations performed this case in the follow-up visits of these families in the congenital syphilis outpatient clinic of the Hospital and Maternity Santa Isabel in Aracaju, SE, northeast Brazil, from December 2021 to May 2022. Complete medical records of infants who presented the criteria for the diagnosis of congenital syphilis of the Ministry of Health updated in 2017 (BRAZIL, 2017) and Center for Disease Transmission Control (CDC, 2019) were included.

Maternal and paternal assessment: age, race/color, education, income, occupation, treatment. Prenatal care: number of visits, start, father and mother treatment and tests performed. Regarding the newborn: criteria for congenital syphilis diagnosis, sex, weight, gestational age, APGAR cranial perimeter, length, Body Mass Index (BMI) at birth and at the first visit, neuropsychomotor development, guthrie test, little ear test, long bone X-ray, fundoscopy, Venereal Disease Research Laboratory (VDRL) in peripheral blood and cerebrospinal fluid, syphilis symptoms, tests to assess liver function, abdominal ultrasound with Doppler. Data were analyzed using descriptive statistics. Microsoft Excel® was used to organize the collected information. This study was approved by the Research Ethics Committee under the code CAAE: 43629120.8.0000.5371.

3 RESULTS AND DISCUSSION

In the present study, 40 medical records were analyzed, 15 of which met the inclusion criteria. Of the pregnant women, they were young, one was white, five had studied less than 8 years, thirteen were not working, family income of 1 minimum wage or less in twelve families. The parents: 2 over 30 years old, 11 worked, one was illiterate, 11 studied less than 8 years (Table 2). The epidemiological bulletin of Brazil corroborates this socioeconomic profile of pregnant women with syphilis (BRAZIL, 2022a).

Table 1 – description of sociodemographic characteristics of pregnant couples with syphilis in a maternity in northeast Brazil from December 2021 to May 2022

Case	Age		Schooling years		Paid or unpaid occupation		Breed	
	Mother	Father	Mother	Father	Mother	Father	Mother	Income
1	37	31	<8	>8	No	Yes	Brown	1/4 salary
2	26	26	<8	0	No	Yes	Brown	1/4 salary
3	34	30	<8	8<	No	Yes	Black	1/4 salary
4	22	21	>8	>8	No	Yes	Brown	1 salary
5	25	22	>8	<8	No	Yes	Brown	1 salary
6	27	19	>8	>8	No	No	Brown	1/4 salary
7	40	49	<8	<8	No	No	Brown	1/4 salary
8	18	17	>8	<8	No	No	White	1/4 salary
9	18	20	>8	<8	No	Yes	Brown	1/4 salary
10	20	23	>8	<8	No	Yes	Brown	1 salary
11	18	21	>8	<8	No	Yes	White	1/2 salary
12	17	24	>8	>8	No	Yes	Brown	1,5 salary
13	25	29	>8	<8	Yes	Yes	Black	1,5 salary
14	30	22	>8	<8	Yes	Deceased	Brown	1.5 salary
15	27	23	<8	<8	No	Yes	Brown	1,5 salary

Source: Elaborated by the authors.

Scientific evidence clearly shows the direct relationship between prenatal care and the reduction of congenital syphilis cases. According to the Ministry of Health (BRAZIL, 2000; 2012), quality prenatal coverage needs to start by the 12th week of gestation, have at least six consultations being one in the first, two in the second, and three in the third trimester. Laboratory tests should be performed in the first trimester (rapid treponemal test for syphilis and, if positive, the VDRL, HIV, cytomegalovirus, toxoplasmosis, rubella, hepatitis B and C) and repeated in the third trimester, in addition to vaccination and educational activities.

According to Silva and collaborators (2022) in an integrative review on prenatal care in the prevention of CS found as main failures: late initiation of prenatal care, inadequate assistance in the diagnosis and treatment of gestational syphilis, lack of training of professionals and difficulties both in the adherence of pregnant women to treatment as in the active search for sexual partners.

In the present study, although thirteen pregnant women had the recommended number of consultations, only one had been treated for syphilis in the first trimester, and seven were adequately treated. The reasons for inadequate maternal treatment were: four due to incorrect interval between doses; one due to incorrect dose; another because she started treatment 29 days before delivery, and two were not treated during pregnancy (Table 2).

According to Clinical protocol and therapeutic guidelines for care people with sexually transmitted infections, in order to be considered adequately treated, a pregnant woman needs to treat syphilis according to the clinical phase of the maternal disease; use benzathine penicillin at the correct dose and interval (primary, secondary, and early latent phase one dose of 2.400.000 IU, and in the tertiary, indeterminate, and late latent phase three doses of 2.400.000 IU seven days apart); start treatment for syphilis 30 days before delivery; finish treatment before delivery, with no risk of reinfection; drop the VDRL in two dilutions up to 3 months and 4 dilutions in six months after finishing treatment for recent syphilis, i.e., with 1 year of evolution, 2 dilutions in 6 months, and 4 dilutions in 12 months for late syphilis (BRAZIL, 2022b)

The VDRL is a non-treponemal test for diagnosis of CS based on complement fixation and reactivity to cardiolipin (VON WASSERMANN et al., 1906). Babies born to VDRL-positive mothers have 56 to 66% of these tests positive. The sensitivity of this method is 4 to 13% and the specificity 99% (HERREMANS et al., 2010). In the current research, of the seven mothers adequately treated in pregnancy, three had increased dilutions in the third trimester, two increased one dilution, one three dilutions, and four had decreased dilution.

Treatment failure may occur in 14% of pregnant women treated for syphilis with reinfections evaluated by increasing VDRL in two or more titers after treatment (BRAZIL, 2006). Hollier and collaborators (2001) in the United States, found 17% in a clinical trial on fetal syphilis and its clinical and laboratory characteristics. In the present study of the untreated or inadequately treated mothers, the dilutions remained the same or increased, none decreased.

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Table 2 – Description of the prenatal care of pregnant couples with syphilis in a maternity in northeast Brazil from December 2021 to May 2022

Case	Amount Consultation		Moment of treatment		Reason for inadequate treatment		VDRL Mother			Exams 1 Prenatal	Exams 2 Prenatal
	Beginning	Prenatal	Mother	Father	Mother	Father	Prenatal	Delivery	1st visit		
1	12	2 months	2t	non treated	adequate	VDRL NR	1:8	1:4	1:8	HIV, TT, VDRL, Rubeola CMV, HBV HC, Toxo	No exams
2	5	3 months	postpartum	non treated	negative rapid test prenatal	VDRL NR	1:4	1:512	1:64	HIV, TT, VDRL, HBV, HCV, Toxo	No exams
3	11	3 months	*1t	non treated	incorrect interval between doses	VDRL NR	1:4	1:16	1:8	HIV, TT, VDRL	HIV, VDRL
4	8	1 month	*2t	2t	adequate	adequate	1:16	1:8	1:8	HIV, TT, VDRL, HBV, Toxo	No exams
5	9	1 month	*3t	3t	started treatment 29 days before delivery	treated on the same day	+	1:256	1:128	HIV, VDRL	No exams
6	5	3 months	postpartum	non treated	postpartum treatment	does not live with him	1:4	1:8	1:4	HIV, VDRL	VDRL

Case	Amount Consultation		Moment of treatment		Reason for inadequate treatment		VDRL Mother			Exams 1 Prenatal	Exams 2 Prenatal
	Beginning	Prenatal	Mother	Father	Mother	Father	Prenatal	Delivery	1st visit		
7	14	2 months	*2t	non treated	adequate	VDRL NR	1:4	1:16	1:8	HIV, TT VDRL	HIV, TT, VDRL
8	8	3 months	*2t	2t	incorrect interval	incorrect interval	1:2	1:16	1:8	HIV, TT, VDRL, HBV, Toxo	HIV, TT, VDRL, HBV
9	8	4 months	*2t	2t	adequate	adequate	1:6	1:4	1:1	HIV, TT VDRL, HBV, Toxo	HIV, VDRL, HBV
10	7	3 months	*3t	3t	adequate	adequate	1:8	1:2	1:2	HIV, TT VDRL, HBV HCV,CMV, Toxo	HIV, VDRL
11	8	2 months	*2t	2t	incorrect interval	incorrect interval	1:8	1:8	1:8	HIV, TT, VDRL, HBV, Toxo	HIV, VDRL
12	8	3 months	*2t	2t	incorrect dosage	incorrect dosage	1:2	1:2	1:2	HIV, TT, VDRL	HIV, TT, VDRL
13	8	3 months	postpartum	postpartum	incorrect interval	incorrect interval	NR	1:2	NR	HIV, TT VDRL, HBV,CMV, Toxo, Rubeola	No exams
14	7	3 months	*2t	deceased	adequate	deceased	1:4	1:16	1:4	HIV, TT VDRL, HBV, HCV, Toxo,	No exams
15	8	4 months	*2t	2t	adequate	adequate	1:8	1:16	1:4	HIV, TT, VDRL	HIV, VDRL

Source: Elaborated by the authors. Caption: *1t-first trimester, *2t-second trimester, *3t-third trimester

According to the updated in 2017 case definition of congenital syphilis the sexual partnerships of pregnant women with syphilis do not fit the criteria for defining adequacy of maternal treatment (BRAZIL, 2017). Rocha and collaborators (2019) in a survey conducted in northeast Brazil on management of sexual partners in pregnancy, found that the rescue to perform partner treatment was delegated to pregnant women, treatment not performed and not followed up.

The sexual partners need to be treated with a dose of benzathine penicillin in cases where they are VDRL non-reactive (BRAZIL, 2022b). In the present research of the parents, only 4 had adequate treatment. The inadequacy of treatment was due to: incorrect dose (1); incorrect intervals (three); starting treatment 29 days before delivery (1). Six were not treated: non-reactive VDRL (4); mother no longer has contact (1); died (1) (Table 2). The acceptance of these partners in prenatal visits and appropriate treatment, according to the clinical stage of the disease, has a positive impact on reducing the prevalence of this disease.

The 15 newborns were diagnosed following the CDC and Brazilian Ministry of Health case definition criteria for CS. When the mother is inadequately treated or untreated it is necessary to look for signs and symptoms of early congenital syphilis (prematurity, low weight, hepatomegaly associated or not with splenomegaly, jaundice, palmoplantar pemphigus, fungella, bone alterations, Parrot's pseudoparalysis, among others). Perform the following tests in the baby: VDRL in peripheral blood and liquor, hemogram, long bone X-ray, total bilirubin and fractions, AST, ALT, alkaline phosphatase, gamma GT, albumin, sodium, potassium, prothrombin time, still in the maternity ward (BRAZIL, 2022b).

The presence of any sign or symptom of CS and/or bone changes, VDRL positivity in peripheral blood and/or cerebrospinal fluid classifies children as carriers of CS and will be treated with procaine or benzathine penicillin in an inpatient regime for 10 days. If there are no signs/symptoms and all laboratory tests are normal, a dose of benzathine penicillin is given and the child continues as an outpatient. When the mother is considered adequately treated, the VDRL of the baby is done and if it is equal or higher than two dilutions of the maternal VDRL, she is considered contaminated and treated for 10 days. If the baby's VDRL is less than two dilutions of the maternal VDRL and has signs and symptoms of internal CS, it should be treated accordingly. If the VDRL is non-reactive, one researches other congenital diseases (Toxoplasmosis, Cytomegalovirus, Rubella, Human Immunodeficiency Virus, Hepatitis B and C, Zika and herpes virus) and follows up outpatiently (BRAZIL, 2017; 2022a).

In the present study, the diagnosis of CS with positive VDRL was given in six infants whose mothers were inadequately treated. Of these infants, five also had metaphysitis on radiographs of the long bones. Two untreated mothers' babies also had neurosyphilis and metaphysitis. Of seven mothers with adequate treatment, five children had metaphyseal disease; as for the other two, one was born with low birth weight and microcephaly and the other hepatomegaly.

The babies were born with good vitality, term, only one low birth weight, nine female, six had hepatomegaly on physical examination, all treated at birth with crystalline and/or procaine penicillin. VDRL was non-reactive in nine babies at the first visit (Table 2). Treatment at birth can prevent serious sequelae in children with congenital syphilis such as deafness, blindness, growth and neurodevelopmental changes (BRAZIL, 2017). It is therefore notorious the importance of proper follow-up of both mother and baby, since even the adequately treated mother's offspring can present congenital syphilis whose treatment at birth can avoid serious sequelae.

In this series of cases, none of the babies were born with non-reactive VDRL, nor did they have two dilutions equal to or greater than the maternal VDRL at birth, and at the first visit eleven of them had already been negative. According to Rawstron and collaborators (2001) and Morshed and Singhb (2015) less than 30% of children with CS have higher than maternal VDRL. Although it is a non-treponemal test with positivity and low sensitivity, it is used for the diagnosis and follow-up of infants due to its good specificity and negativity that prove the cure of the disease.

In the current research, Doppler ultrasonography showed in one baby hepatosplenomegaly and in another splenomegaly, but all had homogeneous liver texture and normal Doppler. Moderate enlargement of the liver with heterogeneous texture and no visualization of the peripheral portal venous vasculature was observed in a case report of syphilitic hepatitis (OGAWA et al., 2020). Doppler abdominal ultrasonography can be performed in the investigation and follow-up of patients with cholestasis, being effective in demonstrating masses, size, change in liver texture, presence of extrahepatic malformations, among others (PINTO; SILVEIRA, 2016). The ultrasound examination, although not part of the CS protocol, is relevant in the follow-up of newborns and has the advantages of being low cost and non-invasive.

Table 3 – Description of the characteristics of 15 cases of congenital syphilis evaluated for syphilitic hepatitis in a maternity in northeast Brazil from December 2021 to May 2022

Case	Gender	APGAR	CP/Height/ Weight/ BMI- at birth	VDRL at		Treatment days	Diagnostic criteria for CS	Doppler ultrasound of the upper abdomen
				Birth	First appointment			
1	F	8/9	adequate	1:16	1:4	crystalline penicillin 10	metaphysitis in all bones,VDRL 1:16	normal
2	F	9/9	adequate	1:512	1:64	crystalline penicillin 7 procaine 3	postpartum treated mother, metaphysitis in all bones and neurosyphilis, VDRL 1:512, hepatomegaly	normal
3	M	9/10	adequate	1:4	NR	crystalline penicillin 10	mother inadequately treated; VDRL 1:4	normal
4	F	9/10	adequate	1:4	NR	penicillin procaine 10	metaphysitis in all bones,VDRL 1:4	normal

Case	Gender	APGAR	CP/Height/ Weight/ BMI- at birth	VDRL at		Treatment days	Diagnostic criteria for CS	Doppler ultrasound of the upper abdomen
				Birth	First appointment			
5	M	5/9	adequate	1:2	NR	crystalline penicillin 10	mother inadequately treated, metaphysitis in all bones, VDRL 1:2, hepatomegaly.	splenomegaly
6	F	8/9	adequate	1:128	1:4	crystalline penicillin 10	mother treated postpartum; metaphysitis in all bones, VDRL 1:128, hepatomegaly.	normal
7	F	9/9	adequate	1:1	NR	crystalline penicillin 10	hepatomegaly, VDRL 1:1	normal
8	M	9/10	adequate	1:2	NR	procaine penicillin 10	Inadequately treated mother, metaphyseal in all bones, VDRL 1:2, hepatomegaly	normal
9	F	9/10	adequate	1:1	NR	crystalline penicillin 8 procaine 2	metaphysitis in all bones, VDRL 1:1, hepatomegaly	normal
10	M	9/10	adequate	1:2	NR	crystalline penicillin 10	metaphysitis in all bones, VDRL 1:2, hepatomegaly	hepato splenomegaly
11	M	9/10	adequate (weight, CP and BMI) low height	1:4	NR	crystalline penicillin 10	mother treated inadequately, metaphysitis in all bones, VDRL 1:4	normal

Case	Gender	APGAR	CP/Height/ Weight/ BMI- at birth	VDRL at		Treatment days	Diagnostic criteria for CS	Doppler ultrasound of the upper abdomen
				Birth	First appoint-ment			
12	F	7/9	adequate	1:1	NR	crystalline penicillin1 procaine 9	mother treated inadequately, metaphysitis in all bones, VDRL 1:1	normal
13	F	8/9	adequate	1:2	NR	crystalline penicillin 10	mother treated inadequately, metaphysitis in all bones, VDRL 1:2	normal
14	M	9/10	adequate	1:8	NR	procaine penicillin 10	metaphysitis in all bones, VDRL 1:8	normal
15	F	9/9	microcephaly, low weight and height for the age, adequate BMI	1:8	1:1	procaine penicillin 10	low weight, VDRL 1:8	normal

Source: Elaborated by the authors.

Regarding the follow-up of these children, the age at first consultation was between 15 days and five months. Of these, two had low weight and low height for their age, one with thinness, two with risks for being overweight and one was overweight. Three had developmental alertness, twelve radiographs with metaphyseal, two with neurosyphilis, normal ear testing, and fundoscopy, when performed, was normal (Table 3). The two children who had neurosyphilis the mothers had fewer than six consultations, were treated in the puerperium, and had only one examination during prenatal care. The severity of congenital syphilis is directly related to the non-treatment of the pregnant woman during pregnancy (HOLLIER et al., 2001). Complete prenatal care is essential, and it is important to have public policies that encourage and offer adequate conditions for its realization.

The tests to evaluate liver function were altered in nine children. We observed: thrombocytopenia (1); increased alkaline phosphatase (4); cholestasis (3); increased aminotransferases (1); increased gamma GT (3), and the association of two altered tests in five children (Table 3). When more than one test is altered, the greater the probability of diagnosing liver diseases (FAWAZ et al., 2017). Those most related to liver changes in CS are serum aminotransferases, bilirubin, alkaline phosphatase,

and prothrombin time. The sensitivity and specificity of tests for the diagnosis of liver disease can be increased when used together.

According to Ogawa and collaborators (2020) and Long and collaborators (1984) the pathogenesis of cholestasis in CS is not known, however, toxic reactions to treponemal lysis products have been speculated as a cause of cholestasis. Feldman and Mack (2015) reported that liver function tests have little value in the differential diagnosis of cholestasis in newborns and infants requiring further complementary tests.

The prenatal tests of the 15 pregnant women did not show positive IgM, which configures an acute illness, for toxoplasmosis, cytomegalovirus, and rubella. Also the screening for HIV, hepatitis B and C, when performed, were negative. These exams are extremely relevant when researching hepatitis because liver serology tests can be altered in these other diseases that can pass from the mother to the fetus. The non-performance and/or non-annotation in the pregnant woman's card of these tests makes the differential diagnosis of neonatal cholestasis difficult. The fifteen babies had normal heel prick tests, which are also part of the differential diagnosis of neonatal hepatitis.

Growth was evaluated using the curves in the child's card, the one born with low weight and microcephaly also had altered neurodevelopment. In DENVER II test, 3 newborns showed alert diagnosis for neurodevelopment, the two with diagnosis of neurosyphilis and the one born with microcephaly. Verghese and collaborators (2018) found that children born to mothers with positive serology for syphilis in pregnancy, whether or not diagnosed with CS, have a high degree of neurodevelopmental impairment and should be referred early for necessary rehabilitation. Therefore, when the child presents one or more delayed milestones for his/her age, he/she should be oriented to perform physiotherapy directed to that delay and return after thirty days for a new evaluation.

Table 4 – Description of the first visit in the series of 15 cases of congenital syphilis evaluated for syphilitic hepatitis in a maternity in northeast Brazil from December 2021 to May 2022

Case	CP/HEIGHT/ WEIGHT/BMI	DNPM	VDRL CSF	Little ear test	Fundoscopy	Long bone radiography	Hepatic serology tests	Heel prick test
1	adequate	normal	NR	normal	normal	metaphysitis in all bones	Thrombocytopenia	normal
2	weight/CP/ height adequate BMI overweight risk	alarming	reagent	normal	not performed	metaphysitis in all bones	cholestasis/ increased GT gamma	normal
3	adequate	normal	NR		not performed	metaphysitis in all bones	Increased ASL/ALT	normal

Case	CP/HEIGHT/ WEIGHT/BMI	DNPM	VDRL CSF	Little ear test	Fundoscopy	Long bone radiography	Hepatic serology tests	Heel prick test
4	adequate	normal	NR	normal	not performed	metaphysitis in all bones	normal	normal
5	CP/BMI adequate. Weight/Height low	normal	NR		not performed	metaphysitis in all bones	Thrombocytopenia/increased GT gamma	normal
6	adequate	alarming	reagent	normal	normal	normal	normal	normal
7	adequate	normal	NR		not performed	normal	increased alkaline phosphatase	normal
8	adequate	normal	NR	normal	not performed	metaphysitis in all bones	colestase, increased alkaline phosphatase	normal
9	Weight/CP/ Height adequate. BMI--overweight risk	normal	NR	normal	not performed	metaphysitis in all bones	increased alkaline phosphatase	normal
10	adequate	normal	NR	normal	not performed	metaphysitis in all bones	normal	normal
11	Weight/CP/ Height adequate BMI overweight risk	normal	NR	normal	normal	metaphysitis in all bones	normal	normal
12	adequate	normal	NR		not performed	metaphysitis in all bones	normal	normal

Case	CP/HEIGHT/ WEIGHT/BMI	DNPM	VDRL CSF	Little ear test	Fundoscopy	Long bone radiography	Hepatic serology tests	Heel prick test
13	Weight/ CP/Height adequate. BMI-thinness	normal	NR	normal	normal	metaphysitis in all bones	normal	normal
14	adequate	normal	NR	normal	normal	metaphysitis in all bones	cholestasis/ increased GT gamma	normal
15	CP/BMI adequate. Low weight/ height	alarming	NR	normal	normal	normal	increased alkaline phosphatase	normal

Source: Elaborated by the authors.

Due to the increasing number of cases of CS in the world, knowledge of the effects of cholestasis and its relationship to liver function in children with syphilis is becoming increasingly relevant. More research is needed to establish protocols that identify severe cases early and determine effective treatments for these patients diagnosed with congenital syphilitic hepatitis (OGAWA et al., 2020). According to Brazil (2022b), if the penicillin dose is delayed by one day, the treatment must be restarted and the VDRL must be repeated monthly in pregnant women with syphilis because 14% of them may present therapeutic failure, in addition to the risk of reinfection.

The prenatal care for pregnant women with syphilis and whose children had congenital syphilis, evaluated in this study, is far below what is recommended. Although the number of consultations is adequate, it is necessary to improve the quality by performing all the recommended tests in the first and third trimester in order to evaluate the results with safe interventions, based on scientific evidence, as early as possible. The health team needs to be trained in the management of syphilis as well as other congenital diseases.

This research has limitations in that it does not present inferential statistics due to the number of records that could be included. Research is needed to assess the real incidence of congenital syphilitic hepatitis as well as long-term follow-up to analyze the complications that these liver changes may cause in syphilitic children.

4 CONCLUSION

In the present research, the children with syphilis were born with good vitality, had adequate treatment, were evaluated for liver changes, and prenatal care was below what is recommended. Nine had abnormal liver biochemical tests and the association of two abnormal tests was present in five children. Furthermore, two had ultrasonographic alterations, but none had altered Doppler, nor heterogeneous liver texture, and neurodevelopment was altered in the two children who had neurosyphilis and the mothers were not treated during pregnancy, as well as in the one born with microcephaly.

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