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ORIGINAL ARTICLES

Congenital syphilis — preventable, yet increasing: 10-year data from a secondary hospital in Azores, Portugal

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ABSTRACT

Introduction: Congenital syphilis (CS), which resultss from vertical transmission of *Treponema pallidum*, presents a broad spectrum of clinical manifestations in neonates. It's effective control relies on early maternal diagnosis and treatment during pregnancy.

Materials and methods: We conducted a retrospective and descriptive study of CS cases in the Neonatal Intensive Care Unit (NICU) of Hospital do Divino Espírito Santo in Ponta Delgada, Azores, between 2013 and 2022. We reviewed the medical records of all discharged patients with CS, defined according to the 2021 Centers for Disease Control and Prevention guidelines. Demographic, clinical, and laboratory data on both mothers and newborns were collected.

Results: Twenty newborns with suspicion of CS were admitted to the NICU between 2013 and 2022. The incidence of CS was stable until 2020, with 0–2 cases per year. From 2020 onwards, there was an exponential increase in the number and severity of cases. Fifteen pregnancies were followed up exclusively in primary care, while four were monitored through outpatient appointments offered by the hospital's high-risk obstetrics service. Mothers were adequately treated in seven cases. Four newborns were born before 37 weeks of gestation, and two between 28 and 32 weeks of gestation. Four newborns presented with severe forms of CS, one of which died. The most common manifestation of CS was jaundice (11/55%); abnormal hepatic parameters were observed in 14/70% of the newborns. Bone involvement was seen in 4/20% newborns. All were treated with penicillin G (median of 14 days, 95% Confidence Interval [CI] 10-14), and CS was confirmed in nine cases (45%).

Discussion and conclusions: An increase in CS was observed from 2020 to 2022, with most pregnancies lacking proper referral or treatment, which is in line with international reports. Prompt diagnosis and appropriate treatment of the mothers can prevent this serious and potentially fatal disease in newborns.

Keywords: congenital syphilis; maternal-fetal infection; vertical infections transmission

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INTRODUCTION

Congenital syphilis (CS), which is caused by the bacterium *Treponema pallidum*, is a vertically transmitted infection responsible for a wide range of clinical manifestations in infants.[1,2] Up to two-thirds of these infants are asymptomatic, and symptomatic cases can be subtle or nonspecific, making it challenging to diagnose and to treat adequately.[1-3]

There are two different types of serologic tests to diagnose syphilis: nontreponemal tests (e.g., Veneral Disease Research Laboratory [VRDL] or Rapid Plasma Reagin [RPR]) and treponemal tests (e.g., *Treponema pallidum* Hemagglutination assay [TPHA], Fluorescent Treponemal Antibody Absorption Test [FTA-Abs], Enzyme immunoassay [EIA], or Immunoblot).[4,5]

Nontreponemal tests, used for syphilis screening, are quantitative and highly sensitive tests that yield results that correlate with disease activity, and thus are used to monitor treatment response, usually becoming negative after proper treatment.[4,6] Treponemal tests are used to confirm syphilis infection after a positive screening test, are highly specific and typically remain positive regardless of adequate treatment.[4,6] Two laboratory serologic tests (one treponemal and one nontreponemal test) are required to establish a presumptive diagnosis of syphilis.[4]

According to the Portuguese national guidelines, adequate routine serologic screening of syphilis during pregnancy involves at least one nontreponemal test (i.e., VDRL) in the first (before 13 weeks) and third (between 32–34 weeks) trimesters.[6,7] In the presence of a positive result, the diagnosis should be confirmed with a treponemal test (TPHA or FTA-Abs).[6]

The maternal syphilis treatment regimen varies according to the stage of infection. If the infection occurred less than one year before diagnosis, a single dose of intramuscular (IM) benzathine penicillin G 2.4 million international units (MIU) is considered to be adequate. However, if the syphilis infection was acquired over one year before diagnosis or has an unknown duration, adequate treatment will consist of a dose of IM benzathine penicillin G 2.4 MIU administered once a week for three consecutive weeks, with the last dose administered at least one month before delivery.[4,5,8] Furthermore, treatment of sexual partners is pivotal, as there is a risk of reinfection of properly treated pregnant women.[4,5,8]

All neonates born to mothers with syphilis should undergo nontreponemal testing and a thorough examination of CS.[2,5] Clinical manifestations of early CS, such as miscarriage, stillbirth, neonatal death, intrauterine growth restriction and prematurity, can be significantly reduced by adequate treatment of pregnant infected women.[2,5,8]

Among symptomatic live-born neonates, multisystemic manifestations include: hepatobiliary dysfunction like jaundice, cholestatic hepatitis, and hepatomegaly; hematological alterations such as anemia and thrombocytopenia; mucocutaneous lesions including *pemphigus syphiliticus*, maculopapular rash, and desquamation; neurosyphilis (in 60% of cases), presenting with seizures, ophthalmologic abnormalities, cranial nerve palsies or cerebral infarcts; skeletal lesions such as osteomyelitis and Parrot's pseudoparalysis; and nephrotic syndrome, syphilitic rhinitis, splenomegaly, and ascites.[1–3,5]

Neonates meeting the criteria for confirmed or highly probable CS should undergo evaluation for neurosyphilis and receive treatment with intravenous (IV) aqueous crystalline penicillin G (50,000 units/kg of body weight/dose) every 12 hours during the first seven days of life, and then every 8 hours after, for a total of 10 days (or 14 days, if there is involvement of the central nervous system) or IM procaine penicillin G (50,000 units/kg of body weight/dose) as a single daily dose for 10 days.[2,4,5,8]

Despite the widespread awareness of this disease and established knowledge of effective preventive measures, CS remains a significant cause of neonatal morbimortality worldwide.[1] In fact, the number of cases has increased steadily over the past decade in the U.S., with a tenfold rise in diagnosed cases between 2012 and 2022 and a current incidence of 1:1,300 live births.[2,9] In 2022 and 2023, the European Centre for Disease Prevention and Control (ECDC) reported 73 and 78 confirmed cases of CS, respectively.[12] In Portugal, the incidence of CS was 15.02/100,000 births in 2019, which are concerning numbers compared to those in the neighboring Spain, with 0.28/100,000 births, and more comparable to the reality in South Africa, with 15.6/100,000 births.[10] From 2019 to 2023, Portugal had a mean of 15.5 cases per 100,000 live births, which is substantially higher than the European average of 2.2 cases per 100,000 live births.

Furthermore, around 90% of cases of CS are preventable, with 42% of these pregnant women receiving delayed or no prenatal care, 31% not being treated adequately, and 14% not being tested in a timely manner, according to international data.[2,3,9] Early detection through prenatal screening, which is unconditionally recommended for all pregnant women, and treatment of maternal syphilis are crucial primary care efforts to prevent CS.[8]

We aimed to determine the trend of CS infections in our NICU and characterize the presentation and severity of these cases over the past ten years, which seemed to be increasing.

MATERIALS AND METHODS

This study was designed as a retrospective and descriptive analysis aimed at investigating the clinical characteristics and outcomes of neonates hospitalized with suspected CS in the NICU of Hospital do Divino Espírito Santo in Ponta Delgada from January 2013 through December 2022. Our hospital serves a population of approximately 144,000 inhabitants, with an average of 1,300 births annually. The NICU is equipped and staffed to provide specialized care for newborns born as early as at 26 weeks of gestation.

The study population was identified by reviewing the

discharge summaries of all newborns admitted to the NICU during the specified timeframe. CS cases were defined according to the 2021 Centers for Disease Control and Prevention (CDC) guidelines.[4] Anemia was defined according to the criteria proposed by Christensen *et al*.[11]

Demographics, clinical findings, syphilis serology, general laboratory, complementary studies, and prescribed treatment data were collected on mothers and newborns. For mothers, the information collected included age, pregnancy monitoring, pregnancy trimester at the time of diagnosis, nontreponemal serologic test results, and details regarding treatment. For newborns, sex, gestational age, birth weight, type of delivery, NICU length of stay, clinical, laboratory and radiologic findings as well as treatment received were collected.

Statistical analysis was conducted using SPSS version 27. Descriptive statistics were employed to summarize the mothers' and newborns' demographic and clinical characteristics. Continuous variables were presented as medians with quartiles and means with standard deviations, while categorical variables were expressed as frequencies and percentages.

RESULTS

During the study period, there were 1484 admission to the NICU and a total of 13 977 births.

Twenty newborns hospitalized in the NICU with suspected CS (0.14% of all births at the hospital) were included in our study group. CS was confirmed in nine newborns (45%), with six (30%) possibly having CS, and five (25%) less likely to have the disease.

The incidence of CS cases was stable until 2020, with 0–2 cases per year, but after 2020 there was an exponential increase in the number of cases in our hospital (**Figure 1**). In 2019 the incidence was 1,4 cases/1000 births whilst in 2022 it was 7 cases/1000 births. Furthermore, in 2022, nine cases of CS were reported, representing 7.2% of the admissions in our NICU.

The mothers of the newborns in our study had a median age of 27 years (IQ_{25-75}: 23.75–32). Pregnancy surveillance (**Table 1**) was carried out exclusively in the primary care setting in 15 cases, in a hospital high-risk service offered by Obstetrics department in four cases, and in a private Obstetrics practice in one, but only two of them had adequate supervision, as previously defined.

Eighteen women had a positive nontreponemal test in at least one trimester of pregnancy: seven in the first trimester, five in the second, and six in the third, including two cases of seroconversion. The remaining two mothers either had no recorded test or did not undergo testing.

Syphilis treatment during pregnancy was adequate in seven cases (in 7/35% of the cases we could not confirm adequate treatment of sexual partners or the possibility of reinfection), inadequate in three/15% (in two cases, treatment was performed less than 30 days before birth and in the other case, only one dose of penicillin was administered), and absent or undocumented in nine. After birth, the antibody titer (RPR/ VDRL) was 1:8 or higher in 15/75% of the mothers.

Out of the 20 CS patients in the sample (**Table 2**), 4/20% were born preterm (<37 weeks), 2/10% were very preterm (between 28 and 32 weeks), and 14/70% were full term babies. The majority (15/75%) presented an appropriate weight for the gestational age, four were small for the gestational age and one was large for the gestational age. All patients had positive nontreponemal serology (RPR/ VDRL), with median titers of 8 dilution (IQ_{25-75}: 2-16), and two of them showed a fourfold or greater titer at delivery than the mother.

Regarding clinical and laboratory findings (**Table 2**), four presented with severe forms of CS at birth, including very premature birth, sepsis with coagulopathy and meningitis, and one of these newborns died. None of the mothers of these symptomatic newborns had been treated.

The most common clinical signs were jaundice in 11/55% and mucocutaneous manifestations (maculopapular rash, desquamation lesions and *pemphigus syphiliticus*) in 3/20 patients (**Figure 2**). Hepatomegaly (3/15%), splenomegaly (2/10%), and ascites (1/5%) were also reported. In patients with radiological data (16/80%), bone involvement was seen in four/20% (**Figure 3**).

Complementary studies at diagnosis are presented in **Table 2**. Alterations in hepatic parameters were observed in 14/70% of the patients. Out of these 14 patients, five (36%) had cholestatic hepatitis and four (29%) had conjugated hyperbilirubinemia. Anemia (hemoglobin > 2 standard deviations (SD) below the mean for postnatal age) was present in 5/25% of patients, with a median hemoglobin value of 11.9 g/dL [IQR 9.7–12.9; mean SD 3,52]. Thrombocytopenia was observed in 4/20 (20%) newborns: one mild case, one moderate, and two severe, with platelet counts of 38,000 and 39,000/µL.

Lumbar puncture was performed in 13/65% patients; in two cases, the procedure was traumatic, resulting in blood-stained cerebrospinal fluid. The remaining newborns did not have clinical stability to undergo the procedure. In those with non-traumatic technique (11 patients), cerebrospinal fluid was altered in 4 (36%): two showed a high white blood cell count and reactive VDRL, and two had only a high white blood cell count.

None of our patients showed Parrot's pseudoparalysis, nephrotic syndrome or ophthalmologic alterations.

All surviving newborns were treated with IV aqueous crystalline penicillin G for 10–14 days (median: 14, 95% CI:10–14). Doses were age- and weight-adjusted and covered a potential involvement of the central nervous system, per the national guidelines. In more severe cases, the recommended antibiotic therapy was combined with gentamicin due to suspected or confirmed neonatal sepsis. Medium length of stay in the NICU was 15,8 days (SD 10,29).

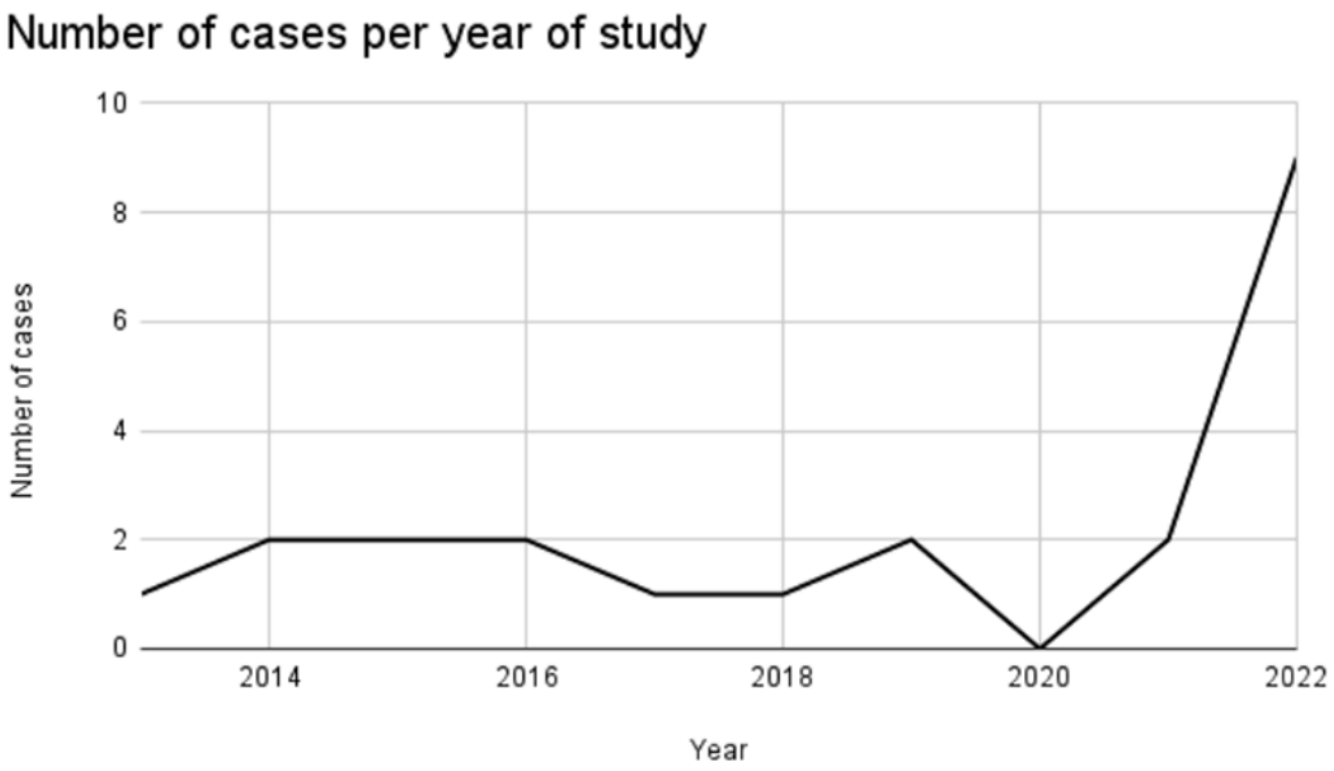


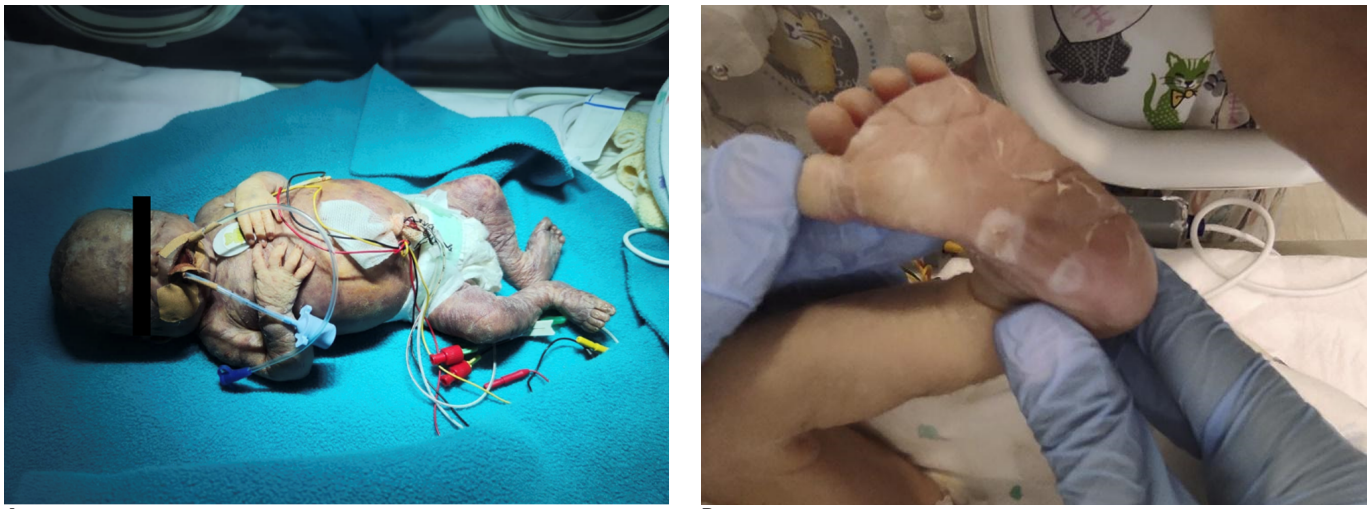
Figure 1 - Number of cases of CS at the NICU of Hospital do Divino Espírito Santo in Ponta Delgada per year of study

Table 1 - Demographic and clinical data on newborns with gestational congenital syphilis in our study population (N=20)

Gestational syphilis	**n**	**%**
Maternal age		
< 20	1	5
20-29	12	60
30-39	6	30
≥ 40	1	5
Non-treponemal test		
Positive	19	95
Non-reactive	0	0
No information	1	5
Adequacy of treatment		
Adequate	7	35
Inadequate	3	15
Not treated/ No information	10	50

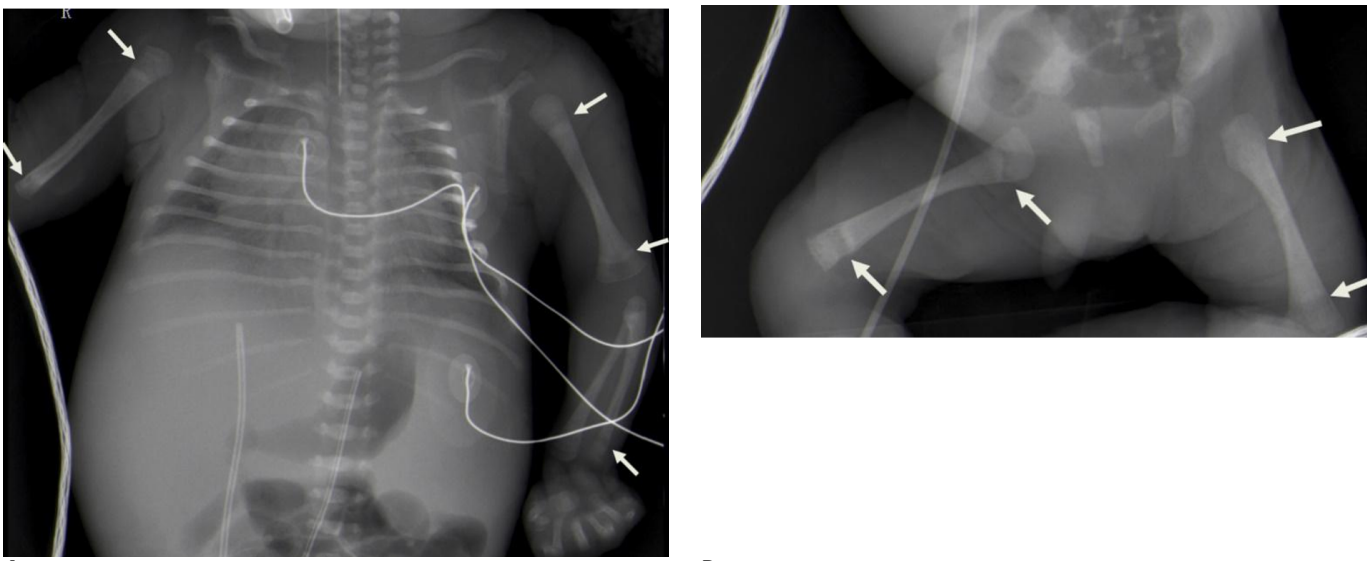
Table 2 – Clinical and laboratory data on newborns with congenital syphilis in our study population (N=20)

Congenital syphilis	n	%
Sex		
Female	10	50
Gestational age		
Very pre-term	2	10
Pre-term	4	20
Full-term	14	70
Type of delivery		
Eutocic	6	30
Ventouse	3	15
Cesarean	11	55
Birth weight		
Very low	2	10
Low	5	25
Adequate	12	60
Macrosomia	1	5
Clinical findings		
Jaundice	11	55
Mucocutaneous manifestations		
Maculopapular rash	3	15
Pemphigus syphiliticus	3	15
Hepatomegaly	4	20
Splenomegaly	2	10
Lymphadenopathies	1	5
Ascites	1	5
Bone involvement		
Pseudoparalysis	0	0
Bone irregularities	4	20
Meningitis	4	20
Other findings		
Septic shock	2	10
Pulmonary hypertension	1	5
Abstinence syndrome	2	10
Laboratory findings		
Anemia	5	25
Thrombocytopenia	4	20
Altered liver enzymes	14	70
Cholestatic hepatitis	5	25
High C-reactive protein (> 1 mg/dL)	6	30
Treatment		
Penicillin	16	80
Penicillin + gentamicin	3	15
Not treated	1	5
Diagnosis		
Confirmed CS	9	45
Possible CS	6	30
CS Less likely	5	25



A B

Figure 2 - Clinical manifestations of congenital syphilis. A: Severe form of CS; B: *Pemphigus syphiliticus*



A B

Figure 3 - Representative radiological images of the metaphyseal region of the long bones. A: humerus, ulna; B: femur

DISCUSSION AND CONCLUSIONS

The rising number of CS cases has become a global concern, prompting numerous studies focused on reducing this preventable disease.[13] The primary issue identified was limited access to prevention, healthcare, and health literacy—challenges that worsened following the COVID-19 pandemic. Raising awareness among clinicians about the prevalence of CS in high-income countries is essential to improving diagnosis and prevention efforts.

The incidence of CS in Portugal is much higher than in other European countries, with a substantial increase in cases in the past years. This increase is largely driven by a surge in syphilis infections among women of childbearing age, particularly young mothers and in marginalized groups, such as the remote populations in the São Miguel Island.[14]

In Portugal, the National Program for Surveillance of Low-Risk Pregnancy includes VDRL testing in the first and third trimesters; pregnant women testing positive are referred to a hospital obstetrician-gynecologist (OB-GYN) for treatment and follow-up.[7] Our review found that while most mothers received a timely diagnosis, treatment and referral practices were often inadequate. This concerning gap is currently under review and may be attributed to the high demand for hospital

services, a limited number of OB-GYN specialists available at the hospital, and challenging working conditions.

Of the 20 newborns included in our study, nearly a quarter presented with severe infection associated with potential long-term morbidity such as developmental delay and bone deformities affecting growth, an outcome that is largely preventable and further underscores the urgency of addressing this public health issue. Moreover, even postnatally, not all mothers and their sexual partners received adequate treatment, likely due to low health literacy or limited access to healthcare services. This shows that it is important that syphilis treatment is performed in the hospital setting to allow adequate follow-up.

Although CS can be a serious condition, the majority of newborns in our study received appropriate treatment and were discharged with minimal sequelae. In the more severe cases, differentiating CS from neonatal sepsis was challenging due to overlapping clinical manifestations, elevated inflammatory markers, and clinical deterioration. In such instances, gentamicin was added to the treatment regimen to mitigate the risk of complications. Additionally, a 14-day course of penicillin was administered in cases where cerebrospinal fluid analysis was positive for the bacterium or not performed.

This study has several limitations inherent to its retrospective design. It relied on the accuracy and completeness of medical records, which may have led to underreporting or misclassification of maternal history, clinical findings or treatment adequacy. The relatively small sample size and single-center setting may have limited the generalizability of our findings. However, since this is the only hospital with obstetric and neonatal intensive care services on the island, and because all pregnant women who had not undergone third-trimester serologic testing were screened upon admission for delivery, most cases of CS were likely identified. Still, some less severe or asymptomatic cases may have gone undetected if third-trimester screening had already been performed and the newborn did not require NICU admission. Additionally, the lack of long-term follow-up and incomplete data on postnatal maternal and partner treatment limited our ability to assess long-term outcomes and the effectiveness of secondary prevention. Lastly, clinical practices and documentation may have varied over the ten-year period, potentially introducing classification inconsistencies.

Early detection and timely notification to public health authorities remain critical for the effective prevention and management of CS in newborns. Educational campaigns focusing on maternal and sexual health, along with a more efficient hospital referral system, could significantly contribute to reducing the incidence of this preventable disease.

AUTHORSHIP

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ENGLISH ABBREVIATIONS

CS: Congenital syphilis
NICU: Neonatal Intensive Care Unit
CDC: Centers for Disease Control and Prevention
VDRL: Veneral Disease Research Laboratory
RPR: Rapid Plasma Reagin
TPHA: *Treponema pallidum* Hemagglutination assay
FTA-Abs: Fluorescent Treponemal Antibody Absorption Test
EIA: Enzyme immunoassay
IV: Intravenous
IM: intramuscular
MIU: million international units
CI: Confidence interval
SD: Standard deviation

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