

CLINICAL CASE REPORTS

Prenatal syphilis screening — can we always trust the result?

Caroline dos Reis Lopes¹ , Ana Pereira Lemos² , Beatriz Costa¹ , Paula Kjölleström³ , Vitória Matos⁴ , Catarina Gouveia² 

ABSTRACT

Introduction: Congenital syphilis (CS) can be acquired by the fetus during pregnancy or delivery. When asymptomatic at birth, newborns usually present the first clinical signs by the age of three months.

Case report: We report the case of a three-month old infant presenting with severe anemia, hepatosplenomegaly, and vesicular rash with shedding palmoplantar erythema. The pregnancy was unremarkable. The blood work revealed severe non-immune hemolytic anemia, thrombocytopenia, and hepatitis. The initial rapid plasma reagin (RPR) screening for syphilis was negative. However, due to a high index of suspicion, a second RPR test was performed, with a positive result, which may be explained by the prozone phenomenon.

Conclusion: This case shows that a negative prenatal syphilis test does not rule out a diagnosis of CS. In the presence of compatible clinical findings and a high index of suspicion, extensive evaluation should be considered. We highlight the importance of serum dilution to overcome the prozone phenomenon.

Keywords: congenital syphilis; infant; Jarisch–Herxheimer reaction; prozone phenomenon

1. General Pediatrics Department, Hospital Dona Estefânia, Unidade Local de Saúde de São José, Lisbon, Portugal. reislopescaroline@hotmail.com; m.costabeatriz@gmail.com
2. Pediatric Infectious Diseases Department, Hospital Dona Estefânia, Unidade Local de Saúde de São José, Lisbon, Portugal. ana1645@gmail.com; cmfgouveia@gmail.com; m.costabeatriz@gmail.com
3. Hematology Unit, Hospital Dona Estefânia, Unidade Local de Saúde de São José, Lisbon, Portugal. p.kjollerstrom@gmail.com
4. Immunology Department, Hospital São José, Unidade Local de Saúde de São José, Lisbon, Portugal. vitoria.matos@ulssjose.min-saude.pt

INTRODUCTION

Congenital syphilis (CS) is caused by *Treponema pallidum*, the spirochete that causes syphilis, and can be acquired by the fetus during pregnancy or delivery, when pregnant women are not properly diagnosed or treated.⁽¹⁾

The rate of CS in the United States of America has been increasing since 2012.^(1,2) In Europe, despite previous small numbers of reported cases and effective national prenatal screening programs, the rate increased between 2010 and 2017, remaining stable since 2018.⁽³⁾

In Portugal, however, there was a threefold increase in reported cases from 2017 to 2019.⁽³⁾ The clinical guidelines for screening low-risk pregnancies in Portugal recommend that a venereal disease research laboratory (VDRL) test be carried out in the 1st and 3rd trimesters.⁽⁴⁾

When asymptomatic at birth (up to two-thirds of cases), most children develop symptoms within the first three months of life, but they may occur as late as two years of age.^(2,5,6)

CASE REPORT

A three-month old female infant was referred to our hospital for severe anemia. The pregnancy was monitored from the 14th week and was unremarkable. The mother's serological

tests for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and rapid plasma reagin (RPR) were negative in the 2nd and 3rd trimesters, and she was immune to rubella and toxoplasmosis. Group B *Streptococcus* screening was negative. The 3rd trimester ultrasound showed polyhydramnios (non-quantified). The baby girl was born at 39 weeks. There were no reported complications during the neonatal period, and she was breastfed from birth, with adequate growth and weight progression, and without any developmental concerns. The family history was unremarkable, namely regarding hematologic, neurologic, cardiac or genetic diseases.

On admission, she was pale with no jaundice, presented a clear nasal discharge, a systolic murmur, and distended abdomen with hepatomegaly (5 cm) and splenomegaly (4 cm). A truncal vesicular rash with shedding palmoplantar erythema was also noted; this had been present for two weeks before admission, and was not previously evaluated (**Figure 1**). The mother denied prior history of fever, jaundice, bleeding, failure to thrive, or lethargy.

Blood tests revealed severe non-immune hemolytic anemia mild thrombocytopenia, hepatitis, mildly elevated C-reactive protein (CRP), and normal renal function (**Table 1**). The evaluation of peripheral blood morphology revealed schistocytes, few elliptocytes, dacrocytes, micro-spherocytes, and target cells.

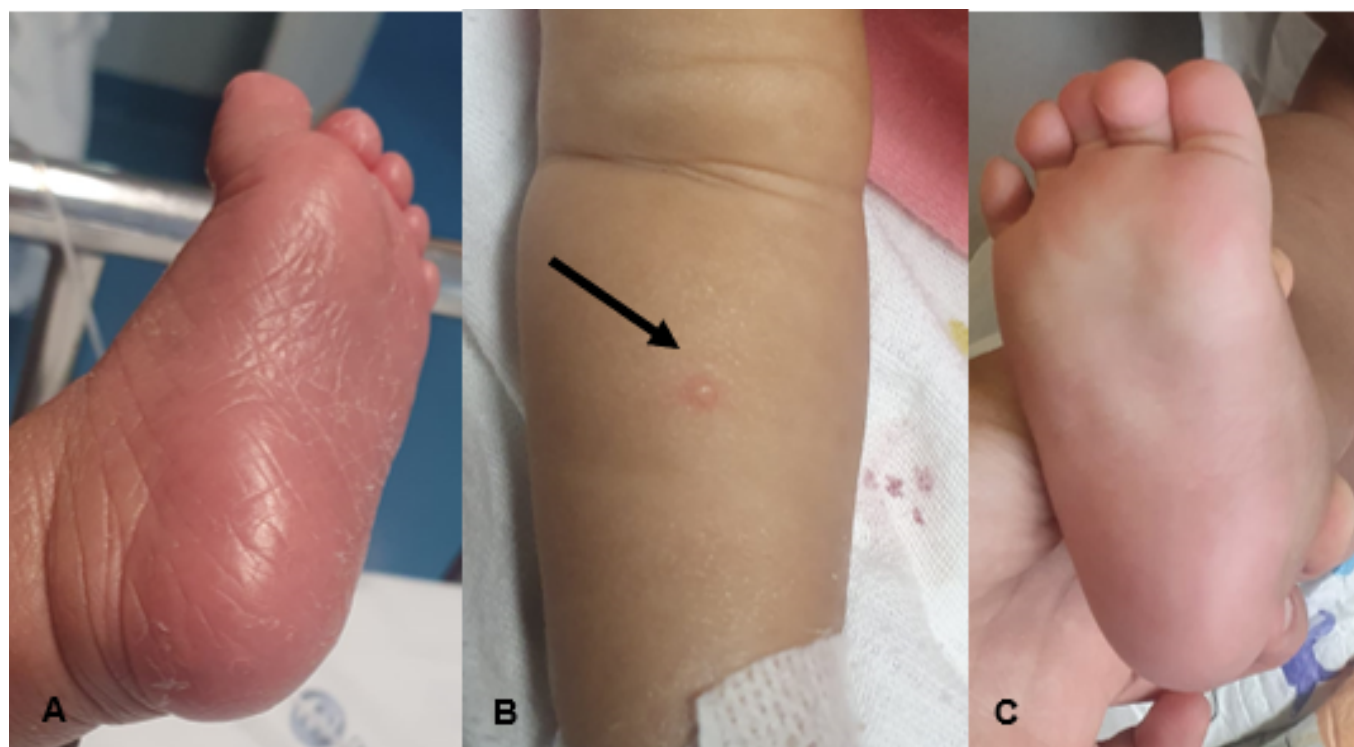


Figure 1

A - shedding palmoplantar erythema on admission

B - vesicular rash on admission

C - minimal erythema of the soles after treatment

Table 1 – Blood work on admission

Blood test	Result	Normal range (3 months)
C-reactive protein	23 mg/L	< 5 mg/L
Coombs	Negative	-
Hematology panel		
Haptoglobin	116 mg/dL	30 - 200 mg/dL
Hemoglobin	4.4 g/dL	9.5 - 13.5 g/L
Mean corpuscular hemoglobin concentration	32.6 g/L	30.0 – 36.0 g/L
Mean corpuscular volume	92 fL	74.0 – 108.0 fL
Platelets	103 x10 ³	200 – 550 x10 ³
Reticulocytes	11%	0.5 – 2.5 %
Metabolic panel		
Alanine transaminase	20 U/L	5 – 33 U/L
Alkaline phosphatase	632 U/L	134 – 518 U/L
Aspartate aminotransferase	95 U/L	20 – 67 U/L
Creatinine	0.58 mg/dL	0.1 – 0.36 mg/dL
Gamma-glutamyl transferase	210 U/L	8.0 – 127 U/L
Glucose-6-phosphate dehydrogenase	23.1 U/g Hgb	7.0 – 20.4 U/g Hgb
Lactate dehydrogenase	508 U/L	163 – 452 U/L
Total bilirubin	0.67 mg/dL	0.20 – 1.20 mg/dL
Urea	7 mg/dL	2.8 – 23.0 mg/dL

Hemoglobin electrophoresis did not detect abnormal fractions, and the complement and ADAMTS 13 studies were normal. An abdominal ultrasound confirmed homogeneous hepatosplenomegaly (7 cm), without ascites or biliary ectasia. The chest X-ray was normal, and the echocardiogram revealed a slight right ventricular dilation with a patent foramen ovale, with left-to-right shunt. A cranial ultrasound revealed bilateral lenticulostriate vasculopathy and grade I subependymal hemorrhage. The patient received a packed red blood cell transfusion, resulting in an adequate post-transfusion hemoglobin level of 8.7 g/dL.

Screening for infectious diseases was performed to investigate the causes of the rash, hepatosplenomegaly, severe non-immune hemolytic anemia, thrombocytopenia, and hepatitis. Syphilis screening tests revealed a non-treponemal positive RPR titer of 1:4; however, due to a high index of suspicion, a second test was performed, with a result of 1:1024. At that time, the results on day two from the referring hospital revealed a titer of 1:512 for the infant. The anti-treponemal IgM antibody was positive, and the *Treponema pallidum* hemagglutination test (TPHA) was reactive, supporting the diagnosis of CS.

The evaluation of the cerebrospinal fluid (CSF) was normal (3 white blood cells, rare red blood cells, glucose 45 mg/dL, protein 17 mg/dL, and negative VDRL essay). The polymerase chain reaction for *Treponema pallidum* was negative on nasal secretions, blood, and CSF. Blood, urine, and CSF cultures were negative, and the remaining screening tests excluded toxoplasmosis, rubella, herpes, and infections with cytomegalovirus, Epstein-Barr virus, parvovirus, and HIV, HBV, and HCV. Long bone radiographs revealed bilateral diaphyseal tibial periostitis with painless mobilization (**Figure 2**).

Chest radiography, liver function tests, abdominal ultrasound, ophthalmologic examination, neuroimaging, and auditory brainstem response evaluation were performed, with normal results.

The patient received crystalline penicillin G from day two of admission (50.000 U/kg intravenously, every six hours for ten days). Six hours after the first dose, an isolated fever spike of 38.1°C occurred. CRP levels continued to increase to 66.5 mg/L until 24 hours after the start of treatment, accompanied with high procalcitonin levels (25.59 ng/mL). After confirmation of the diagnosis of CS, the mother, who had had a negative result on prenatal screening, tested

positive, with a RPR of 1:8 and a reactive TPHA, and received a single dose of intramuscular benzathine penicillin G (2.4 million units for early latent syphilis). Screening tests for other sexually transmitted infections were negative. The father was referred to his family physician for screening and treatment.

After ten days of antimicrobial treatment, there was significant improvement of the rash, hepatosplenomegaly, and anemia, and the patient was discharged. A follow-up appointment four months after the diagnosis showed complete resolution of the rash and nasal discharge, minimal erythema of the soles (**Figure 1**), and adequate growth and psychomotor development. There was a decrease in VDRL titers (1:1024 to 1:64), supporting the adequacy of the treatment received. The cranial ultrasound was repeated and was normal. The patient was then lost to follow-up and referred to child protection services.

DISCUSSION

This case deserves attention, because it provides several important lessons for clinicians. First of all, the mother's screening in the 3rd trimester was negative. Based on this result, we could have ruled out CS. However, the clinical presentation was strongly suggestive of CS. As the infection was acquired late in pregnancy, the newborn seemed to be healthy when discharged from the maternity ward, but developed severe and fully symptomatic CS during the first months of life.

Another very important finding that needs to be highlighted, and never ignored, is the prozone phenomenon (PP). PP occurs when an excess of antibodies interferes with the formation of the antigen-antibody lattice, which is necessary to visualize positive flocculation in a laboratory test. If serum dilution is not performed, the diagnosis will be missed.⁽⁷⁾ This explains the discordant non-treponemal positive RPR test from the referring hospital (1:512) and our institution (1:4). Therefore, clinicians should always notify the laboratory of the suspected diagnosis.

As treponemal tests become positive before nontreponemal tests, some clinical laboratories are using reverse sequence screening for syphilis.^(1,8) Following this approach, a screening test with a treponemal test (treponemal enzyme immunoassay or chemiluminescence immunoassay) is used and, if positive, a quantitative nontreponemal test is performed to confirm a recent infection.^(1,7,8) If negative, a second treponemal test (preferably TPHA) is performed in the same specimen, because it may reflect early disease or a false positive on the initial treponemal test.^(1,7,8)

The third lesson is the presence of a Jarisch–Herxheimer reaction (JHR), which is usually observed in adults. Within 24 hours of initiation of penicillin therapy, some infants may develop a JHR, an acute inflammatory response likely due to rapid killing spirochetes and release of endotoxins, lipopolysaccharides, cytokines, and prostaglandins. It is characterized by fever, tachypnea, tachycardia, hypotension,

worsening cutaneous lesions, or even death.^(1,6) Our patient had one isolated episode of low-grade fever and rash six hours after initiating penicillin, which we attributed to a JHR.

Our patient had a high baseline CRP level and presented a peak after treatment with penicillin, which could be explained by the increased inflammatory response associated with phagocytosis of spirochetes.⁽⁹⁾ Procalcitonin was also markedly elevated. We hypothesize that the cytokine inflammatory response to syphilis triggered this massive procalcitonin production.

In this case, the missed appointments did not allow us to maintain the planned follow-up. However, three months after treatment, VDRL titers were more than four times lower than initially diagnosed, which is within the expected range, and there was marked clinical improvement. Developmental follow-up, as well as routine ear and eye examinations, should also be performed to rule out late hearing loss and retinitis, not yet possible to perform in this patient.

In conclusion, this case illustrates that a negative syphilis test during pregnancy does not rule out a diagnosis of CS. Blood tests for syphilis performed in the 3rd trimester and repeated at delivery should be considered in high-prevalence settings.^(6,8) Additionally, according to local epidemiological data, reverse screening should be considered to potentially avoid misdiagnosis. In our case, due to the PP, the CS diagnosis could have been missed. -

AUTHORSHIP

Caroline dos Reis Lopes - Writing – original draft; Writing – review & editing

Ana Pereira Lemos - Writing – review & editing; Validation

Beatriz Costa - Writing – review & editing

Paula Kjällerström - Writing – review & editing

Vitória Matos - Writing – review & editing

Catarina Gouveia - Writing – review & editing; Validation; Supervision

REFERENCES

1. Cooper JM, Sánchez PJ. Congenital syphilis. *Semin Perinatol*. 2018 Apr;42(3):176-184. doi: <https://doi.org/10.1053/j.semperi.2018.02.005>. Epub 2018 Apr 5. PMID: 29627075.
2. Rowe CR, Newberry DM, Jnah AJ. Congenital Syphilis. *Advances in Neonatal Care*. 2018;18(6):438–445.
3. European Centre for Disease Prevention and Control. Congenital syphilis. In: ECDC. Annual epidemiological report for 2019. Stockholm: ECDC; 2022.
4. Direção-Geral da Saúde. Programa Nacional para Vigilância da Gravidez de Baixo Risco [serial online]. September 2016. www.dgs.pt.
5. Keuning MW, Kamp GA, Schonenberg-Meinema D,

- Dorigo-Zetsma JW, van Zuiden JM, Pajkrt D. Congenital syphilis, the great imitator-case report and review. *Lancet Infect Dis*. 2020 Jul;20(7):e173-e179. doi: [https://doi.org/10.1016/S1473-3099\(20\)30268-1](https://doi.org/10.1016/S1473-3099(20)30268-1). Epub 2020 Jun 2. PMID: 32502432.
6. Rac MWF, Stafford IA, Eppes CS. Congenital syphilis: A contemporary update on an ancient disease. *Prenat Diagn*. 2020 Dec;40(13):1703-1714. doi: <https://doi.org/10.1002/pd.5728>. Epub 2020 Jul 20. PMID: 32362058.
 7. Catueno S, Tsou PY, Wang YH, Becker E, Fergie J. Congenital Syphilis and the Prozone Phenomenon: Case Report. *Pediatr Infect Dis J*. 2022 Jun 1;41(6):e268-e270. doi: <https://doi.org/10.1097/INF.0000000000003522>. Epub 2022 May 6. PMID: 35446812.
 8. American Academy of Pediatrics. Committee on Infectious Diseases, Kimberlin DW, Barnett ED, et al. Red book : 2021-2024 report of the Committee on Infectious Diseases. In: *American Academy of Pediatrics*; 2021:729–744.
 9. Butler T. The Jarisch-Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis. *Am J Trop Med Hyg*. 2017 Jan 11;96(1):46-52. doi: <https://doi.org/10.4269/ajtmh.16-0434>. Epub 2016 Oct 24. PMID: 28077740; PMCID: PMC5239707.

CORRESPONDENCE TO

Caroline dos Reis Lopes
Hospital Dona Estefânia
Unidade Local de Saúde de São José
Rua Jacinta Marto 8ª, 1169-045 Lisbon
Email: reislopescaroline@hotmail.com

Received for publication: 27.06.2024
Accepted in revised form: 05.03.2025