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Diagnosis of congenital syphilis in the newborn: a literature review and a case report

Diagnosticiranje kongenitalnega sifilisa pri novorojenčku: pregled literature in prikaz primera

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Abstract

Syphilis is a chronic systemic infection caused by a spirochaete *T. pallidum*. The diagnostic method of choice is serological tests: treponemal-specific tests and nontreponemal tests. Untreated syphilis infection in pregnant women can also be transmitted to the foetus, which can cause possible long-term consequences. In Slovenia, screening for syphilis infection in pregnant women is mandatory at the first prenatal visit. Timely diagnosis and treatment during pregnancy may prevent the majority of transmissions of the infection to the foetus. The diagnosis of congenital syphilis is made by comparing serological tests in mother and child. Management of the newborn depends on the risk of having congenital syphilis. We present a clinical case of treating a pregnant woman with a positive pregnancy screening test and a newborn with suspected congenital syphilis.

Izvleček

Sifilis je kronična sistemska okužba, ki jo povzroča spiroheta *T. pallidum*. Metoda izbire za postavitev diagnoze so serološki testi, in sicer testi za treponemska in testi za netreponemska protitelesa. Nezdravljena okužba v času nosečnosti lahko povzroči bolezen tudi pri otroku z možnimi dolgotrajnimi posledicami zanj. V Sloveniji je presejalno testiranje nosečnic na sifilis ob prvem pregledu v nosečnosti obvezno. S pravočasno postavitvijo diagnoze in z zdravljenjem nosečnice lahko v veliki večini primerov preprečimo prenos okužbe na plod. Diagnozo kongenitalni sifilis postavimo s primerjavo seroloških preiskav pri materi in otroku. Zdravljenje je odvisno od tveganja za prisotnost kongenitalnega sifilisa pri otroku. Predstavljamo klinični primer obravnave nosečnice s pozitivnim presejalnim testom v nosečnosti ter obravnavo novorojenčka s sumom na kongenitalni sifilis.

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Ključne besede: nosečnost; Treponema pallidum; serološko testiranje; izid zdravljenja; prirojena okužba

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1 Introduction

1.1 Syphilis, pregnancy, and congenital syphilis

Syphilis is a chronic systemic infection caused by a spirochaete *Treponema pallidum* subsp. *pallidum*. It is transmitted horizontally, primarily by risky sexual contacts. However, the vertical transmission of the infection through the placenta from a pregnant woman with active syphilis to the fetus is also possible (1).

The disease is divided into early and late syphilis depending on the duration. Early syphilis includes primary, secondary, and early latent syphilis. The European Centre for Disease Prevention and Control (ECDC) defines early syphilis as syphilis acquired less than a year before treatment. Late syphilis includes late latent and tertiary syphilis (2).

Congenital syphilis is a disease acquired by the fetus during pregnancy. The transmission of syphilis to the fetus during pregnancy is possible at any stage of the mother's illness. The probability of transmission of the infection to the fetus in an untreated mother in the primary or secondary syphilis phase is 60–90%, in the stage of early latent syphilis up to 40%, and in the stage of late latent syphilis <10% (3). Most transmissions of the infection to the fetus occur late in pregnancy (mostly after the 28th week). Successful treatment of a pregnant woman with penicillin before this period usually effectively prevents congenital syphilis (2,3).

The clinical picture of congenital syphilis is diverse. It manifests either as an asymptomatic infection (in two-thirds of infected newborns), fetal growth restriction, prematurity, multiple organ failure, or fetal death in the most severe cases. In case a newborn does not show any clinical signs and symptoms of congenital syphilis immediately at birth, the clinical picture may appear in the first weeks, months, or years of life. Congenital syphilis is divided into early (appearance of symptoms less than two years after birth) and late (two years after birth and later) (3,4).

Congenital syphilis is still a common cause of fetal and early neonatal mortality globally, especially in developing countries. Since 2000, after a previous decline in the number of infections, an increase in the incidence of syphilis has been observed in the countries of the European Union and the United States as well, including an increase in syphilis in pregnancy and the appearance of a higher number of cases of congenital syphilis (5,6).

In Slovenia, the statutory preventive detection of syphilis infection is carried out in pregnant women at the first examination during pregnancy (7). According to the recorded data of the National Institute of Public Health, the last child with confirmed congenital syphilis in Slovenia was born in 1986. In the last three years, eight children were registered at the National Institute of Public Health and treated for suspected congenital syphilis (8).

1.2 Diagnostics

Syphilis is confirmed in the laboratory by direct methods, such as dark-field microscopy, immunohistochemical staining of formalin-fixed tissue samples, with detection of polyclonal antibodies against *T. pallidum*, and molecular methods. The latter are based on amplification of specific nucleotide sequences of treponemal DNA by polymerase chain reaction (PCR) in secretions from primary and secondary lesions in tissues or body fluids. In this article, we will focus on serological methods of proving infection with *T. pallidum*, which enable a probable diagnosis of syphilis (2,9). Figure 1 presents the treatment algorithm for suspected congenital syphilis in a newborn child (2).

1.2.1 Serological tests

With nontreponemal tests (NTT), such as the VDRL (Venereal Disease Research Laboratory) test or the RPR (Rapid Plasma Reagin) test, the patient's heterophilic IgG and IgM antibodies are detected against complex antigens consisting of cardiolipin, lecithin, and cholesterol. NTT seroconversion occurs 10–15 days after the appearance of chancre (about six weeks after infection). NTT titers correlate with disease activity and treatment success. In the case of treating a patient with early syphilis, the NTT titer should decrease by four times (by two titers) in 6–12 months. In that case the treatment is considered successful. In patients with higher initial titer values, the decrease in titer values is slighter. Often (but not always), when early syphilis is successfully treated, the antibodies disappear from the bloodstream. In late (latent) syphilis, the NTT serological response is often absent, so in the case of persistently positive NTT in low titer, further follow-up is not necessary. In the case of an untreated infection, the NTT titer reaches its peak between the first

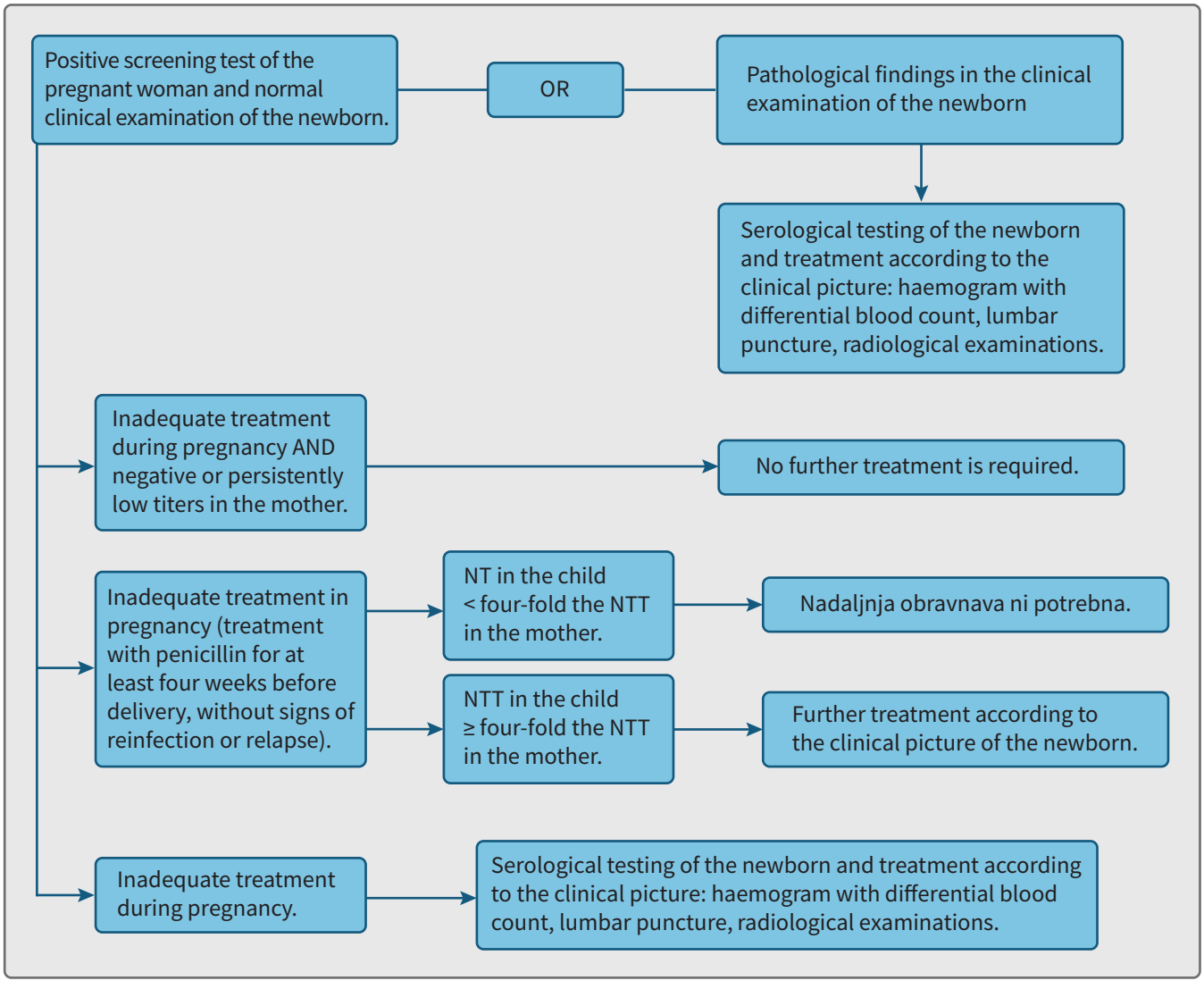

Figure 1: Algorithm for treatment of suspected congenital syphilis in a newborn. Adapted from Kwak J et al. (12).
Legend: NTT – nontreponemal test; TT – treponemal test.

and second year after infection. The titer remains positive even in the late stage of syphilis, as spontaneous seroreversion is extremely rare in tertiary syphilis (9-11).

With treponemal tests (TT), such as TPHA test (*T. pallidum* Haemagglutination Test), TPPA test (*T. pallidum* Passive Particle Agglutination Test), FTA-ABS test (Fluorescent Treponemal Antibody Absorption Test), EIA test (Treponemal Enzyme Immunoassay), CIA test (Chemiluminescence Immunoassay), or LIA test (Line Immuno Assay, IgG immunoblot Test), we determine the patient's IgG and/or IgM antibodies against treponemal native or recombinant antigens. Usually, TTs are positive as early as one to two weeks after the appearance of clinical signs of infection, and the tests that determine treponemal IgM antibodies as early as three weeks after infection. Except for congenital syphilis, the TT titer is non-diagnostic and should not be used to assess disease activity and monitor treatment. Most patients have the antibodies for life, regardless of whether the disease has been treated or not (2,9,12).

1.2.2 Screening tests

People with suspected syphilis are screened using TT (the reverse algorithm) or NTT (the traditional algorithm) or a combination of both. In most well-equipped European laboratories, automated TT is used to screen asymptomatic groups such as blood donors, showing both patients with previously treated syphilis and patients with untreated syphilis. TT screening is more sensitive than NTT screening for detecting very early syphilis. Traditional NTT screening, however, only detects

Table 1: American guidelines for the management of newborns with suspected congenital syphilis. Adapted from Kwak J et al. (12).

Treatment criteria	Recommended treatment regimen
A child with proven or highly probable diagnosis of congenital syphilis, including: • characteristic clinical, laboratory, or radiographic signs, • serum quantitative nontreponemal titers ≥ 4-fold the maternal titer, • evidence of *T. pallidum* by microscopy.	aqueous crystalline penicillin G IV: 10 days, procaine penicillin G IM: 10 days.
Children with a normal clinical examination and an NTT titer less than four-fold higher than the mother's in case of inadequate treatment of the mother.	aqueous crystalline penicillin G IV: 10 days, procaine penicillin G IM: 10 days, benzathinepenicillin G IM: single dose.
Children with a normal clinical examination and an NTT titer less than four-fold higher than the mother's, in case of adequate treatment of the mother.	benzathine penicillin G IM: single dose.
Children with a normal clinical examination and an NTT titer less than four-fold higher than the mother's, in the case of adequate maternal treatment and seronegative status of the mother at delivery.	no treatment is required.

Legend: NTT – nontreponemal test; TT – treponemal test.

persons with active syphilis. The combination of TT and NTT is suitable for screening people with very early disease, e.g. patients with recent syphilitic ulcers or cases of contacts with persons with syphilis, because in some cases NTT is reactive before TT. A positive screening TT is confirmed with an NTT and vice versa, a positive NTT is confirmed with a TT (2).

At the Institute of Microbiology and Immunology, the Faculty of Medicine at the University of Ljubljana, the TPPA and RPR tests simultaneously or the automated TT CIA test is performed to screen patients with suspected syphilis in the blood (9).

1.2.3 Treatment during pregnancy

According to European guidelines, the first-line treatment for early syphilis (disease duration less than one year) in pregnancy is a single dose of benzylpenicillin G at a dose of 2.4 million IU intramuscularly. Treatment of late latent syphilis (disease duration of more than one year or unknown duration since infection) is the same as in the general population: three doses of benzylpenicillin G at a dose of 2.4 million IU intramuscularly at an interval of one week. In the case of penicillin allergy, desensitization is required (2).

Treatment during pregnancy is not successful in case of treatment with a non-penicillin antibiotic, if the pregnant woman was treated less than four weeks before delivery, in case of inadequate response to treatment (≤ four-fold decline in NTT titer) or evidence of reinfection or relapse of infection (≥ four-fold increase in the NTT titer), and in case the treatment is not documented (2,12).

1.2.4 Congenital syphilis

Confirmed congenital infection

Congenital syphilis is confirmed by the identification of *T. pallidum* using the aforementioned direct methods using the placenta or autopsy material, exudate from suspicious lesions or body fluids (e.g. nasal discharge) (2,12).

Presumed congenital infection

The diagnosis of presumed congenital infection is made with the help of serological tests. A newborn likely has congenital syphilis if a positive TT at birth is combined with one or more of the following criteria:

- The characteristic clinical picture of congenital syphilis (persistent rhinitis, osteitis, periostitis, osteochondritis, ascites, skin and mucosal lesions, hepatitis, hepatosplenomegaly, glomerulonephritis, haemolytic anaemia);
- Radiological abnormalities of long bones characteristic of congenital syphilis;
- Positive NTT in cerebrospinal fluid;
- At least four-fold higher TT titer in the blood than the mother has at birth;
- At least four-fold higher NTT titer in the blood than the mother has at birth;
- At least a four-fold increase in NTT titer within three months after birth;
- Evidence of IgM antibodies against *T. pallidum* in a child;
- A newly diagnosed infection of the mother that was not adequately treated (2).

Table 2: Showing the value of serological tests for syphilis in mother and child.

Date	Timeline	Person	RPR (agglutination)	TPPA (agglutination)	Syphilis EIA IgM test	Syphilis LIA IgG Immunoblot test	Syphilis CIA
27. 8. 2020	Screening	Mother	Reactive (1:2)	Positive (1:640)	Negative	Positive	Reactive
14. 10. 2020	First examination by an infectious disease specialist – initiation of treatment	Mother	Non-reactive	Positive (1:640)	/	/	/
28. 10. 2020	Check-up	Mother	Non-reactive	Positive (1:1280)	/	/	/
31. 1. 2021	The birth of a boy	Mother	/	/	/	/	/
		Boy	Non-reactive	Positive (1:1280)	Negative	Positive	/
4. 2. 2021	Another sample taken three days after birth	Mother	Non-reactive	Positive (1:1280)	/	/	/
		Boy	Non-reactive	Positive (1:1280)	/	/	/
24. 3. 2021	Check-up	Mother	Reactive (1:2)	Positive (1:1280)	Negative	/	/
		Boy	Non-reactive	Positive (1:320)	Negative	Positive	/

Legend: RPR – Rapid Plasma Reagin; TPPA – T. pallidum Passive Particle Agglutination test.

The diagnostic algorithm for the management of suspected congenital syphilis from the American guidelines is summarized in Appendix (12).

According to the 2020 European guidelines, the first-line treatment in a newborn is intravenous benzylpenicillin at a dose of 150,000 IU/kg daily, divided into four doses over 10–14 days. If central nervous system infection is ruled out, treatment with a single dose of benzylpenicillin intramuscularly in the amount of 50,000 IU/kg or with procaine penicillin intramuscularly in the amount of 50,000 IU/kg daily for 10–14 days is also possible (in case of poor availability of benzylpenicillin) (2). The latest US guidelines from 2015, in which the method and duration of treatment are recommended according to the probability of congenital infection, are presented in Table 1 (12).

2 Case presentation

We are presenting a clinical case of a 33-year-old pregnant woman. In September 2020, her tests for non-treponemal and treponemal antibodies (RPR 1:2, TPPA 1:640) during routine pregnancy screening were positive. This was her fourth pregnancy; in the past, she had given birth to two healthy children and had one miscarriage with her first partner. In her previous pregnancy nine years ago, the screening test for syphilis was negative. She then became pregnant with a new, different partner. She had no history of problems typical of syphilis. According to her, she was healthy during her pregnancy, without any special therapy. We defined syphilis in this pregnant woman as latent syphilis of unknown duration.

Treatment at the Department of Infectious Diseases, University Medical Centre in Ljubljana began in October 2020, when she was four months pregnant. She received three doses of depot penicillin (penicillin G 2.4 million IU IM). Testing for other sexually transmitted infections was also performed: infections with *Ureaplasma urealyticum*, *Ureaplasma parvum*, and *Mycoplasma hominis* were laboratory confirmed, while infections with HIV, HBV, HCV, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* were excluded. She did not return for the planned check-up at the end of the pregnancy.

In January 2021, she gave birth to a healthy, slightly premature boy, gestational age 36 weeks, BW 3450g (50–90p), BL 52 cm (90–95p), Apgar score 8/9. During the clinical examination, no deviations from the normal state were found. He also had no signs of congenital syphilis. Haemogram and differential blood count were within normal limits. He needed phototherapy for 20 hours due to jaundice.

At birth, blood was taken for syphilis serology from the umbilical vein (whether from the artery or vein was not recorded), and TPPA antibodies were present in a titer of 1:1280. A maternal blood sample was not taken at

delivery. A diagnosis of possible congenital syphilis was made. After consultation with a pediatric infectious disease specialist, the boy received a single dose of penicillin G intramuscularly. The intention was to monitor the child and perform serological tests in the Department of Infectious Diseases until the antibodies became negative. The results of serological examinations of the mother and child are presented in Table 2, according to the time course.

3 Discussion

3.1 Establishing a diagnosis in a pregnant woman

In Slovenia, the screening of pregnant women for *T. pallidum* infection with TT is part of the first examination during pregnancy (7). In our case, the lady had a positive CIA TT during the screening, which we confirmed with a reactive NTT (RPR, titer 1:2) as well as positive TPPA (titer 1:640) and LIA IgG TT. During subsequent checkups, the value of the RPR titer alternated between a low positive titer of 1:2 and a non-reactive RPR test, due to a low concentration of nontreponemal antibodies.

A serological pattern with a positive TT and a negative NTT can occur in patients with very early syphilis, in patients with treated early syphilis, and very rarely, in late tertiary syphilis in the event of spontaneous seroreversion (9,11). The combination of a negative NTT in combination with a positive TT is also seen in the case of accidental treatment of syphilis during antibiotic therapy for some other infection (2). The woman very likely had late latent syphilis of unknown duration, which can also lead to a marginally positive NTT.

Infections with HIV and toxoplasmosis, which can cause false-positive values of the TPPA test, were excluded during the examination of the pregnant woman by an infectious disease specialist. False-positive TT results also occur in autoimmune diseases, especially in rheumatoid arthritis, even before the appearance of clinical signs of the disease. In light of this, monitoring in the Department of Rheumatology would also make sense (13).

In the literature, we can find many cases of children with congenital syphilis who were born to mothers with false-negative screening results in pregnancies with NTT. This is due to the prozone phenomenon, which occurs in the primary and secondary syphilis stage and is caused by an excess of antibodies. In our case, the prozone phenomenon was excluded (14).

All pregnant women with confirmed syphilis must also be tested for other sexually transmitted diseases (6,12). In our case, it turned out that, along with syphilis, the mother also had confirmed infection with *Ureaplasma urealyticum*, *Ureaplasma parvum*, and *Mycoplasma hominis*, but infections with HIV, *Chlamydia trachomatis*, and *Neisseria gonorrhoaee* were excluded.

3.2 Treatment of the mother and the treatment efficacy

The drug of choice for all stages of syphilis is penicillin G. The duration and method of administration varies according to the clinical picture and stage of the disease (2,12).

About a third of women with syphilis are unaware of the symptoms and signs of the disease. Ulcers often appear in the vagina or cervix and they can be overlooked entirely (3). Even in our case, the pregnant woman denied any symptoms or signs of the disease, so the stage of the disease cannot be accurately determined based on her medical history. However, we know that the screening tests were negative during the previous pregnancy nine years ago, so the infection must have occurred in the interim period. The disease was defined as late latent syphilis of unknown duration. Taking this into consideration and according to guidelines, she was treated with three intramuscular doses of depot penicillin G (2).

A pregnant woman who is serologically positive is considered to be potentially infectious if it is not clear from the medical documentation that she has been properly and successfully treated. Successful treatment results in a corresponding decline in the NTT serum antibody titer (four-fold). The treatment of a pregnant woman is considered unsuccessful in case of treatment with a non-penicillin antibiotic, treatment ≤ four weeks before delivery, an inadequate decline in antibody titer (≤ four-fold drop), with evidence of reinfection or relapse in the mother (≥ four-fold rise in titers) (2,12).

In our case, the pregnant woman was treated with penicillin G three months before delivery, which is appropriate according to the guidelines. At the time of diagnosis, a low RPR titer (1:2) was present, so it was not possible to monitor the four-fold drop in titer nor to assess the effectiveness of the treatment.

With treponemal tests, we cannot monitor the disease's activity and the treatment's effectiveness, nor can we distinguish between an active infection and a disease in the past (15). We can conclude that the TT titers in our case will remain unchanged despite the treatment, and the titer value fluctuations result from method error.

3.3 Treatment of the newborn

Diagnosing congenital syphilis is complex. In order to correctly identify the disease, it is first necessary to make a reliable diagnosis of syphilis in the mother, to check the correctness and success of her treatment, to carry out a clinical, laboratory and, if necessary, radiological examination of the newborn child, as well as to compare the results of serological examinations of the mother and the child. Transfer of maternal treponemal and non-treponemal antibodies through the placenta may be diagnostically important, but is not the only criterion for evidence of intrauterine infection. Blood sampling from the umbilical cord is unsuitable for proving a newborn's infection because of the possibility of false-positive and false-negative results (2,16).

The diagnosis of congenital syphilis is probable in a stillborn child with a positive TT. A newborn with a positive TT at birth and clinical, laboratory, and/or radiologic evidence of syphilis also has presumed congenital syphilis. A child with a positive TT at birth and/or at the same time with a positive NTT in the cerebrospinal fluid and/or with at least a four-fold higher TT titer in the blood and/or at least a four-fold higher NTT titer than the mother has at birth probably has syphilis. The child of a mother who was not properly treated for syphilis before or during pregnancy is also likely to have congenital syphilis. Congenital syphilis is also probable if the child has a four-fold or more increase in the NTT titer within three months after birth. Confirmation of the child's treponemal IgM antibodies, which do not cross the placenta, is diagnostically important, although the fact that they cannot be determined in all cases of congenital syphilis. Congenital syphilis is also very likely if a child has a positive TT after one year or more (when sexual abuse is excluded) (2,12,16).

Congenital syphilis is definitively confirmed by PCR in placental samples, post-mortem tissue samples, swabs from suspected ulcers, or body fluids (e.g. swab of the bullous rash or nasal discharge) (2,12).

Congenital syphilis can be ruled out in the case of normal clinical status of the newborn, effective and timely treatment of the mother, and ≥ four-fold lower NTT titers in the child compared to the mother's titers. In our case, due to the low values of the RPR titers in the mother, it was not possible to determine either the effectiveness of the treatment or the transmission of the infection to the fetus. We diagnosed probable congenital syphilis, and the boy received appropriate treatment (2,12).

Serological tests may be negative in a child infected late in pregnancy and should be repeated. This happens when the pregnant woman is treated only in the last trimester of pregnancy, because syphilis can still develop in the child (16).

The positive TPPA and LIA IgG antibodies in the boy in our case can be explained by the transfer of IgG antibodies through the placenta, and they do not mean fetal infection. With a negative EIA (IgM) result, congenital syphilis cannot be reliably ruled out, as the test is of low sensitivity (10,17).

Treponema tests are not helpful for evaluating the effectiveness of treatment in a child, as they may remain positive despite treatment. In the case that it was only a passively transferred mother's treponemal IgG, we can expect a gradual decline in titers until complete seroreversion at the age of around 15 months (2,3,12).

The plan is to follow the boy in the Department of Infectious Diseases. According to the guidelines, children with positive serological tests at birth, born at delivery to seroreactive mothers, should be monitored every three months until complete seroreversion or a ≥ four-fold decline in NTT titers. A decline in the NTT titer is expected at the age of three months and complete seroreversion by the age of six months, when passively transmitted maternal antibodies should disappear from the baby's circulation. The same laboratory methods must be used for each test (2,12). As the NTT was already low at birth in our case, monitoring the effectiveness of the therapy in this way is not possible. The treatment can only be considered efficient if the clinical picture of congenital syphilis does not develop.

4 Conclusion

Congenital syphilis is very rare in Western civilisation today, but it has lately frequently been appearing. Transplacental transmission occurs mainly in the third trimester and is associated with a high rate of adverse outcomes. The risk of congenital syphilis can be reduced by early diagnosis (e.g. with a screening test during pregnancy) and early treatment of the pregnant woman. In the case of confirmed infection in the mother, careful treatment of the child immediately after birth and monitoring of the clinical condition and laboratory tests (with an emphasis on serological tests) is necessary until it is possible to exclude congenital infection reliably.

Conflict of interest

None declared.

Inform consent of the patient

The patient gave informed consent for the publication of her case.

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