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Diagnosis and management of syphilis infection in pregnancy: a literature review



I Gde Sastra Winata^{1*}, William Alexander Setiawan¹, Ni Luh Wita Astari Widhusadi¹,
DPG Jananuraga Maharddhika¹, Fenyta Christyani¹, Putu Bagus Darmayasa¹,
Anthony Stephen Halim¹, Ernest TB Sianturi¹

ABSTRACT

Treponema pallidum, which causes the infectious disease syphilis, has a high rate of vertical transfer from mother to kid. Untreated maternal infection increases the risk of perinatal morbidity and mortality and unfavorable pregnancy outcomes, notably congenital syphilis. It is necessary to check for gestational syphilis during the prenatal period, and its diagnosis is straightforward. Nevertheless, this illness still affects two million pregnant women globally, indicating its significant prevalence. Congenital syphilis clinical symptoms are regulated by gestational age, maternal syphilis stage, maternal therapy, and fetus immune response. Early and late congenital syphilis have historically been used to describe it. The direct identification of treponemes, serological tests, and clinical signs all contribute to the diagnosis of maternal infection. Penicillin is typically used in the treatment, which also includes sexual partners. Fetal infection can be treated and prevented from spreading from the mother to the fetus with proper maternal infection management. To lower the prevalence of congenital syphilis, screening, early detection, and appropriate care are crucial during pregnancy and the preconception period.

Keywords: syphilis, transmission, early detection.

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¹Department of Obstetrics and Gynaecology, Faculty of Medicine, Universitas Udayana, Denpasar, Bali.

*Correspondence:
I Gde Sastra Winata;
Department of Obstetrics and Gynaecology, Faculty of Medicine, Universitas Udayana, Denpasar, Bali;
Sastra@unud.ac.id

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INTRODUCTION

Treponema pallidum, the bacteria that causes the sexually transmitted disease (STD) syphilis, is especially dangerous during pregnancy due to the possibility of the fetus contracting the infection through the placenta.¹ Vertical transmission rates are significant, reaching 100% during the first two stages of maternal illness. Low- and middle-income countries, particularly Indonesia, have the largest disease burden. A total of 13,774 cases of primary and secondary syphilis were reported to the Centers for Disease Control and Prevention (CDC) in 2010.² According to the World Health Organization (WHO), almost half of all untreated pregnant women experience negative pregnancy outcomes. The WHO estimates that each year, nearly 1.5 million pregnant women are infected with likely active syphilis.³ More than half of pregnant women with active syphilis experience negative outcomes due to untreated or ineffective treatment, which can include early fetal loss, stillbirth, prematurity,

low birth weight, neonatal and infant death, and serious sequelae in liveborn infected children.⁴ Without screening and treatment, about 70% of infected women will have an adverse pregnancy outcome.⁵ The most severe syphilis pregnancy complication is congenital syphilis. Congenital syphilis can be avoided, and mother-to-child transmission of the disease can be stopped by using successful early detection and treatment methods for syphilis in pregnant women.⁶ Syphilis screening during pregnancy offers a good opportunity to identify the condition early and prevent congenital syphilis. This fact highlights the direct link between the prevalence of the condition and the caliber of primary and women's healthcare provided during pregnancy.⁷ All pregnant women should be checked for gestational syphilis because the disease has a straightforward diagnosis. If the mother obtains proper care in the early stages of pregnancy, ideally before the second trimester, the fetus can be easily treated, and the chance of negative outcomes

is limited.⁶ Penicillin is typically used during the procedure, and the mother's sexual partners should also receive therapy. Preventing negative outcomes and lowering lifetime medical expenses require screening, early identification, and appropriate infection therapy in pregnant women.⁸ Moreover, CDC recommends that all persons who have syphilis should be tested for HIV infection.⁹ This study aims to provide a literature review of the diagnosis and management of syphilis infection in pregnancy.

EPIDEMIOLOGY

The second most frequent infectious cause of stillbirth worldwide is syphilis, a significant contributor to infant morbidity and mortality that can be easily avoided.¹⁰ In 1995, the WHO estimated that there were roughly 12 million new cases of syphilis in adults worldwide, with 5.8 million cases thought to have originated in South and Southeast Asia.¹⁰ Some professions, such as long-distance truck driving and commercial sex work, other

STDs, the lack of male circumcision, and a degree of education, are linked to a high prevalence of syphilis. Due to active intervention methods and the availability of penicillin, congenital syphilis is uncommon in these pregnancies. With a global congenital syphilis rate of 473 per 100,000 live births and 661,000 total congenital syphilis cases, including 355,000 adverse birth outcomes and 306,000 non-clinical congenital syphilis cases (infants born to untreated mothers without clinical signs), the estimated global maternal syphilis prevalence in 2016 was 0.69% (95% CI: 0.57-0.81%). According to the updated 2012 estimates, there were 748,000 congenital syphilis cases (539 per 100,000 live births), 397,000 unfavorable birth outcomes, and 0.70 percent (95% CI: 0.63-0.77%) mother prevalence.¹¹ Between 2012 and 2016, there was a global decline in congenital syphilis, but maternal prevalence remained steady. Increased access to prenatal care (ANC), syphilis screening, and treatment are believed to have contributed to the estimated decline in congenital syphilis case rates between 2012 and 2016. Furthermore, a recent study found that the demographic profile of mothers who give birth to syphilitic children is similar to that of women who have other STDs and those who do not receive enough ANC.¹⁰

Syphilis transmitted from mother to child (MTCT) during pregnancy can majorly affect the fetus in the second or third trimester and cause complications, particularly congenital infections in newborns.¹² The WHO created international guidelines and standards to validate the elimination of MTCT (EMTCT) for HIV and syphilis in 2014. Each country must achieve three process targets in order to validate the EMTCT

of syphilis, including achieving at least 95% coverage of ANC with at least one visit (ANC1), at least 95% of pregnant women in ANC testing for the disease, and at least 95% of women with positive syphilis rec tests.¹³ According to the WHO, the estimated number of pregnant women with probably active syphilis decreased from 1.36 million in 2008 to 930,000 in 2012; moreover, the number of unfavorable birth outcomes decreased from 520,905 in 2008 to 351,000 in 2012.^{14,15}

TRANSMISSION

Syphilis is most frequently communicated by intercourse (vaginally, anogenitally, or orogenitally), followed by placental transfer and congenital transmission.¹⁶ Kissing, blood transfusions, and unintentional vaccinations have all been documented as other transmission routes but are not as significant.¹⁶ Most infants with congenital syphilis are infected while still in the womb, but the baby can also contract the disease by touching an active genital lesion when the mother is giving birth.^{17,18} Young children sharing a bed with an infected individual and healthcare professionals before the common usage of gloves have both been reported to experience suspected nonsexual transmission resulting in finger and hand lesions.¹⁶⁻¹⁹ It seems unlikely that sharing needles contributes to the spread of syphilis, but this is not certain.

Rare cases of blood and organ donation acquisition, as well as those brought on by occupational and other exposures, have also been documented. Improved donor selection, universal serologic testing of all blood donors, and a switch from transfusing fresh blood to transfusing refrigerated blood components have

all reduced the danger of transmission through the blood to a minimal level.²⁰ Although theoretically unlikely, transmission through blood products is still possible because organisms can live for up to 5 days in chilled blood.¹⁶

CLINICAL MANIFESTATIONS

The clinical manifestations of syphilis in pregnant and non-pregnant women do not differ (Table 1). Each stage of maternal syphilis that can transmit to the fetus is directly proportional to the number of *Spirochaeta T. pallidum*.²¹ The incubation period can last for 3-12 weeks.²² Through direct contact with a chancre, a syphilitic sore that is contagious, syphilis is spread from person to person. It takes about three weeks for primary syphilis sores to appear after contact. They frequently show no symptoms. The small, round, solid, and painless syphilitic sore lasts for three to six weeks. Genital Herpes, which creates tiny, painful blisters filled with clear or straw-colored fluid, should be distinguished from it.⁴

Primary syphilis can be diagnosed with a hard ulcer, a mostly solitary ulcer with a round or slightly oval shape, clean surface, indurated edges, and painlessness.²¹ In women, it is often undetectable because it is mostly hidden, such as the cervix, vagina, labia, and perineum. If not appropriately treated, an ulcer will go away in 3 to 8 weeks without leaving a scar.^{21,22}

Usually starting 4 to 8 weeks after the initial lesion has disappeared, the secondary stage might extend for several weeks or months. The rash, frequently called roseola syphilitic, is an erythematous maculopapular lesion with a diameter of 0.5 to 1 cm that does not itch on the body or extremities.^{21,22} Conditions,

Table 1. Clinical manifestation of syphilis in adults²³

Stage	Clinical Manifestation	Duration
Primary	Ulcus, mostly solitary, painless, well-defined border, induration with regional lymph node enlargement (lymphadenopathy)	3 weeks
Secondary	Polymorphic red patches, mostly on the palms and soles, papulosquamous skin and mucosal lesions, fever, malaise, generalized lymphadenopathy, condyloma lata, patchy alopecia, meningitis, uveitis, retinitis	2 – 12 weeks
Tertiary		
Gumma	Tissue destruction in infected organs and sites	1 – 46 years
Cardiovascular syphilis	Aortic aneurysm, aortic regurgitation, ostium stenosis	10 – 30 years
Neurosyphilis	Varies from asymptomatic to headache, vertigo, personality changes, dementia, ataxia, Argyll Robertson pupils	>2 – 20 years

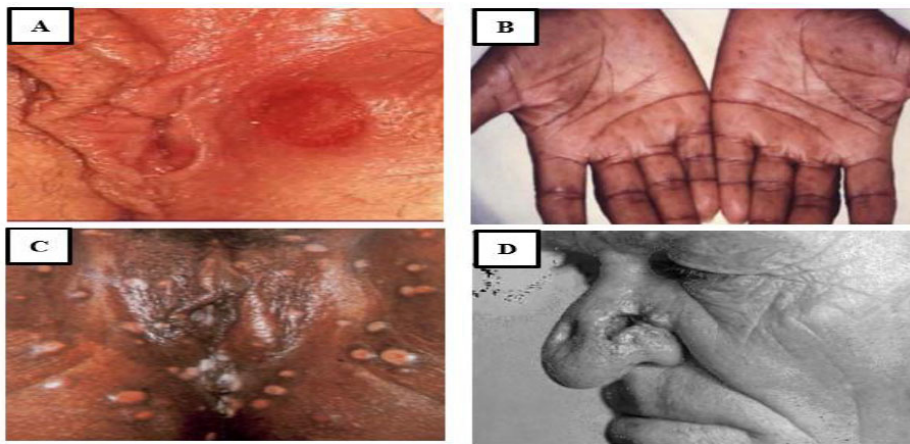


Figure 1. Clinical appearances of syphilis infection. (A) Chancre in genital; (B) Syphilitic roseola; (C) Condylomata lata or condyloma lata; (D) Syphilitic gumma.^{21,23}

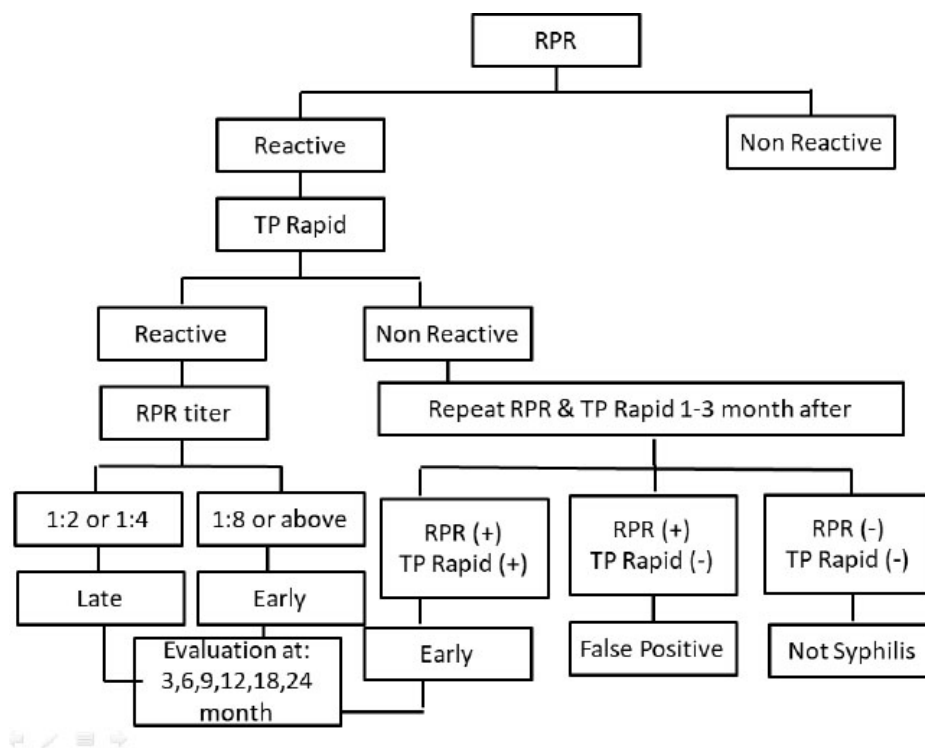


Figure 2. Flowchart of syphilis diagnosis with serology test.²³

including widespread lymphadenopathy, fever, headache, and malaise, may also accompany the rash.⁹ Condyloma lata may also be seen in secondary syphilis. Condyloma lata is common in the genital area but can also occur in other moist folds (between the fingers and toes, axillae, and umbilicus). Due to the direct spread of *Treponemas* from the primary lesion (ulcer durum), these lesions can also be observed close to the primary lesion. All outward signs of the disease disappear if secondary syphilis is left undetected

and untreated, and the patient enters a dormant stage that can linger for years.^{21,22}

Latent syphilis occurs after secondary syphilis. A person is said to have latent syphilis if there is a serologic history of syphilis. It has never been treated and does not show clinical manifestations.^{21,22} Early latent syphilis progresses to late latent syphilis. This phase remains clinically asymptomatic, but non-treponemal serological tests slowly decline and can be found in very low to negative levels. The late latent stage begins 1 year

after infection or when the duration of infection is unknown. In the late latent syphilis stage, *T. pallidum* is no longer transmitted through sexual contact but can still be transmitted transplacentally from a pregnant woman to the fetus. There is a 20-30% chance of patients with late latent syphilis developing tertiary syphilis within 3 – 10 years.^{21,22}

Tertiary syphilis occurs in various clinical syndromes consisting of three main groups: neurosyphilis, cardiovascular syphilis, and advanced benign syphilis.²¹ Clinical signs of tertiary syphilis include destructive ulcerative nodular lesions called gummas, osteomyelitis, osteitis, stiffness and pain with movement, seizures, loss of consciousness, different cardiovascular diseases, and neurosyphilis.²² Syphilis during pregnancy can spread to the fetus, resulting in miscarriage, early birth, low birth weight, stillbirth, or congenital syphilis.²¹ Clinical appearances of syphilis infection during pregnancy are provided in Figure 1.

DIAGNOSIS

Based on a thorough history that includes sexual history, clinical signs, laboratory, and serological tests, the diagnosis can be made.^{21,22,24} The parents' history was made by asking questions about the risk of syphilis infection, such as suspected coitus, history of blood transfusion in the mother, and previous infectious infections. When durum and condylomata lata ulcers are present, a direct examination for *T. pallidum* bacteria under a dark field microscope is the most accurate and specific test.^{21,22} Specimens are obtained from lesions of skin ulcers and erosive mucosa. However, serology is still the most reliable method for the laboratory diagnosis of syphilis. Serological tests are divided into non-treponemal and treponemal tests.^{21,22}

Non-treponemal tests are the RPR (Rapid Plasma regain) and VDRL (Venereal Disease Research Laboratory) tests (Figure 2). Serological tests in this group detect immunoglobulins and antibodies to the lipid materials of destroyed *T. pallidum* cells. These antibodies can occur in reaction to syphilis infection but in various other conditions, such as acute viral infections and chronic

autoimmune diseases. Therefore, this test is non-specific and can show false-positive results. Non-specific tests are used to detect active infection and reinfection and monitor therapy's success. Because this non-specific test is much cheaper than the treponemal-specific test, it is often used for screening.²²

The treponemal tests include TPHA (*Treponema Pallidum* Haemagglutination Assat), TP Rapid (*Treponema Pallidum* Rapid), TP-PA (*Treponema Pallidum* Particle Agglutination Assay), FTA-ABS (Fluorescent *Treponema* Antibody Absorption). The treponemal test will detect antibodies that are specific for treponemes. Therefore, this test rarely gives false-positive results. This test can be lifelong positive or reactive even after successful syphilis therapy. This type of test cannot be used to differentiate between an active infection and an infection that has been adequately treated. A treponemal test only shows that a person has been infected with treponemes but cannot show whether a person has an active infection. This test also cannot distinguish *T. pallidum* infection from other treponemal infections.²²

The conventional serological diagnosis uses a two-step approach. The first step is screening by a non-treponemal method and then using a confirmatory test using the treponemal antigen method to confirm a positive screening test result. Screening for a pregnant woman can be done at the first antenatal visit. Serological tests can be carried out twice in the third trimester, once at 28–32 weeks of gestation and once during birth, for high-risk female populations. Syphilis serology testing should be done on women with a history of fetal death beyond 20 weeks of gestation.²⁰

If a pregnant woman has a positive syphilis serologic test, she should be treated and assumed to be infected until a complete medical history and acceptable, low, or stable antibody titers are present. A nontreponemal test titer in a pregnant woman, particularly one of 1:8, may indicate an early infection and bacteremia. High antibody titers in pregnant women suggest either treatment failure or reinfection. If the mother has a history of syphilis, it is important to determine

whether her previous therapy was effective. Every three months, until the test becomes nonreactive or the titer drops by fourfold, all sero-active infants (or infants whose mothers were sero-reactive at delivery) should undergo a medical examination and serological testing. Treponemal testing on newborn serum is not advised since it may result in erroneous conclusions. Nontreponemal serological testing should be used to assess all neonates born to moms with non-treponemal and reactive treponemal results. An 18-month reactive treponemal test can identify congenital syphilis. At a gestational age of more than 20 weeks, an ultrasound examination can be done to check for congenital syphilis symptoms such as hepatomegaly, a thickened placenta, hydramnios, ascites, fetal hydrops, and an enlargement of the middle cerebral artery.^{20,22}

MANAGEMENT

Fetal infection can be treated and prevented from spreading from the mother to the fetus with proper maternal infection management. Penicillin G is the primary medication for treating syphilis when administered parenterally. Clinical experience and randomized controlled trials were used to determine the efficacy of penicillin. Penicillin levels in the blood are treponemicidal for weeks, although it is ineffective at crossing the blood-brain barrier.²⁴

If both RPR and TPHA test results are positive, the patient will be treated as per their clinical stadium. The World Health Organization recommends providing benzathine penicillin 2.4 million IU intramuscularly, administered once, without any other medicine, to pregnant women with early syphilis, whether primary, secondary, or early latent. WHO advised giving benzathine penicillin 2.4 million IU once weekly for three weeks for late syphilis.²³ CDC recommends that pregnant women should be treated with the penicillin regimen appropriate for their stage of infection.⁹

Some pregnant women cannot use penicillin due to being allergic to penicillin, or penicillin stock is unavailable. Using ceftriaxone 1 g intramuscularly once daily for 10 to 14 days or taking erythromycin 500 mg four times daily orally for 14 days

with caution is an alternative therapy option for early syphilis. Utilizing 2 g of azithromycin orally once daily is an additional choice. WHO advised taking 500 mg of erythromycin four times daily for 30 days for late syphilis.²³

The Jarisch-Herxheimer reaction might happen 2 to 12 hours following therapy in the case of active syphilis. The syndrome, which manifests as fever, headache, myalgia, and malaise, is brought on by releasing substances resembling treponemal endotoxins during penicillin-mediated lysis. During the second half of pregnancy, the Jarisch-Herxheimer reaction can raise the risk of early labor or fetal distress. If delivery occurs within 30 days of therapy or if the maternal antibody titer at delivery is four times higher than the pre-treatment titer, maternal treatment may not be sufficient.²⁵

Giving prophylaxis is necessary because syphilis can be transferred vertically from mother to kid. Infectivity often ends after 24 to 48 hours of appropriate penicillin treatment. The most effective medication for treating pregnant women and avoiding mother-to-child transmission of syphilis is benzylpenicillin, given parenterally in a single dosage. However, mothers who have latent syphilis are unaffected. Women who are allergic to penicillin should be desensitized prior to receiving benzylpenicillin.²⁶

In addition to proper therapy, syphilis screening or early discovery may hold the key to lowering the prevalence of congenital syphilis. If a woman is at risk for syphilis, the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics advises prenatal syphilis screening during the first prenatal appointment and again at 32 to 36 weeks.²⁷ The CDC recommends that all pregnant women undergo a syphilis serological screening at their initial prenatal appointment and third trimester and delivery screenings for high-risk patients.⁹ A syphilis test should be performed on every mother who delivers a stillborn child after 20 weeks of pregnancy.²⁸ During pregnancy's first and third trimesters, all pregnant women should be offered a syphilis serological screening.

CONCLUSION

Infection with syphilis during pregnancy is still a serious public health issue worldwide, especially in Indonesia. Penicillin, a powerful medication used to prevent congenital syphilis, is an effective treatment for syphilis and can be used to detect the condition with minimal expense. If the woman is at risk for syphilis, screening or early detection of prenatal syphilis is advised at the first prenatal appointment and again at 32–36 weeks. Syphilis testing should be performed on every mother who delivers a stillborn child after 20 weeks of pregnancy. Additionally, preconception counseling may be crucial in assessing the lady and her partner for STD exposure, identifying high-risk behaviors, and disseminating health promotion information. At all levels of the health care system, there needs to be an effort to raise knowledge of the severity and scope of syphilis in pregnancy, supported by high-level commitment.

ETHICAL CLEARANCE

Not applicable.

AUTHOR CONTRIBUTION

All authors contributed equally to the writing of this article.

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CONFLICT OF INTEREST

All authors have no conflicts of interest.

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