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A Review on Current Management of Syphilis in Pregnancy: Persistent Risk to The Public's Health

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ABSTRACT

Syphilis is a bacterial sexually transmitted diseases (STI) caused by *Treponema pallidum.* Due to their high rates of morbidity and mortality, maternal and congenital syphilis are important public health issues in every country. According to the World Health Organization (WHO), there are around 5,6 million new infections worldwide each year, and Syphilis-positive pregnant women have to 80% chance of having a negative pregnancy outcome, such as a stillbirth or spontaneous abortion. Pregnant women typically don't get treated for syphilis at one or more prenatal visits. Because of this, it is necessary to have up to date understanding the effects of syphilis infection on maternal and newborn outcomes, as well as for guidelines for current syphilis treatment and care.

Keywords: Syphilis, Pregnancy, current treatment, Sexually transmitted diseases (STI), *Treponema pallidum.*

INTRODUCTION

The quality of life is negatively impacted by sexually transmitted diseases (STIs), which also cause significant morbidity and mortality. Through infertility, malignancies, and pregnancy difficulties, STIs have a direct influence on reproductive and child health. Between the ages of 15 and 49, an estimated 357 million new cases of treatable STIs *gonorrhea*, *chlamydia*, *syphilis*, and *trichomoniasis* occurred globally in 2012, including 5.6 million cases of syphilis. Syphilis prevalence instances are thought to number 18 million.[(1),(2)]

Syphilis is a systemic disease caused by human pathogenic bacteria, namely *Treponema pallidum* subspecies *pallidum.* Through sexual contact with individuals who have infected lesions on their mucous membranes or skin that has been rubbed raw, through blood transfusions, or transplacentally from a pregnant mother to her fetus, syphilis can be spread. The infection can advance to later stages and produce many serious clinical manifestations, such as neurosyphilis, blindness, and cardiovascular diseases, if it is not caught in the early stages. Additionally, congenital transmission can happen when a pregnant syphilis patient who is untreated or undertreated passes T. pallidum onto her unborn child through the placenta, and sporadically through direct contact with syphilitic sores when the baby enters the birth canal.[(1),(2),(3)]

Maternal syphilis is predicted to cause 50–80% of afflicted pregnancies to have adverse birth outcomes (ABOs), with stillbirth or newborn death accounting for more than half of these negative outcomes when left untreated. If syphilis in pregnancy is left untreated or is treated too late, preterm birth, low birth weight, and congenitally infected infants are also frequent outcomes. The Centers for Disease Control and Prevention (CDC) reported in 2015 that 21.8% of moms who gave birth to children with congenital syphilis had no prenatal treatment. Of moms who had one or more prenatal visits, 43% did not receive any syphilis treatment while pregnant, and another 30% had insufficient care. These results emphasize the significance of addressing prenatal care that is adequate as

well as syphilis screening, diagnosis, and treatment throughout pregnancy.[(1),(2)]

This becomes a Persistent Risk to Public Health, therefore we will discuss the current management of syphilis in pregnancy at the present time, this review will offer recommendations. Furthermore we will also review the current understanding of the effects of syphilis infection during pregnancy on maternal and newborn outcomes as well as the many screening procedures and algorithms for syphilis diagnosis.

CLINICAL SYMPTOMS OF SYPHILIS

Syphilis is a persistent infection that has several stages, both symptomatic and asymptomatic. When the spirochete of *Treponema pallidum* enters the mucous membranes during sexual contact or through a skin breach, infection results. Early syphilis (primary and secondary syphilis) has the highest spirochete load in patients, which increases the risk of transmission. Syphilis has four clinical subtypes: primary, secondary, latent, and tertiary. In addition, any of the aforementioned stages can coexist with neurosyphilis development.[(1),(2),(4),(5)]

Primary Syphilis

There is an incubation period of roughly 21 days following syphilis transmission before the start of clinical symptoms. One or more painless ulcerative lesions (also known as chancres) that develop on the genitalia around the site of inoculation are the hallmark of primary syphilis. Regional lymphadenopathy without any discomfort is sometimes present in ulcerative lesions. With or without therapy, lesions may spontaneously disappear within 4 to 6 weeks. After six to eight weeks, 25% of patients with untreated primary syphilis will progress to secondary syphilis.[(1),(2),(3),(5)]

Secondary Syphilis

Approximately 25% of untreated female patients have secondary syphilis, which typically develops 4 to 10 weeks after the chancre first appears. The typical symptoms of diffuse maculopapular skin rash, mucosal lesions (oral lesions include mucous patches and genital condyloma lata), and systemic lymphadenopathy define this clinical stage. Secondary syphilis widespread and localized lesions may also go away on their own without therapy in 1 to 6 months. [(1),(2),(4),(5)]

Laten Syphilis

The absence of clinical signs or symptoms despite positive serologies characterizes the latent phase of syphilis. Approximately 12 months after the original infection, it can manifest as early latent syphilis or late latent syphilis. Maternal to fetal transmission of syphilis is still conceivable in late or early latent forms. After 15 to 30 years of untreated syphilis infection, the advent of inflammatory lesions affecting skin (e.g., gummas), the cardiovascular (e.g., aortitis), and/or skeletal (e.g., osteitis) systems marks the transition to tertiary syphilis. Neurosyphilis is the medical word for involvement of the central nervous system. Meningitis, cranial nerve palsy, cognitive impairment, dementia, and/or tabes dorsalis are some of the possible symptoms. Additionally, there could be ocular involvement in the form of Argyll-Robertson pupils, optic neuritis, or anterior uveitis.[(1),(2),(5)]

Tertiary Syphilis

Synonymous with late symptomatic syphilis, can occur in about one-third of people. After the initial infection, it may take months or years to show. Tertiary syphilis refers to benign gummas and cardiovascular syphilis, but not neurosyphilis, and is uncommon in those who are of reproductive age. Although it is not contagious, it can cause granulomatous lesions that affect different body organs and cause irreparable cardiovascular, neurological, and neurological problems. [(1),(2),(4),(5)]

Syphilis In Pregnancy

Patients with syphilis who are expecting run the risk of transferring *T. pallidum* to their unborn child. Vertical transmission happens either at delivery when the neonate is in close contact to a genital lesion or, less frequently, transplacentally. Breastfeeding does not cause transmission unless the infant comes into contact with a breast lesion that is actively syphilitic. At just 14 weeks of gestation, spirochetes can penetrate the placenta and infect the fetus. In comparison to late maternal syphilis, untreated early maternal syphilis has a higher probability of vertical transmission. [(1),(2),(5),(6)]

Additionally, greater maternal nontreponemal titers increase the chance of vertical transmission. In one study, congenital syphilis occurred in 25% of moms with greater nontreponemal titers (1:8) compared to 4% of mothers with lower titers (1:8). Congenital syphilis can be present in certain newborns but not always cause symptoms. Hepatosplenomegaly, bone problems, anemia, skin rash, blindness, and hearing can also occur in other newborns. Congenital syphilis may also make pregnancy more difficult and, in 25% of infected pregnancies, result in miscarriage and stillbirth. Early syphilis infection in pregnancy increases the risk of fetal loss. Fetal immunocompetence and the fetal-placental immune response increase the likelihood of asymptomatic disease and prevent fetal loss when infection arises later in the third trimester.[(1),(2),(4),(6)]

SCREENING AND DIAGNOSTIC

All pregnant women should be screened for syphilis during the initial antenatal care visit, according to the 2017 WHO guideline on Syphilis Screening and Treatment for Pregnant Women. A single on site test, such as a rapid diagnostic test (RDT) or on site rapid plasma reagin (RPR), should be used in settings with low coverage of syphilis screening and/or treatment or in settings with limited laboratory capacity, it further advises, citing the urgency of ensuring prompt treatment in pregnancy to prevent congenital syphilis. The CDC, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists urge repeat screening in the early third trimester and at delivery in high-risk groups even though there are no studies evaluating its efficacy in pregnancy. Women who reside in high prevalence areas, those who test positive for the human immunodeficiency virus, expectant mothers who have a sexually transmitted disease, and those with a history of incarceration or commercial sex work are among the high-risk categories.[(2).(4),(6),(7)]

The foundation of a laboratory diagnosis of syphilis is serological testing. Treponemal and nontreponemal are the two main classifications of serological testing. The diagnostic algorithms for syphilis infections use a combination of the two. An individual may have an active infection now or may have had one in the past if their treponemal assay results are positive. Synthesis of antitreponemal immunoglobulin G antibodies starts 2 weeks after exposure to *T. pallidum*, and antitreponemal immunoglobulin M antibodies start to appear 2 weeks after that.[(5),(7),(8),(9)]

Treponemal testing used to refer to hand-held tests like the agglutination of *T. pallidum* particles and the absorption of fluorescent treponemal antibodies (TP-PA). Enzyme-linked immunosorbent assays (EIAs) and chemiluminescence immunoassays are two examples of how treponemal testing has lately become more expedient and automated (CIAs). Contrarily, nontreponemal testing identifies antibodies that are generated in reaction to cell injury beginning roughly six weeks after the initial infection. Examples of nontreponemal diagnostics include rapid plasma reagin (RPR) and the venereal disease research laboratory (VDRL). Nontreponemal testing has a 98% same specificity to treponemal testing.[(4),(6),(7),(8)]

Since titers rise with an active disease and fall with therapy, nontreponemal tests are particularly useful as quantitative indicators

for disease monitoring. False-positive treponemal test findings, seroconversion of nontreponemal antibodies, or early primary syphilis in which nontreponemal antibodies have not yet developed can all result in discrepancies between treponemal and nontreponemal testing.[5],[7],[8],[9]

SYPHILIS EFFECT ON NEWBORN OUTCOMES

It has been demonstrated that the *T. pallidum* spirochete crosses the placenta as early as 8 to 9 weeks of gestation. Pregnancy related complications from untreated syphilis are severe. Fetal loss and stillbirth were 21% more common in women with syphilis compared to healthy controls, according to a meta analysis of 6 case control studies. According to the World Health Organization, stillbirth, miscarriage, or other unfavorable pregnancy outcomes occur in 50% to 80% of syphilis-affected pregnancies. The inflammatory reaction to *T. pallidum* is what causes the distinctive ultrasound findings of prenatal syphilis infection. Because the embryonic immune system does not fully develop until around 20 weeks of gestation, it is uncommon to identify prenatal syphilis infection with ultrasound before this time.[1],[2],[3],[9]

Fetal hepatomegaly and placentomegaly, which are linked to hepatic malfunction and placental involvement, respectively, are early ultrasonography abnormalities. It is believed that syphilitic hepatitis, increased extramedullary hematopoiesis, and/or hepatic congestion from fetal heart failure are the primary causes of hepatomegaly, which is also the most frequent finding in postnatal research. The inflammation brought on by the syphilis infection is thought to be the cause of placentomegaly.[2],[3],[9]

Hematologic dysfunction is followed by the aforementioned early abnormalities. Elevated peak systolic velocity of the middle cerebral artery (MCA) on Doppler ultrasound indicative of fetal anemia and polyhydramnios, on ultrasound, may indicate this.[2],[3]

CURRENT TREATMENTS

A multidisciplinary team is required to manage syphilis during pregnancy. Antibiotics, partner notification, testing and screening for additional STIs, and counseling regarding safe sexual behavior should all be part of management. Women who had sex within the previous 90 days with a partner who has been diagnosed with primary, secondary, or early latent syphilis are advised to have treatment for suspected early syphilis. Initial serologic testing for syphilis is advised if the exposure took place more than 90 days before to the patient's diagnosis. If testing is not possible, therapy for suspected early syphilis should be given. Negative serologic results do not require treatment. Clinical staging is carried out in the event of positive serologic results, and treatment suited to the infection's clinical stage is started.[4],[5],[9],[10]

The WHO's recommended treatment for pregnant women is a single dose of benzathine penicillin G 2.4 MU. When the diagnosis is made in the third trimester, a second dose is advised since the physiological changes of pregnancy cause penicillin concentrations to drop. 2.4 MU of BPG injected once into the muscle (IM) in early syphilis (primary, secondary, or early latent). The recommended treatment is BPG 2.4 MU IM once weekly for three consecutive weeks for pregnant women with late latent syphilis or infection of uncertain duration. If a patient misses a scheduled dose, the treatment course is restarted. [1],[4],[5],[10],[11]

It states that erythromycin 500 mg orally four times daily for 14 days, ceftriaxone 1 g IM once daily for 10-14 days, or azithromycin 2 g orally can be administered, although with caution, when benzathine or procaine penicillin cannot be used due to allergy or are not accessible. According to this WHO recommendation, erythromycin and azithromycin can be used to treat pregnant women, but they cannot reliably reach the fetus due to the placental barrier. As a result, any child born to a syphilitic woman who was not given BPG must be

regarded as having congenital syphilis. [(2),(3),(5)]

Doxycycline use during pregnancy was also discouraged in the publication for safety concerns. Recommended for treating babies with congenital syphilis with procaine penicillin 50,000 U/kg/day single dose IM for 10-15 days or aqueous benzyl penicillin 100,000-150,000 U/kg/day intravenously for 10-15 days. BPG 50,000 U/kg/day single dose IM is an option for infants who are thought to have a very low risk of congenital syphilis.[(1),(3),(5)]

The Jarisch-Herxheimer reaction, which happens when a lot of bacteria die after receiving penicillin and produce cytokines that trigger an immediate inflammatory response, is one significant adverse effect (reaction) of treating syphilis patients with penicillin. It can be identified in 40–45% of pregnant women who are receiving syphilis therapy, especially if the medication is started in the second half of the pregnancy. Fever, chills, and a skin rash are common symptoms of this within the first 24 hours of treatment. Admission to the hospital and symptomatic therapy are consequently advised because preterm uterine contractions and fetal discomfort have been recorded.[(3),(4),(5)]

Women should get counseling regarding the likelihood of these symptoms as well as the proper use of antipyretics prior to beginning treatment. Fetal heart rate monitoring should be used for additional evaluation in cases where there are signs of premature labor or decreased fetal movement. Women with ultrasound evidence of congenital infection in a possibly viable fetus are advised to seek first care at a facility with the ability for emergent delivery and neonatal stabilization. This is because fetal heart rate tracing anomalies may appear in a seriously impacted fetus. Because of potential Jarisch-Herxheimer reactions, treatment for mothers with high nontreponemal titers, early clinical stages, or severely afflicted fetuses shouldn't be postponed. For a woman with preterm labor symptoms or whose fetus exhibits signs of impairment such that an urgent delivery may be necessary, antepartum corticosteroid therapy may be taken into consideration.[(1),(5),(12)]

Alternative Syphilis Therapies

Successful maternal treatment is defined as both the remission of the presenting clinical symptoms and a four-fold decrease in the maternal Rapid Plasma Reagin (RPR) titer from the time of diagnosis compared to the time of delivery. The lack of congenital syphilis was referred to as congenital syphilis prevention.[(1),(5),(12),(13)]

Amoxicillin

Two case patients were treated with oral amoxicillin as an alternative to penicillin in a case series by *Katanami et al*. in Japan. They frequently use benzylpenicillin benzathine hydrate, amoxicillin, or ampicillin. One mother at 13 weeks gestation got oral amoxicillin 6g and probenecid 1g daily for a 14-day regimen in their case series. The patient's RPR titer decreased 6 months following treatment, going from 1:16 to 1:4. The second case-patient was treated with injectable ceftriaxone 2g daily for days 7 through 14, oral amoxicillin 1.5g with probenecid 750mg daily for days 1-3, and oral amoxicillin 3g daily with probenecid 750mg daily for days 4-6. RPR titer decreased in patient 2 from 1:32 to 1:4 six months following treatment. There was no sign of congenital syphilis in the babies.[(1),(12),(13)]

Cephalosporin Antibiotics

In their study, *Zhou et al*. described the use of injectable ceftriaxone to treat 11 pregnant women with primary or secondary syphilis. Intramuscular ceftriaxone 250mg was administered over the period of 7 days to 3 case-patients who had primary syphilis. 1 case patient also received this treatment again at 28 weeks of pregnancy. A 10-day course of 250mg intramuscular ceftriaxone was administered to each of the 8 casepatients with secondary syphilis. In 7 case patients, this treatment was repeated when they were 28 weeks pregnant. The

researchers said that all case patients received successful treatment and that there was no sign of congenital syphilis in the babies of these patients.[(1),(10),(12),(13)]

Macrolide and Azalide Antibiotics

Fenton and Light described the treatment of a 32-week pregnant woman with oral erythromycin stearate 750mg four times per day for 12 days. Although the newborn developed secondary syphilis by the time she was 11 weeks old, she experienced at least a 4-fold drop in RPR titer.[(12),(13)]

Tetracycline

The use of tetracycline was described by *Mascola et al* in one case. Initial prenatal lab results for the case pregnancy patient's were syphilis negative. She underwent a two week course of oral tetracycline 500mg four times per day treatment for a urinary tract infection in the eighth month of her pregnancy. The newborn had nonreactive serologies, but the patient tested positive for syphilis at the time of delivery three weeks later with a Venereal Disease Research Laboratory (VRDL) test titer of 1:4 and a reactive microhemagglutination assay-*Treponema pallidum* (MHA-TP). 2.4 million units of benzathine penicillin G were administered to the mother. Congenital syphilis was discovered in the baby at the age of 10 weeks thanks to positive serologies, including a 1:128 VDRL test titer.(1),(12),(13)[1,12,13]

Recommendations	**Quality of the evidence and the strength of the recommendation.**
Early syphilis (primary, secondary and early latent syphilis of not more than two years' duration)	
Recommendation 1 The WHO STI guideline prefers benzathine penicillin G 2.4 million units administered intramuscularly over no therapy for pregnant women with early syphilis.	Strong recommendation, very low quality evidence
Recommendation 2 The WHO STI recommendation recommends procaine penicillin 1.2 million units intramuscularly once daily for 10 days instead of benzathine penicillin G 2.4 million units once intramuscularly in pregnant women with early syphilis. The WHO STI guideline advises using, with caution, erythromycin 500 mg orally four times daily for 14 days, ceftriaxone 1 g intramuscularly once daily for 10-14 days, or azithromycin 2 g once oral when benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock outs).	Conditional recommendation, very low quality evidence
Late syphilis (infection of more than two years' duration without evidence of treponemal infection)	
Recommendation 3 The WHO STI guideline recommends benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks above no treatment for pregnant women with late syphilis or undetermined stage of syphilis.	Strong recommendation, very low quality evidence
Recommendation 4 The WHO STI guideline recommends benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks above procaine penicillin 1.2 million units intramuscularly once a day for 20 days for pregnant women with late syphilis or undetermined stage of syphilis. The WHO STI guideline recommends using erythromycin 500 mg orally four times per day for 30 days when benzathine or procaine penicillin cannot be administered (e.g. due to penicillin allergy where penicillin desensitization is not practicable) or are not accessible.	Conditional recommendation, very low quality evidence

Table 1. Treponema pallidum and Congenital syphilis treatment recommendations for Pregnant women.[(1)]

The clinical and sociodemographic characteristics of expectant mothers, along with shortcomings in medication delivery, prescription, and treatment monitoring by the health system, are the main causes of suboptimal treatment of syphilis during pregnancy. In addition to the temporary lack of medication, failures in prenatal care (absence or delay), including the delay in receiving the first dose of penicillin, lack of

tests or treatment performed less than 30 days before childbirth/abortion, and failures in prescriptions, some of these stand out, including coinfection (syphilis-HIV), history of treatment of the disease prior to the current pregnancy, low education, maternal income and age, and low partner compliance with treatment.[14],[15]

CONCLUSION

Treponema pallidum, a human pathogenic bacterium, is the source of the systemic disease known as syphilis. Syphilis can be transmitted by sexual contact with people who have sores that are infected on their mucous membranes or skin that has been rubbed raw, through blood transfusions, or transplacentally from a pregnant woman to her fetus. The clinical subtypes of syphilis include primary, secondary, latent, and tertiary. Additionally, the progression of neurosyphilis can occur during any of these stages. The initial prenatal care visit should include a syphilis screening for all expectant mothers. Congenital syphilis risk is lower when syphilis infection is screened for during pregnancy. Syphilis management during pregnancy requires a multidisciplinary team. The WHO advises giving pregnant women one dose of benzathine penicillin G, 2.4 MU. Erythromycin and azithromycin, on the other hand, can also be used to treat pregnant women, but the placental barrier prevents them from reaching the fetus. Remission of clinical symptoms and a four-fold drop in maternal Rapid Plasma Reagin (RPR) titers from the time of diagnosis to the time of delivery were considered signs of a successful maternal treatment. In order to lower the high rates of inadequate syphilis treatment during pregnancy, which will lower congenital syphilis and problems related to neonates, an integral and high-quality prenatal care program is essential.

Declaration by Authors

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