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SYPHILLIS IN PREGNANCY: A LITERATURE REVIEW

I Putu Bagus Mulyana Yoga, Anak Agung Gede Raka Budayasa
Wijaya Kusuma University, Surabaya, Indonesia
Subdivision of Feto Maternal, Obstetric and Gynecologist Department,
Sanjiwani General Hospital, Bali, Indonesia
Email: myoga4587@gmail.com, rakabudayasa@ymail.com

Abstract

Syphilis is a bacterial sexually transmitted disease (STI) caused by Treponema pallidum. Syphilis can be transmitted through sexual contact, blood transfusion and vertical transmission from mother-to-child. Syphilis in pregnancy that is left untreated might lead to miscarriage, stillbirth, neonatal death, premature birth, low birth weight, and congenital syphilis. Syphilis in pregnancy, although results in high morbidity and mortality, is actually preventable through early screening and treatment. Diagnosis of syphilis in pregnancy is made through history taking, physical examination, laboratory testing and radiology. Screening for syphilis in pregnant women is important as many people with syphilis are often asymptomatic or experience very mild symptoms. Screening can be done in the first trimester using non-treponemal tests such as rapid plasma regain (RPR) or Venereal Disease Research Laboratory (VDRL), and can then be confirmed with treponemal tests such as (Treponema pallidum haemagglutination assay (TPHA) or fluorescent treponemal antibody absorption (FTA-ABS). All pregnant women who are tested positive for syphilis should promptly receive Benzathin penicillin G as the first-line treatment. Screening and treatment of syphilis in early pregnancy may help reduce morbidity and mortality of congenital syphilis.

Keywords: congenital syphilis, syphilis, syphilis in pregnancy

Introduction

Syphillis is a sexually transmitted disease (STD) that is still prevalent globally with substantial morbidity and mortality.[1] In 2088, WHO estimated that there would be 1.4 billion pregnant women with probable active syphilis (PAS) or syphilis infection sufficiently active to result in mother-to-child-transmission (MTCT), with an estimated 52% of PAS cases resulting in adverse pregnancy outcomes (APOs).[2]

Syphillis might be transmitted through sexual contact, blood transfusion and vertical mother-to-child-transmission (MTCT).[1,3] It is estimated that the risk of transplacental infection ranges from 20-80% depending on various factors such as maternal stage of infection. This number is far above the risk of transmission of HIV from mother-to-child which is estimated to be 20%.[7]

Transmission of syphilis from mother to fetus results in high morbidity and mortality as syphilis often lead to adverse pregnancy outcomes (APOs) as well as

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congenital syphilis.[1,4,5] Adverse pregnancy outcomes (APOs) due to syphilis might be in the form of early preganancy loss, stillbirths, premature births, and low birth weight, among others. Besides APOs, syphilis transmitted from mother to child might also lead to congenital syphilis which often results in permanent sequels such as saddle nose, Hutchinson's teeth, and mental retardation.[3,5,6]

Eventhough APOs and congenital syphilis result in high mortality and morbidity, these are preventable through early screening and prompt treatment of preganant women with syphilis. Unfortunately, many pregnant mothers do not realize that they are being infected, especially in the early stage of the disease as the signs and symptoms are often not specific.[5] Therefore, it is important for us to review and understand syphilis in pregnancy, which includes its transmission, pathogenesis, clinical manifestations, screening and diagnosis, as well as the correct treatment strategies.

EPIDEMIOLOGY

Syphillis is a chronic systemic disease caused by bacteria *Treponema pallidum (T. pallidum).*[1,5,6] The origin of syphilis is still controversial, but its morbid entity has been known since the end of the 15th century when there was a big syphilis pandemy in 1940 – 1500, which was termed "The Great Pox". For a long time, syphilis was believed to be a psychiatric disease. This opinion was later disputed in 1908 when Ilya Mechnikov, who worked at the Pasteur Institute in Paris at the time, successfully incoculated monkeys with *T. pallidum*. This research was able to confirm the infectious nature of syphilis.[5]

Syphilis has long been well known for its high morbidity and mortality rates. In 2012, WHO estimated that globally, there were 5.6 billion new syphilis cases in the age group 15-49 years old, with the global incidence of 1.5 cases per 1000 females and 1.5 cases per 1000 males. Overall, it was estimated that in 2012, there were 18 billion syphilis cases, which resulted in the global prevalence of 0.5% in females, and 0.5% in males aged 15-49 years old. Furthermore, it was also estimated that there were 930.000 pregnant women suffered from syphilis in 2012.[1,8]

Syphilis in pregnant women that is inadequately treated would increase the risk of vertical transmission from mother-to-child and result in adverse pregnancy outcomes (APOs) or congenital syphilis.[9] There are >50% infants suffering from congenital syphilis as a result of untreated primary and secondary maternal syphilis.[4] The risk of APOs such as stillbirths, premature birth, and low birth weight increases 12 folds in untreated pregnancy. In a systematic review, APOs occurred in 76.8% of pregnant women with untreated syphilis, whereas in pregnant women who were not infected by syphilis, APOs occurred in 13.7% of pregnancies.[4,7,10] The risk of congenital syphilis is thought to be especially higher in women who are infected for the first time when they are pregnant.[11]

The morbidity and mortality rates associated with congenital syphilis is also substantially high. In 2012, it was estimated that syphilis caused 350,000 APOs, with 143,000 cases of early fetal deaths/stillbirths, 62,000 cases of neonatal deaths, 44,000

cases of premature births/low birth weight, and 102,000 cases of babies with congenital syphilis. In 2016, there were more than 500,000 cases of congenital syphilis worldwide, which resulted in more than 200.000 neonatal deaths and stillbirths.[9] Besides, the risk of HIV transmission from mother-to-child increases when there is syphilis and HIV coinfection during pregnancy.[1,6] The burden of disease is currently highest in low to middle income countries, especially African countries.[1,12]

There is currently no comprehensive data regarding syphilis in Indonesia. However, according to Dirjen P2P Kemenkes RI in 2017, there were 3,295 pregnant women with syphilis among 39,660 pregnant women who underwent syphilis screening during antenatal care (ANC). This number was lower than what was previously obtained in 2016, which was 4,169.[3]

ETIOPATHOGENESIS

Syphilis is caused by gram-negative bacteria *Treponema pallidum subspecies pallidum* (ordo *Spirochaetales*).[1,6,13] The bacteria is spiral shaped and very motile, which moves in spiral motion due to the movement of the filaments of its flagella.[4,5,13] *T. pallidum* is approximately 5-15 µm in length and 0,15 µm in width.[5] There are three organism in the same genus that do not cause sexually transmitted disease. *T. pallidum subspecies pertenue* causes yaws, *T.pallidum subspecies endemicum* is known to result in nonvenereal syphilis (has been eradicated) and *T. carateum* causes pinta.[6,13] These subspecies are difficult to be distinguished from their morphology and antigenicity, but they differ in the age of onset, transmission modes, clinical manifestations, their ability to invade the central nervous system and placenta, as well as in their genomic sequence.[13]

Treponema pallidum is a human obligat that has high ability to invade and escape the immune system. The clinical manifestations of syphilis are the results of local inflammation response initiated by the presence of spirochetes in tissues. Patients with syphilis often go through different stages of the disease, which are primary, secondary, latent and tertiary stages which may span for $\geq$ 10 years. Early syphilis is usually defined as an infection transmitted via sexual contact (be it primary, secondary, or early laten stage) and may also be termed active syphilis (infectious). WHO defines 'early syphilis' as an infection with < 2 years duration, whereas guidelines from the United States and Europe defines it as an infection with < 1 year duration.[1,13]

Treponema pallidum has a long generation time, that is 30-33 hours, which makes long-acting penicillins such as benzathin penicillin G, as drugs of choice for treating syphilis. Since the widespread use of penicillin in 1940s, the prevalence of syphilis has continuously dropped in regions with adequate syphilis testing and treating.[5,13] Nevertheless, outbreaks still happened in various regions in the world.[13]

Syphilis can be transmitted via sexual relationships, blood transfusion and vertical transmission from mother-to-child.[3-5,13] Besides that, syphilis is also known to be transmitted from mother to child during delivery if the baby comes into contact with the

mother's genital lesions. Syphilis cannot be transmitted through breastfeeding, unless there are lesions in the mother's breasts.[3]

Sexually transmitted syphilis may happen within the first 1-2 years of exposure to *T. pallidum*, that is in the primary, secondary or early laten stage.[13] Spirochetes of *T. pallidum* are able to penetrate mucous membranes or breaks in the skin, and then spread throughout the body. The incubation period ranges from 21 days to 6 months.[4,5]

Congenital syphilis is the result of *T. pallidum'*s transplacental transmission from mother to child. The bacteria are able to penetrate the placenta since 10-20 weeks, in which the risk of fetal infection would increase as the gestational age increases.[3] At the gestational age of 16 weeks and above, the bacteria would be able to spread to different organs and cause damages to the placenta and the umbilical cord (microvascular proliferation and inflammation).[7] Transmission of syphilis would continue to occur until fetal immune system matured. The bacteria will then invade the fetal reticuloendothelial system and cause spirochaetemia (disseminated spread of spirochetes). The bacteria which at first entered via the blood system will now be able to invade other organs such as the skin, mucous membranes, bones, and the central nervous system. *Treponema pallidum* is able to adhere to endothelial cells which leads to proliferation of endothelial cells and occlusion of the lumen of blood vessels. This further leads to destruction and necrosis of tissues surrounding them. In the early stage of fetal infection, *T. pallidum* causes destruction of placenta, which then progresses into hepatic dysfunction, infection of the amniotic fluid, hematologic disturbances, and organ failure in later stage.[3]

Based on the stages of infection, the risk of transmission from mother to fetus is the highest in the primary and secondary stages, followed by early latent stage. Nevertheless, the risk of transmission is still present up to 4 years after the first exposure to *T. pallidum*.[13] The risk of transmission at primary stage or secondary stage without adequate treatment is approximately 50-60%. The risk of transmission at laten or tertiary stage is approximately 10-20%.[3]

The clinical manifestations of syphilis infection in fetus depends on maternal clinical stage. About 30% pregnancies resulted in intrauterine fetal death, stillbirths (fetal deaths at the end of second trimester or third trimester), and deaths right after delivery. Infants born from mothers with syphilis are often born prematurely, with low birth weight or with clinical manifestations similar to neonatal sepsis, such as poor feeding, lethargy, skin rash, jaundice, hepatomegaly and anemia.[1-5,13]

CLINICAL MANIFESTATIONS

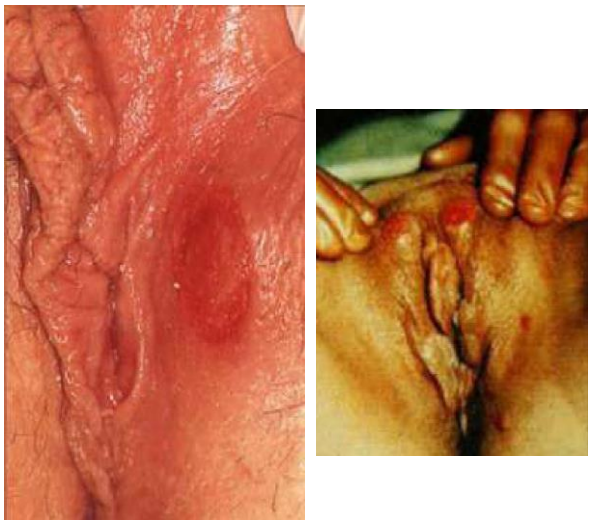
Syphilis is often called the Great Imitator or Great Mimicker for its varied and unspecific clinical manifestations.[13] There is no differences in the clinical manifestation of syphilis among the preganant and non-pregnant populations.[3] Clinically, syphilis is divided into primary, secondary, latent and tertiary stages.

Primary Syphilis

Patients with primary syphilis often present with single ulcer (chancre) or multiple lesions in their genitals or in any other parts of the body where inoculation of *T. pallidum* occurred, as well as regional lymphadenopathy.[3-5,13] These primary lesions often occur within 3 weeks of exposure to *T. pallidum*, have flat bases, elevated margins, appear erythematous, are usually about 0.5 – 2 cm in diameter, almost always painless, and would resolve spontaneously. Multiple lesions are more often observed in HIV patients.[5] Regional lymphadenopathy may persist until months after the primary lesions have healed. Oftentimes, the lympnodes are hard, non-supurative, and painless.[3]

Primary syphilis is often left unnoticed by most patients, especially women, as besides the lesion are painless, they are often located at the entrance of the vagina.[4,5] The resolution of primary lesions occur within 3-6 weeks, after which the patients would enter the secondary stage 6-8 weeks later.[5,13]

Secondary Syphilis



Picture 1
Primary syphilis ulcers at the labia

The manifestations of secondary syphilis occur in patients who do not receive adequate treatments during their primary stage. Secondary syphilis is also termed spirochaetemia (bacteremia) stage as spirochetes have spread through various organs in the body.[4,5] Clinically, dermatological manifestations are the ones that are most frequently found. About 90% of women with secondary syphilis show non-pruritic maculopapular rash in the flank, shoulder, arms, chest, and back regions, with frequent involvement of the palms of the hands and soles of the feet.[5,13] Besides that, we may also find superficial silver or grey-coloured erosions on the genitalia, anus, and/or oral mucous membranes. The dermatological manifestation might also be in the form of condyloma lata, which appear as grey plaques found in intertriginous regions such as the labium major and minor.[5]

Constitutional symptoms such as fever, headache, pharyngitis, malaise, arthralgia, and myalgia are the second most frequent manifestations of secondary syphilis.

Furthermore, invasion of bacteria into the central nervous system is frequently found in this stage, with 40% adult patients showing abnormalities in their cerebrospinal fluids.[3-5]

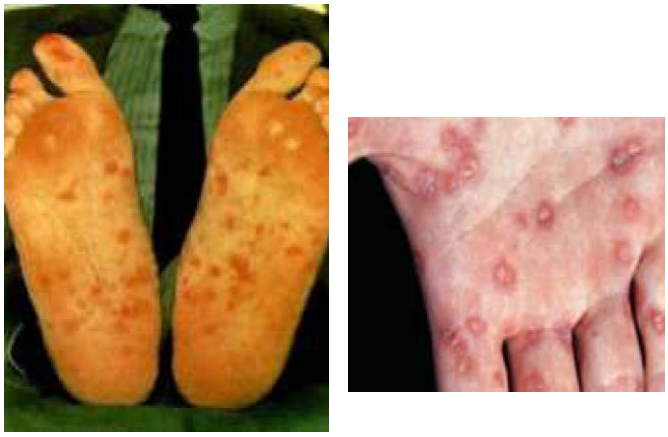
As syphilis is often termed "The Great Imitator", during secondary stage, we may also find hepatitis, gastritis, uveitis, keratitis, optic neuritis, otosyphilis, neurosyphilis, and bone infections.[5] Within 2-6 weeks, the signs and symptoms would improve, and hence patients would enter the latent phase which may last for years. In the first 1-2 years of latency, the patients are still infectious because there is 25% risk of relapse as secondary syphilis-like form.[13]

Latent Syphilis

Latent syphilis is divided into early latent phase (< 12 months) and late latent phase (> 12 months). In the early latent phase, relapses occur in 20-25% of female patients, whereas relapses in the late latent phase are far less frequent and the patients are deemed no longer nfectious via sexual contact. Nevertheless, some reports suggest that vertical transmission from mother-to-child can still occur whether the mother is in the early or late latent phase, although the risk of transmission is still lower compared to that of primary and secondary syphilis. In the latent phase, there are no signs or symptoms, but serological tests would show positive results for syphilis.[3,5]

Tertiary Syphilis

Tertiary syphilis is estimated to occur in 1 in 3 patients who do not receive treatments and may occur years after the initial infection.[5] Several early literatures



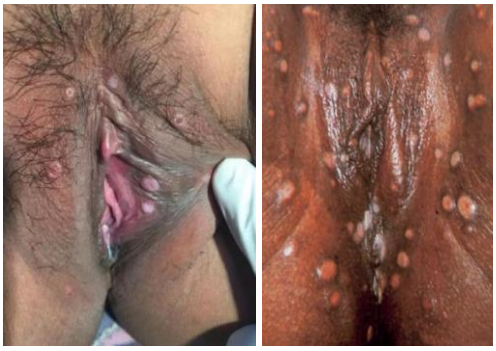
Picture 2
Erithematous rash on the palms of the hands and soles of the feet.[6]

suggest that 15-40% untreated patients would enter the tertiary stage. Tertiary syphilis presents as heart and nervous system disorders, severe skin lesions or visceral organ lesions (gumma) and bone involvement.[5,13]

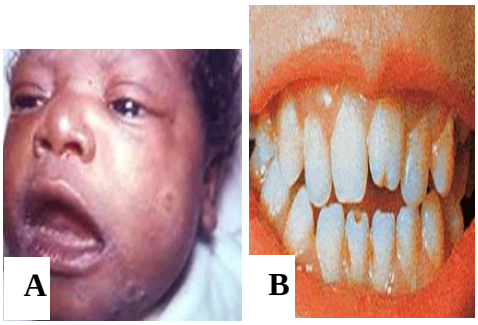
Approximately half of tertiary syphilis patients show benign syphilis in the form of gumma, which are destructive granulomatous lesions in various organs. In half of the

rest of the patients, about a quarter suffer from cardiovascular syphilis in the form of aorta necrosis which may lead to saccular aneurism.[5] In the other one quarter rest of the patients, they suffer from neurosyphilis.[4,5] Most of syphilis-related deaths are due to cardiovascular syphilis.[4]

Neurosyphilis causes various manifestations, such as chronic meningitis, meningoavascular stroke-like syndromes and other manifestations that are often found in tertiary syphilis patients (tabes dorsalis, general paresis, progressive dementia).[13] One of the pathognomonic sign of neurosyphilis is the presence of Argyll-Robertson pupil.[5] Recent literatures report that tertiary syphilis are not as frequent as before because of the widespread use of antibiotics.[13]



Picture 3. Condiloma Lata.[3,15]



Picture 4. Congenital Syphilis. (A) Mucocutan lesion, (B) Hutchinson teeth.[6]

Sifilis Kongenital

Pregnancy does not alter the clinical course of syphilis, but syphilis affects the course of pregnancy.[4] Clinical manifestations of congenital syphilis depend on gestational age, maternal syphilis stage, treatment received by the mother, and fetal immune response.[14] The risk of congenital syphilis is closely related to the degree of maternal spirochaetemia and the duration of maternal syphilis, with primary and secondary syphilis pose the greatest risk.[5] The clinical spectrum of congenital syphilis include stillbirths, neonatal death, and non-immune hydrops. Besides that, congenital syphilis can also be classified into early congenital syphilis (age < 2 years old) and late congenital syphilis (age > 2 years old).[3,5,6]

Early congenital syphilis manifests as maculopapular rash that may progress into desquamation (70%), hepatosplenomegaly (70%), fever (40%), pneumonitis (20%), neurospyhilis (20%), osteochondritis, flu syndrome, and iritis.[3,5] Hepatomegaly in these patients is taught to be the result of syphilitic hepatitis, increased extramedullary hematopoiesis, cardiogenic hepatic congestion, or therapeutic paradox.[4]

In cases where congenital syphilis remain undetectable or has not been treated adequately, late congenital syphilis may be found. The classic triad of late congenital syphilis include Hutchinson's teeth, interstitial keratitis, and sensorineural deafness. Other signs of late congenital syphilis are saddle nose due to destruction of hard

palatum and nasal septum by gumma, bone sclerosis that causes anterior-bowing of tibia (saber shin), mulberry teeth, protrusion of frontal bone, syphilic rhinitis infantile which manifests as fissures around mouth and nose with angular cheilitis, seizure, and mental retardation.[3,5] These stigmata will remain throughout life and are unable to be cured completely.[3,11]

SCREENING AND DIAGNOSIS

Syphilis diagnosis is based on detailed anamnesis including of sexual history, clinical manifestations, laboratorium examinations and serologic examinations.[1] Unfortunately, supporting examinations for *T. pallidum* are often difficult as the bacteria cannot be cultured in-vitro or visualized with light microscopy. [4,5] Despite these challenges, there are several methods that are used to visualized spirochetes in order to support syphilis diagnosis. Below are several supporting examinations that are used to screen and diagnose syphilis.

Direct Observations

The most sensitive examination to diagnose syphilis is the Rabbit Infectivity Tests (RIT), in which a rabbit is given intratesticular injection of infected fluid or tissue. If the rabbit becomes seropositive, the lymphatic product of this first rabbit will then be injected into a second rabbit. Diagnosis is made if the second rabbit becomes infected with syphilis.[5] Examination using darkfield microscope is also a sensitive and specific tool to diagnose syphilis if there are skin lesions (hard ulcers or condyloma lata) from which exudates may be obtained.[3,5] The result of darkfield microscopy is often positive even before serologic tests show positive results.[15] However, darkfield microscopy may not be available in many places and most syphilis cases are asymptomatic.[4] Currently, polymerase chain reaction (PCR) of exudates from syphilis lesions is often done to diagnose syphilis. PCR is known to have higher diagnostic accuracy compared to darkfield microscopy. The use of PCR to test blood sample or cerebrospinal fluid is still under continuous research.[5]

Serologic Tests

Currently, the gold standard for diagnosing syphilis is a combination of nontreponemal and treponemal tests.[9]

Nontreponemal antibody tests

Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) are two nontreponemal serologic tests that are widely used. These tests measure the levels of antibody IgG and IgM patients in response to antigens that are products of cellular degradation (cardiolipin, cholesterol, lecithin).[4,5,14] The specifity of these tests ranges from 97-99% and is not affected by patients' clinical stage. The results of these tests are reported as titers, with higher titers represent increased disease activity and lower titers suggest disease resolution.[4]

Higher titers are found during primary and secondary syphilis if compared to latent syphilis.[4] Besides, RPR titer is usually higher than VDRL titer. For the purpose of patient's evaluation, it is recommended to use the same test type and laboratory (be it RPR or VDRL) to obtain consistency in results.[1]

False negative results might be due to prozone reaction where the level of nontreponemal antibodies is too high and hence prevents agglutination. This can be prevented by diluting the specimen at least 16 times.[1] On the other hand, false positive results might be obtained if there are other bacterial or viral infection, malignancy, drug use, pregnancy, autoimmune diseases, and aging process.[5]

Treponemal antibody tests

Treponemal serologic tests use specific antibody towards *T. pallidum*, and hence is appropriate as confirmation tests. Some examples of treponemal tests are fluorescent treponemal antibody absorption (FT-ABS) test, Treponema pallidum haemagglutination assay (TPHA) test, and Treponema pallidum particle agglutination (TP-PA) test.[1-5] FT-ABS dan TP-PA has specificity of 97-99% although they are non-quantitative in nature.[4]

Treponemal tests are more expensive and harder to perform, therefore, its use in screening process is often limited. Several new tests such as chemiluminescence immunoassays (CIA) dan multiplex bead enzyme immunoassay (EIA) are currently being developed to allow testing of fast number of samples with lower costs. [4,5] These two tests have similar specificities as FT-ABS and TP-PA and have better sensitifities for early stage syphilis that is often undetected by traditional treponemal tests.[4]

After patients receive therapy for syphilis, the result of nontreponemal antibody would be nonreactive although in small number of patients, the titers remain persistently low positive (serofast syphilis) with titer <1/8.[1,4,5] Serofast syphilis is usually found in latent syphilis. [4] On the other hand, if the treponemal tests are positive, 85% patients would remain positive for the rest of their lives. [1,5] In some cases whereby the nontreponemal and treponemal tests show positive results but the patients are showing no signs or symptoms, the differensial diagnosis would be serofast syphilis or latent syphilis, in which examination and treatment history should be obtain to distinguish them.[4]

Diagnosis Algorithm in Pregnant Women

All pregnant women should be screened for syphilis when they come for their first prenatal examination, and for those belonging to high-risk population, repeat examinations should be done at 28 weeks and right before delivery.[5] Centers for Disease Control and Prevention (CDC) recommends traditional algorithm for the diagnosis of syphilis. In this algorithm, nontreponemal test is done first. If the result is reactive, the patient will then be tested with treponemal confirmation test. However, in 2009, Association of Public Health Laboratories, UK Health Protection Agency and International Union Againts Sexually Transmitted Infections suggested the use of

reverse algorithm, whereby treponemal test is done first with CIA or EIA. If the result is reactive, the patient will then be tested with qualitative nontreponemal test such as RPR.[4,5] In cases where treponemal test results are reactive but nontreponemal test results are nonreactive, a second treponemal test will then be obtained with TP-PA.[4] this reverse algorithm shows better sensitivity, specificity, and diagnostic accuracy compared to traditional algorithm. In populations where syphilis is highly prevalent, the results of any discrepancy in the reverse algorithm in pregnant women should be deemed as early syphilis, and therefore, if the clinical manifestations lead to syphilis, treatment should be started promptly.[4] In patients who had been diagnosed with syphilis in the past, reverse algorithm should not also be used because confirmation tests would remain positive.[5]

Currently, rapid point-of-care testing (POCT) for syphilis has started to be used, which allows faster screening in pregnant women.[6,9] POCT tests that currently fullfil WHO criteria are mostly treponemal tests that use immunochromatography principle. However, recently, there are more POCT tests being developed that use the combination of treponemal and nontreponemal tests. POCT is a good alternative for areas in which resources are limited so that more screening and treatment could be done, especially for pregnant women.[1,9] In Indonesia, TP Rapid (*Treponema pallidum* rapid), which is a treponema rapid test, is allowed to be used as a screening tool in pregnant women. However, it can only be used as a replacement for TPHA. While TP Rapid provides faster results, unfortunately its price is still much higher than TPHA.[6]

Antenatal Diagnosis of Congenital Syphilis

Ultrasonography (USG) examination is very useful in diagnosing congenital syphilis before birth. Several anomalies that may be seen through USG are hepatomegaly (70%), Doppler velocitometry of medial cerebral arteri (MCA) (33%), placentomegaly (27%), polyhidramnion (12%), ascites (10%) and fetal hydrops. The administration of treatment to pregnant women will result in resolution of those signs in the order of Doppler abnormalities, ascites, and polyhydramnion. The last sign that resolves with adequate therapy are placentomegaly and hepatomegaly.[4]

Congenital syphilis was diagnosed after birth in 39% infants who had previously abnormal USG.[4,5] Therefore, besides for identifying the probability of congenital syphilis, USG may also be used to gauge the effectiveness of therapy given to the mothers.[5] Rac et al. recommends several structures/components that have to be visualized and documented during USG examination for pregnant women with syphilis. These structures include (i) liver length; (ii) placental thickness; (iii) peak systolic velocity of MCA; (iv) amniotic fluid index (AFI); and (v) evaluation for ascites or hydrops.[4] Normal USG results do not exclude the possibility of congenital syphilis as $\pm$ 12% neonates with normal USG results eventually needed therapy for congenital syphilis when they were born. Several bone manifestations are also undetected by USG.[4]

TREATMENT

The only recommended treatment for syphilis in pregnant women is currently benzathin penicillin G (BPG).[1,3-6] BPG has an efficacy of 99.7% in treating syphilis in pregnant women, and 98.2% in preventing congenital syphilis in all stages of maternal syphilis.[4]

The WHO guideline recommends the administration of a single dose 2.4 millions unit BPG injected intramuscularly in pregnant women with early syphilis (primary, secondary or early laten with duration of disease < 2 years). In pregnant women whose syphilis duration is > 2 years or in whom the stage of disease is undetermined, WHO recommends the administration of 2.4 millions unit of BPG once a week for 3 consecutive weeks.[1,6]

It is recommended that maternal treponemal titer is obtained on the same day as the start of the therapy in order to determine the effectiveness of the therapy given. This is particularly important in places where diagnostic test and initiation of therapy are done on separate days. Nontreponemal titers should then be obtained in the 1st, 3rd, 6th, 12th and 24th months after initiation of therapy.[3,5] A reduction of 4-fold in nontreponemal titer can usually be observed in the 6th month, and will be non-reactive in the 12th to 24th months.[1,5]

The reduction in titer can vary depending on gestational age. There are only 35% mothers who are able to reduce their titer until 4 folds. According to CDC guideline, if the titer does not reduce 4 folds, serologic surveillance should be done postpartum. If instead of decreasing, the titer increases, along with persistent signs and symptoms or relapses, re-treatment should be considered. Any failures in maternal therapy should always be suspected as neurosyphilis.[5]

Failure in fetal therapy is defined as the presence of congenital syphilis despite adequate treatment received by the mothers. Several risk factors for failure in fetal therapy include early syphilis (<1 year), abnormalities found during USG examination, and therapy initiated in advanced gestational age. The timing of therapy does not affect the rate of maternal recovery, but it does affect the probability of congenital syphilis, in which as the interval between birth and initiation of therapy becomes shorter ($\leq$ 30 days), the risk of congenital syphilis becomes higher.[5]

If mothers are allergic to penicillin, desensitization protocol should be initiated and then BPG administration is initiated. If desensitization is not possible, WHO recommends the administration of erythromycin 4 x 500 mg per oral for 14 days, or 1 gram ceftriaxone intramuscular once daily for 10-14 days, or single dose azithromycin 2 grams per oral in early syphilis.[1] In syphilis of > 2 years in duration, the patients can be given erythromycin 4 x 500 mg per oral for 30 days. One of the disadvantages of using macrolides is its inability to cross placental barrier and hence are not able to treat congenital syphilis.[1]

Jarisch-Herxheimer (JH) Reaction

Treatments against spirochetes may trigger JH reaction as a result of rapid killing of spirochetes which lead to the massive release of endotoxins, lipopolisaccharides, porstaglandins, and cytokines, leading to acute inflammation reaction.[3-5] The clinical manifestations of JH are temporary and in the form of systemic manifestations and local exacerbations. Symptoms and signs include fever, tachycardia, chills, athralgia, pharyngitis, headache, leukocytosis with lymphopenia, and the worsening of cutaneous lesions that is often termed therapeutic paradox.[3-5] Symptoms and signs that are specific to pregnancy include uterine contractions (56-67%), decrease in fetal movements (67%), and fetal heart rate decceleration (50%). Clinical manifestations appear within 2-8 hours after the initiation of PBG and resolve within 24 hours.[4]

Management for JH reaction is symptomatic in nature, such as the administration of antipyretic and intravenous fluid. JH reaction occurs in 44% of pregnant women and may induce preterm labour, fetal heart rate abnormalities and even stillbirths. JH reaction occurs in 100% primary syphilis, 60% secondary syphilis, and in more than half of syphilis with unknown duration. Therefore, the first administration of BPG in pregnant women should always be done in a healthcare facility with continuous observation of the fetus for 24 hours.[4]

Conclusion

Syphilis is a sexually transmitted disease that may also occur in pregnant women. Syphilis in pregnancy does not alter maternal syphilis course of disease or manifestations, but it may severely affect the pregnancy and the fetus, which leads to high mortality and morbidity. Fortunately, early screening and prompt treatment have been proven to help reduce the risks of APOs and congenital syphilis in the unborn child

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