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Syphilis in pregnancy

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ABSTRACT

Syphilis is a disease caused by *Treponema pallidum* subspecies *pallidum* (*T. pallidum*) through sexual contact or vertical transmission during pregnancy. It is responsible for several hundred thousand stillbirths and neonatal deaths every year worldwide. Prenatal screening for syphilis is critical in order to detect syphilis infection and to prevent congenital syphilis. There are two types of antibodies, treponemal and non-treponemal and two algorithms available for diagnosis. Treatment should be administered according to the stage of syphilis and the antibiotic of choice for pregnant women with syphilis is penicillin G (benzathine penicillin). Non-treponemal antibodies are used for follow-up. There is no vaccination for syphilis that protects both the mother and the fetus. Reducing the incidence of congenital syphilis requires coordinated action involving public health authorities and medical care units.

Keywords: syphilis, pregnancy, transmission, diagnosis, treatment, prevention

INTRODUCTION

Sexually transmitted infections or diseases (STIs or STDs) are the most prevalent infections associated with pregnancy [1]. The tools used in antenatal care, in order to reduce the prevalence of these disorders are education, prevention and screening [1]. Since they could harm both the mother and the fetus, they should be actively diagnosed and treated [1].

Treponema pallidum subspecies *pallidum* is a spirochete bacterium that causes a systemic disease called syphilis [2]. It is only transmitted between humans via sexual contact or vertical transmission during pregnancy [2]. This disease has a major impact on the course and outcome of pregnancy because syphilis is associated with an increased risk for still birth and or/abortion (21%), preterm delivery 6%), neonatal mortality (9%) and congenital infection [3-6].

This paper aims to review the epidemiology, etiology, clinical manifestations, diagnosis, and current treatment of syphilis in pregnant women and neonates, who have been exposed to syphilis during pregnancy or at birth.

EPIDEMIOLOGY AND RISK FACTORS

Despite the near eradication of syphilis with the discovery of penicillin as a uniquely successful cure in the 1940s, the disease continues to be a major public health problem [7,8].

An estimated 6 million new cases of syphilis are diagnosed every year in people aged 15 to 49 throughout the world [9-12]. Syphilis is responsible for over 300,000 fetal and neonatal fatalities.

In 2016, WHO (World Health Organization) published a new plan to fight STIs between 2016 and 2021[10,12]. By 2030, the strategy aims to eliminate congenital syphilis and to reduce the global syphilis

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incidence by 90 % and 50 or fewer cases per 100,000 live births of congenital syphilis in 80% of countries [10,12]. The means used to reach these targets consist in implementing comprehensive syphilis screening and treatment among pregnant women and specific populations [10,12].

Risk factors associated with STDs in pregnant women are multiple sex partners in the past year, incarceration, substance abuse, young age, African American and Hispanic ethnicity, low socioeconomic status, less education, inadequate prenatal care, prostitution [13,14].

PATHOPHYSIOLOGY AND TRANSMISSION

T. pallidum is a Gram-negative, highly mobile bacterium with a spiral form [15,16]. It has the ability to elude the immune system and is known for its invasiveness [17].

The spirochetes reach the human body directly through an injury of the vaginal or anal mucosal surfaces, through oral-genital or genital-genital contact with an infected partner [14]. Other ways of transmission are trans-placentally following maternal spirochetemia or vertically, at the time of delivery, when the newborn gets in contact with maternal genital lesion(s) [14,18]. The disease has approximately 21 days incubation period before onset of clinical symptoms [19].

Transplacental transmission is most common during the early stages of fetal development (14-16 weeks of gestation), when *T. pallidum* spirochetes can pass through the chorionic layers of the amniotic sac and infiltrate the developing fetus [20-22]. As the maternal infection remains untreated, the pathophysiology of fetal syphilis is defined by early hepatic and placental involvement, followed by amniotic fluid infection, hematologic dysfunction, ascites, and eventually fetal IgM production [23].

The transmission of this disease to the fetus depends on the time elapsed between the mother's infection and the beginning of pregnancy [4,5]. Early-stage syphilis carries the highest likelihood of infection [19-24]. In the event of untreated primary or secondary maternal syphilis, the transmission rate is higher (60-90 percent), lowers to 40% in early latent syphilis, and is below 10% in late latent mother syphilis [4,5]. Centers for Disease Control and Prevention (CDC) reports from 2019 show that congenital syphilis appears in 50 to 80% of women with untreated primary, secondary or early latent syphilis and in about 10% of women with late latent syphilis [25].

CLINICAL MANIFESTATIONS

Syphilis can be classified in 2 stages depending on the time of the diagnosis and clinical features: early stage (<12 months from acquisition to diagnosis) and late stage (>12 months from acquisition to diagnosis) [19]. Early stage is subclassified in primary, secondary, and early latent syphilis [19].

Primary syphilis occurs during the first 3 months after exposure [20]. Its characteristic clinical manifestation is a painless chancre, raised, red, firm border, with a smooth base [2,20,26]. The chancre appears wherever the bacteria enter the body [26]. For pregnant women, it often occurs intravaginally, as result of sexual intercourse [20]. Another clinical manifestation that may occur is localized lymphadenopathy [8,20,26]. Primary syphilis usually resolves in 3-8 weeks without treatment [20].

Secondary syphilis appears in 4-10 weeks after the chancre, being the result of hematogenous systemic dissemination of the bacteria [8,26]. Clinical manifestations of secondary syphilis include multiple organs and systems [26]. Ninety percent of women with secondary syphilis have dermatological abnormalities such as diffuse macular rash, plantar and palmar target-like lesions, patchy alopecia and mucous patches [26]. Genital tract lesions appear in 20% of women and include condyloma lata and generalized lymphadenopathy [26]. Women may present fever, malaise, anorexia, headache, arthralgias and myalgias in 70 percent of the cases. Central nervous system abnormalities appear in 40% of cases and 1-2% of women can develop aseptic meningitis [26]. Other clinical manifestations that could be seen in women with secondary syphilis are hepatitis, nephrotic syndrome, ocular changes, anterior uveitis, and periostitis [8,26]. The lesions in secondary syphilis may also resolve within 1 to 6 months [19,25,27].

Early latent syphilis is an asymptomatic, yet infectious stage [26]. It develops if primary or secondary syphilis is not treated [26]. This stage lasts no longer than 12 months after the disease has been acquired [14].

Late latent syphilis is an asymptomatic stage. Frequently in this phase the risk of transmission is rarely, but there are some cases of maternal to child transmission [26]. Fifteen to forty percent of patients from this stage develop tertiary syphilis [8].

Tertiary syphilis is not usually seen in the reproductive age groups [26,28].

CONGENITAL SYPHILIS

Congenital syphilis can occur at any gestational age, but ultrasound (US) findings, if present, can be detected after 18–20 weeks' gestation [23]. The most common US abnormalities found are hepatomegaly (80%), fetal anemia as evidenced by elevated peak systolic velocity (PSV) in middle cerebral artery (MCA) Doppler (33%), placentomegaly (placental

thickness exceeding 4 cm) (27%), polyhydramnios (12%), ascites and/or fetal hydrops (10%) [8,23,29-31]. Other less common US abnormalities include small bowel dilatation or hyperechogenicity, splenomegaly, cardiomegaly, pericardial effusion and bent long bones [23].

Prenatal US has limitations, and it may not detect all cases of congenital syphilis [23]. This matter should be addressed in patient counseling and neonatal assessment [23].

The majority of infants delivered by mothers with untreated syphilis are asymptomatic at birth and have no clinical or laboratory signs of infection, but, if left untreated, they may develop disease symptoms months or years later [3,32,33]. There are two characteristic syndromes of congenital syphilis: early congenital syphilis and late congenital syphilis [8].

Early congenital syphilis refers to the disease diagnosed in the first 2 years of life [8]. Clinical manifestations may involve symptoms comparable to those in adult secondary syphilis [8].

Clinical examination could find signs of non-immune hydrops fetalis, intrauterine growth restriction or small for gestational age, hepatomegaly (possible with jaundice), splenomegaly, lymphadenopathy (specifically epitrochlear nodes), maculopapular skin rash (palmar, plantar, perianal, perioral), condyloma lata, hearing loss, cataract, glaucoma, chorioretinitis, uveitis, central nerve palsies and seizures [34].

Laboratory tests could find hemolytic anemia, thrombocytopenia, hypoglycemia, elevated liver enzymes (ALT, AST), elevated alkaline phosphatase, direct hyperbilirubinemia, elevated proteins in cerebrospinal fluid [34].

Radiography identifies bone abnormalities (periostitis, osteochondritis) [34].

Late congenital syphilis syndrome is diagnosed after two years of life [8]. Clinical manifestations of late congenital syphilis are presented in table 1. The association of interstitial keratitis, deafness due to damage to the eighth cranial nerve and Hutchinson's teeth is pathognomonic for late congenital syphilis and is called the Hutchinson triad [4,5,35].

TABLE 1. Late congenital syphilis clinical manifestations (4,5,8,35)

Dentition:	Hutchinson's teeth; Mulberry molars
Eye:	Interstitial keratitis; healed chorioretinitis
CNS:	Hydrocephalus; seizures; optic nerve atrophy; cranial nerve palsies; developmental delay
Bones:	Saddle nose deformity; frontal bossing; short maxilla; protuberant mandible; high palatal arch; saber shin; sternoclavicular joint thickening.
Other:	8th nerve deafness; rhagades

CNS: central nervous system

PRENATAL SCREENING

United States Preventative Services Task Force (USPSTF) recommends that screening for syphilis should be done in all pregnant women as early as possible in the pregnancy, preferably during the first prenatal visit [36] [37]. Serologic testing should be performing at 28-32 weeks of gestation and again at birth in populations with a high incidence [1,36]. Any mother that experience fetal demise should be tested for syphilis [36].

DIAGNOSIS AND MANAGEMENT

Direct methods of diagnosis

Syphilis is a difficult disease to diagnose since *T. pallidum* cannot be cultured and can only be seen directly in primary syphilis using dark-field or fluorescence microscopy [19]. The microscopic methods have limitations, such as being time-consuming, the probe must be examined rapidly, within minutes after collecting, the probe has to be operated by individuals with vast experience and specific training and requires expensive equipment. The direct methods are not used for routine screening [38].

Serologic testing

Serological testing is the pillar of syphilis laboratory diagnosis. There are two types of antibodies, treponemal and non-treponemal.

The non-treponemal antibodies are direct antibodies against lipoidal antigens such as cardiolipin and lecithin [19,38]. Rapid plasma reagin (RPR) test and the Venereal Disease Research Laboratory (VDRL) technique are examples of non-treponemal tests [19,38]. These tests can be run qualitatively or quantitatively and has a low specificity for syphilis, and a high rate of false-positive results [38].

The treponemal antibodies are IgM and IgG antibodies directed against *T. pallidum* membrane lipoproteins [38]. Examples of treponemal tests: fluorescent treponemal antibody absorption (FTA-ABS) test, *Treponema pallidum* particle agglutination (TP-PA) assay microbead immunoassays, enzyme immunoassays (EIA), and chemiluminescent immunoassays (CIA) [38]. EIAs and CIAs have similar sensitivities (95-99%) and specificities (95-99%) and are better in diagnosing primary syphilis [39-43].

For diagnosing syphilis there are two algorithms used, the traditional and the reverse algorithm. The traditional testing algorithm for syphilis (Figure 1) uses firstly a qualitative nontreponemal test for screening (RPR or VDRL) [17]. If the RPR is positive, a confirmatory treponemal test (TP-PA or FTA-ABS) is performed in order to rule out any false-positive result [17,43]. This method is less expensive than reverse screening algorithm and does not require

highly specialized laboratory equipment, but it is limited by the technologist's subjective interpretation [17]. If a confirmatory treponemal test is not performed, there is a risk that previously treated, early untreated and late latent cases to be missed and biologically false-positive cases can be over treated [17].

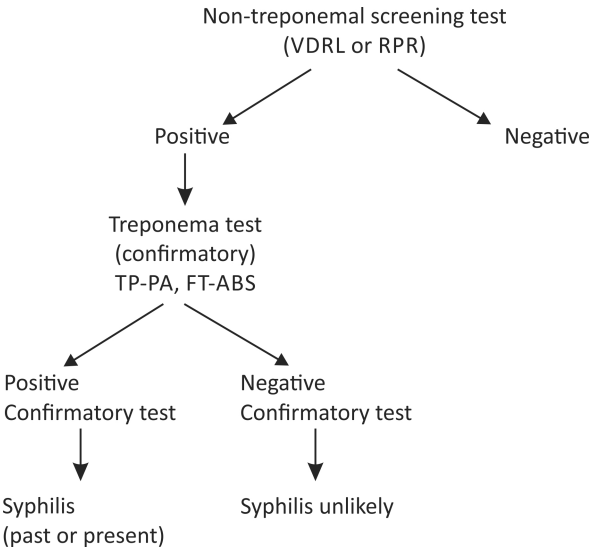

FIGURE 1. Common algorithm for diagnosing syphilis [17] *(VDRL: Venereal Disease Research Laboratory; RPR: rapid plasma regain; TP-PA: treponema pallidum partical agglutination test; FTA-ABS: fluorescent treponemal antibody absorption)*

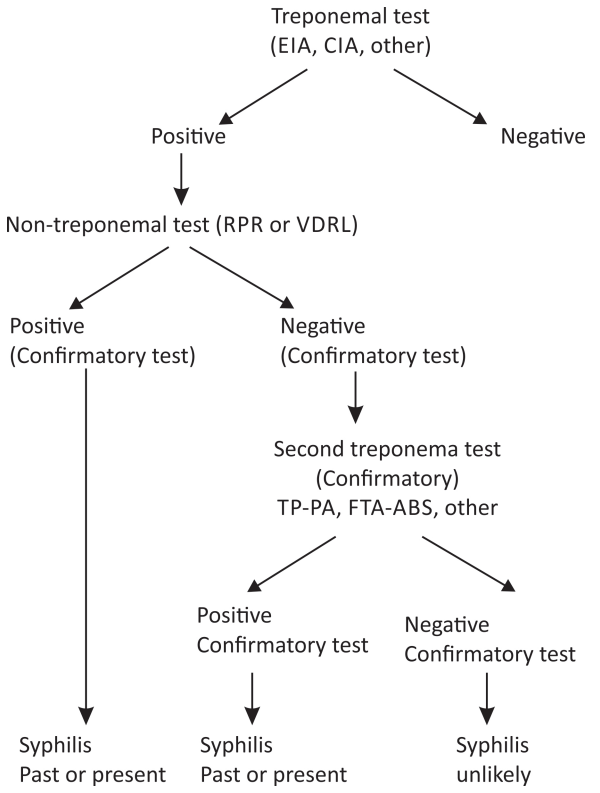

FIGURE 2. Reverse algorithm to diagnose syphilis [17] *(EIA: enzyme immunoassay; CIA: chemiluminescence immunoassay; RPR: rapid plasma regain; VDRL: veneral disease research laboratory; TP-PA: treponema pallidum partical agglutination test; FTA-ABS: fluorescent treponemal antibody absorption)*

The reverse algorithm (Figure 2) uses firstly a treponemal test with recombinant *T. pallidum* antigens (EIA or CIA) [17]. When reactive, a non-treponemal test (RPR or VDRL) is followed [17]. If the non-treponemal test is negative, a different treponemal test, that was not used for the initial screening, is performed (TP-PA or a FTA-ABS) [17]. This technique has greater initial setup costs than the standard algorithm [17]. A positive treponemal test should be ideally followed by another treponemal test or a non-treponemal test, because EIAs and CIAs are non-specific and have a high false positive rate [17]. However, considering the severe consequences of syphilis in pregnancy, a patient with a positive treponemal test should be treated [17]. The studies comparing the reverse and traditional algorithms show that, while reverse algorithms have a greater false-positive rate in both low- and high-prevalence areas, they discover syphilis cases that traditional testing would have missed [19,44-47].

TREATMENT

The treatment of choice for pregnant women with syphilis is penicillin G (benzathine penicillin) [14,19]. Fortunately, there were no *T. pallidum* resistant to penicillin identified [48]. Penicillin treatment has 98.2% effectiveness in pregnant women [19]. When diagnosing pregnant women with it, is important to treat promptly, to also consider treating the sexual partners to minimize the risk of reinfection [49].

For the treatment of early-stage syphilis in pregnant women, the WHO guidelines and European guidelines are identical [50,51]. The dosage of penicillin is determined by the stage of syphilis as shown in table 2 [19,50,51].

TABLE 2. Dosage of penicillin to treat each stage of syphilis (19,50,51)

Stage of syphilis	Treatment
Early stage (primary, secondary, early latent)	Benzathine penicillin G 2,4 mil.u,IM, 1 dose
Late latent syphilis	Benzathine penicillin G 2,4 mil. u, IM, weekly, for 3 doses
Syphilis of unknown duration	
Tertiary syphilis	
Neurosyphilis	Aqueous crystalline penicillin G, 18-24 mil.u, IV, daily, for 10-14 days.

Some studies suggest that pregnant women with early-stage syphilis should receive a second dosage

of penicillin one week following the first [6,19,50,52]. It is important to take the entire regimen [19]. If any doses are missed, the full regimen should be repeated [19].

For pregnant women there are no other treatment options. Doxycycline, tetracycline, azithromycin, and cephalosporins are not acceptable alternatives in pregnancy [19,53].

Pregnant women with a history of penicillin allergy should be skin tested to confirm the risk of anaphylaxis [26]. If confirmed, the recommendation is: penicillin desensitization and after that benzathine penicillin G regimen [26,36].

Penicillin desensitization entails a gradual increase in diluted dosages, with either oral or IV regimens, until the desired dose is reached [19,50,54,55]. Either regimen is equally effective and takes approximately 4 to 12 hours to complete [19]. Desensitization should occur in hospital setting due to the risk of anaphylaxis and epinephrine and other anti-anaphylaxis medicines should be available [19]. Each time penicillin is needed in the future, the desensitization procedure should be performed [19].

CDC and WHO have different treatment recommendations for congenital syphilis. CDC recommends treatment of neonates in case of probability of having congenital syphilis.

In 2016, WHO issued the following recommendations for the treatment of congenital syphilis presented in table 3.

TABLE 3. The WHO recommendations for the treatment of congenital syphilis [56]

Clinical status of infants	Treatment
Infants with confirmed congenital syphilis 100,000 u/kg/day	Aqueous benzyl penicillin to 150,000 u/kg/day, IV, for 10-15 days **or**
Infants clinically normal, but mothers had: u/kg/day, single – Untreated syphilis – Inadequately treated syphilis (within 30 days of delivery)	Procaine penicillin 50,000 dose, IM, for 10-15 days.
– Syphilis treated with non-penicillin regimens	Close monitoring If decided to treat:
Infants with no clinical signs of infection and whose mothers had syphilis adequately treated with no sign of reinfection	Benzathine penicillin G 50,000 u/kg/day, single dose, IM.

FOLLOW-UP

Providers must document that women are appropriately treated for the syphilis stage and verify that clinical and antibody responses are suitable for the patient's disease stage, which necessitates coordinated prenatal care and treatment [36]. For follow-up the non-treponemal antibodies are used [19].

The 9-month length of pregnancy complicates follow-up surveillance [19,57]. CDC recommends that health providers document if pregnant women with syphilis are adequately treated for the syphilis stage [36]. In pregnant women, if the disease is diagnosed before 24 weeks of gestation, the follow up consists in repeating serologic titers in 8 weeks after completing the treatment [36]. They should be tested again upon delivery [36]. If reinfection or treatment failure is suspected, titers should be redone sooner than 8 weeks [36]. Serologic titers should be repeated after delivery for syphilis identified and treated after 24 weeks of pregnancy [36].

In pregnancy, there are no targets established for non-treponemal antibodies decline [19]. Serologic titers should be tested regularly for women at high risk of reinfection to monitor for substantial titer changes [19]. After delivery women should become part of the general follow-up scheme if maternal titers have not dropped by four-fold at the time of birth [19].

PREVENTION

For syphilis there is no vaccine to provide protection for both mother and fetus. In order to develop a vaccine for syphilis there is the necessity to guarantee safety and efficacy during pregnancy and with HIV coinfection [8]. Another requirement for the syphilis vaccine is to protect both the individual from disseminated illness after initial infection and partners following exposure to primary chancres [8,58].

Lithgow KW et al. described a vaccine candidate that targets the adhesion protein Tp0751, which is thought to play a crucial role in the spread of organisms from the main chancre [8,59].

CONCLUSIONS

Syphilis is the most prevalent congenital infection in the world. In order to reduce the incidence of congenital syphilis and neonatal sequelae, all pregnant women should be tested for syphilis and infected mothers should be treated. Coordinated actions involving public policy reform, health agencies, clinical care delivery locations and physicians, are required to work together to reach this goal.

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