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Review Article

Syphilis in pregnancy

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ABSTRACT

Congenital syphilis is showing a rising trend globally. Materno-fetal transmission of syphilis can be prevented by ensuring early diagnosis and prompt treatment of infected pregnant women. The risk of transmission from mother to child is directly related to the quantity of *Treponema pallidum* in the maternal circulation. Maximum number of the organisms is seen in early syphilis. Hence, early syphilis in mother (in comparison to late syphilis) places the baby at a higher risk for congenital syphilis. Amniocentesis and cordocentesis may help in the prenatal detection of congenital syphilis. Ultrasonography and Doppler studies supported by serological tests, and polymerase chain reaction, and dark field microscopic examination of the specimen from suspected lesions of early syphilis of mother may help to diagnose congenital syphilis prenatally. Benzathine penicillin G in appropriate dose is the ideal drug for syphilis in pregnancy, except for neurosyphilis for which the drug of choice remains crystalline penicillin.

Keywords: Congenital syphilis, Amniocentesis, Cordocentesis, *Treponema pallidum*, Pregnancy

INTRODUCTION

Syphilis is a great imitator. Maternal syphilis continues to be an important cause of perinatal mortality and morbidity.[1] Syphilis showed a marked decline in the late phase of 20th century probably due to the adoption of safe sex practices in the setting of human immunodeficiency virus (HIV) infection. But with the introduction of highly active anti-retroviral therapy, HIV has become a manageable disease and with it a relaxation is witnessed among high-risk groups regarding adoption of safe sex practices.[2]

Untreated syphilis in females of reproductive age assumes significance since they can transmit the infection to the fetus.[3] Congenital syphilis can be eliminated by effective screening and adequate treatment of infected, pregnant women.

SYPHILIS IN PREGNANCY: RECENT TRENDS

Trivedi *et al.,* reported a rise in syphilis among pregnant women after analyzing the United States national case report data for 2012–2016.[4] Congenital syphilis in the United States increased from 9.2 cases per 100,000 live births in 2013 to 48.5% cases per 100,000 births in 2019.[5] A similar picture was observed in other countries as well.[6]

Using a mathematical model, national syphilis seropositivity data, data on antenatal care coverage from the WHO (World Health Organization), and published literature, researchers estimated the number of pregnant women who had an active syphilis infection as 1.4 million in 2008. A more

disturbing information was the fact that 80% of them had attended antenatal care services. Adverse outcomes estimated due to maternal syphilis were 520,000 in 2008. This included stillbirths or fetal deaths (215,000) and neonatal deaths (90,000). Sixty five thousand were preterm or low birth weight infants. One hundred and fifty thousand infants had congenital heart disease. It was reported that 66% of those who suffered adverse effects were women, who were either not tested or treated for syphilis, despite accessing antenatal care facilities. Most of these adverse outcomes (87%) were reported from Africa and Asia.[7]

Using 2016 data, WHO in 2019, estimated that more than 900,000 pregnant women were infected with syphilis. The estimated numbers for congenital syphilis, adverse birth outcomes, and non-clinical cases ("infants without clinical signs born to untreated mothers") were 661,000, 355,000, and 306,000, respectively.[8] Fifty seven percentage of adverse birth outcomes (which included infants with clinical features of congenital syphilis, preterm or low-birth weight infants, neonatal or early fetal deaths and stillbirths) occurred in pregnant women who were enrolled in antenatal care (ANC), but not screened for syphilis. Those not enrolled in ANC contributed to 21% of adverse outcomes, while 16% and 6% of adverse birth outcomes were seen in screened, but untreated and enrolled, screened, and treated mothers respectively.[8]

INITIATIVES FOR PREVENTION OF CONGENITAL SYPHILIS

The WHO initiative for "the global elimination of congenital syphilis," launched in 2007 had aimed to ensure screening for syphilis in at least 90% of pregnant women by 2015. Another goal envisioned was ensuring adequate treatment to at least 90% of seropositive pregnant women. The strategy was focused around four public health factors. They were: "political advocacy and community engagement, adequate coverage and quality of ANC, access to and quality of syphilis testing in ANC, and routine surveillance, monitoring, and evaluation."[9] The initiative was integrated with elimination of mother to child transmission (MTCT) of HIV.[9]

The WHO released the first edition of "The global guidance on criteria and processes for validation: Elimination of mother-to-child transmission of HIV and syphilis" in 2014.[8] The WHO established the "Global validation advisory committee for elimination of mother to child transmission (EMTCT)" in 2015.[8] The second edition of the guidance, which was published in 2017, made it more relevant by including prevention of vertical transmission of communicable diseases under the realms of maternal and child health services. "EMTCT of HIV, syphilis, and hepatitis B virus (HBV)" is recommended as the "triple elimination initiative" in the third version (2021) of the guidance. The goals set include "zero new HIV infections in infants and young children, elimination of congenital syphilis and viral hepatitis as public health threats and ≤0.1% prevalence of HBsAg (hepatitis B surface antigen) among children ≤5 years of age by 2030." Whether to apply for single/dual/triple elimination is left to individual country, though it is advised to report data regarding all three infections, irrespective of whether a triple validation is sought or not.[8]

MATERNAL RISK FACTORS FOR SYPHILIS IN PREGNANCY

Multiple partners, substance use during sex or transactional sex, late entry to prenatal care or no prenatal care, incarceration of the woman or her partner, unstable housing or no house, high risk behaviors, and inadequate of treatment of the patient or partner are the maternal risk factors for syphilis in pregnancy.[10]

EFFECTS OF SYPHILIS ON PREGNANCY

Usually primary, secondary, and early latent syphilis (asymptomatic syphilis in the first year of infection) are considered as the infectious stages of the disease. However, the chance of an untreated pregnant woman with syphilis passing on the infection to the fetus is 70% during the first 4 years of disease.[10] The factors that determine the frequency of vertical transmission are gestational age and duration of maternal infection. With advancing gestational age, the risk of vertical transmission increases, but the severity of fetal infection decreases.[11] A shorter duration of maternal infection, increases the risk of vertical transmission.[12] Although vertical transmission can happen at any stage of maternal disease, the chances are much less after the first 10 years of infection.[12] A higher load of treponemes is seen in early syphilis; hence early syphilis in pregnancy carries a higher risk of transmission to fetus in comparison to late syphilis.[11,13] Early diagnosis and prompt management of syphilis in pregnancy may help to avoid the maternal and fetal complications.

Fetal loss, stillbirth, hydrops fetalis, neonatal and infant death, prematurity, low-birth weight, active congenital syphilis in the neonate, congenital defects, and long-term sequelae such as deafness and neurological impairment among new born babies are the adverse outcomes due to syphilis in pregnancy.[10] Gestational age of infection, stage of maternal syphilis, treatment received by the pregnant woman and the immunological response mounted by the fetus determine the clinical outcome.[10]

Untreated primary and secondary syphilis may result in intrauterine death in 25% of affected women. Among the remaining pregnant women with untreated primary and secondary syphilis, 50% deliver babies with congenital

syphilis, 25% give birth to seropositive infants, and 25% deliver uninfected babies.[14]

If the mother has untreated, early latent syphilis, the adverse outcomes reported are stillbirth (10%), premature delivery (20%), early neonatal death (4%), and babies born with congenital syphilis (40%). Untreated late latent syphilis in mother causes congenital syphilis in 10% of newborns and preterm delivery or stillbirth in another 10%. If left undetected and untreated, 25% of newborns with signs and symptoms of syphilis die shortly after birth.[14]

A systematic review of six case-control studies reported that pregnant women with syphilis had a 52% higher frequency of developing any adverse pregnancy outcome in comparison to women without syphilis.[7] A comparison of adverse pregnancy outcomes between women who had untreated syphilis during pregnancy and those without syphilis showed an absolute difference of 21% for stillbirth or fetal loss. Absolute differences were 9% and 5% for neonatal death, and prematurity or low-birth weight respectively.[7]

Another systematic review that evaluated 54 observational studies documented a dramatic reduction in the incidence of congenital syphilis, preterm birth, low-birth weight, stillbirth, and neonatal death among pregnant women with syphilis who received treatment during pregnancy in comparison to those who had untreated syphilis.[15] The absolute difference was 21% for fetal loss or stillbirth, 9% for neonatal death, and 6% for prematurity or low-birth weight. However, when the affected person received treatment in the third trimester, only a slight reduction in stillbirth or fetal loss was observed, when compared to women who had untreated syphilis during pregnancy.[15] To ensure adequate treatment, the treatment of pregnant woman should be completed at least 30 days before delivery.[4]

Table 1 shows the adverse pregnancy outcomes due to maternal syphilis as reported in some previous studies.[16-18]

Kassowitz law states that the severity of fetal infection due to maternally transmitted syphilis decreases in successive pregnancies.[19] A pregnant woman with syphilis suffers an abortion (usually after 5 months of gestation) initially. In subsequent pregnancies the outcome varies from pre-term stillbirth, term stillbirth, alive child with signs of congenital syphilis, apparently healthy infant developing signs of early congenital syphilis in the first few weeks or months of life or a late congenital syphilis in later life, birth of an infant with serological positivity only, and finally birth of a healthy child.[19]

In addition to the adverse pregnancy outcomes, syphilis increases the risk of acquisition and transmission of HIV by 2- to 5-fold since syphilitic lesions cause disruption of mucosal and epithelial barriers. Moreover, syphilitic lesions contain mononuclear cells with enhanced expression of chemokine receptor type 5 (CCR5), the co-receptor for HIV.[20] A previous study found syphilis to be the second common sexually transmitted infection (following herpes genitalis) coexisting with HIV.[21]

PATHOGENESIS OF CONGENITAL SYPHILIS

Syphilis initially infects the placenta. *Treponema pallidum* (*T. pallidum*) can cross the placenta and infect the fetus as early as the 9th week of intrauterine life.[14] However, the fetus is unable to mount an immunological response before the 4th month of intrauterine life.[14] Moreover, certain biochemical requirements of the organism is believed to be deficient in the fetus.[14] Hence, the pathological changes occur only after 18–20 weeks of intrauterine life, when the fetus becomes immunocompetent.[14]

The pathological changes observed in both congenital and acquired syphilis are due to endarteritis obliterans and its consequences.[22] Treponemes can infect any organ of the fetus.[22]

Although congenital syphilis is the frequently used terminology, prenatal syphilis is considered as a better term since the signs and symptoms may occur before or after delivery. Mothers may transmit the disease either transplacentally or during delivery when the baby comes in contact with the infected genital lesion. Breastfeeding is not considered as a mode of transmission for congenital syphilis in the absence of infective lesions on the breast.[14]

DEFINITION OF CONGENITAL SYPHILIS

Confirmed congenital syphilis

When *T. pallidum* is identified in lesions, placenta, umbilical cord, or autopsy tissue of the infant.[14]

Presumptive congenital syphilis

(i) Any infant whose infected mother was either not treated or treated with antibiotics other than penicillin before delivery.[14]
(ii) Any infant or child with reactive treponemal test (TT) for syphilis and any one of the following[14]
   (a) Evidence of congenital syphilis on physical examination or X-ray of long bones
   (b) Cerebrospinal fluid (CSF) of infant showing reactive venereal disease research laboratory test (VDRL) or elevated lymphocyte count and protein (without other cause)
   (c) Rapid plasma reagin (RPR) four-fold higher in baby than in mother (both drawn at birth)
   (d) Infant with reactive immunoglobulin M – treponemal antibody test in serum

Syphilitic stillbirth

A fetal death after a 20-week gestation or death of a fetus weighing >500 g of a mother, who had untreated or inadequately treated syphilis at delivery.[14]

Table 1: Adverse pregnancy outcome in maternal syphilis.

Study	Study setting	Status of infection	Sample size	Pregnancy outcome (in percentage)			
				Stillbirth	Pre-term birth	Low birth weight	Congenital syphilis
Wan *et al.*	All syphilis infected pregnant women who delivered ≥ 28 gestational weeks and were registered in China's Information system of prevention of mother-to-child transmission in Jiangxi Province, between 1.1.2013 and 31.12.2019	Untreated	1364	1.8	10.5	7.8	2.3
		Inadequately treated	1299	1.8	11.7	7.9	2.7
		Adequately treated	1547	0.5	5.6	3.7	0.7
Watson-Jones *et al.*	Study participants were recruited in the delivery suites of the 2 main government hospitals in Mwanza City and of a district hospital serving a rural population in Sengerema, Tanzania from 1.6.1998-31.4.2000	Past/treated syphilis	9	0	0	11	-
		Low titer, active syphilis	27	0	0	4	-
		High titer, active syphilis	73	25	20	33	-
Hira *et al.*	An intervention project conducted in Lusaka, Zambia that recruited pregnant women from three study and control centers when presented in labor at the University Teaching Hospital (September 1985-January 1986 and February-June 1987)	Less than 50% of seroreactive women could be treated.	230	7	12.2	21.3	2.2

FEATURES OF CONGENITAL SYPHILIS IN THE NEWBORN

A newborn with congenital syphilis is often asymptomatic at birth with some of them manifesting rash, hemorrhagic rhinitis, lymphadenopathy, skeletal anomalies, anemia, hepatosplenomegaly, blindness or deafness during the initial weeks of life. An apparently healthy child developing signs of congenital syphilis after a few weeks of delivery is not uncommon and is referred to as Profeta's law.[7,23]

EFFECT OF PREGNANCY ON SYPHILIS

Primary syphilis is often unrecognized in women as it may remain asymptomatic or may manifest in the hidden parts of the genitalia. Hyperemia, eversion, and friability of cervix in pregnancy facilitate the entry of organisms.[12] A quantitative maternal non-treponemal titer above 1:8 dilution could be a marker of early infection and bacteremia.[12]

It is obvious that syphilis can produce harmful effects on pregnancy. On the contrary, pregnancy is considered to have a benign effect on syphilis. Moreover, pregnant women with syphilis are less likely to develop cardiovascular or neurosyphilis.[23]

INVESTIGATIONS

Serological tests may help to arrive at a presumptive diagnosis of congenital syphilis.

Table 2 shows the investigations that are found useful in syphilis in pregnancy.[1,14,24-27]

When lesions of primary or secondary syphilis are evident, darkfield microscopy serves as a specific and early diagnostic test.[1] However, a failure to detect the organism on darkfield microscopy does not exclude syphilis since the sensitivity of the same to detect *T. pallidum* varies from 71–90%.[28] Poor technique and prior intake of systemic or topical antibiotics may lead to false negative reactions. Specimens such as serum or amniotic fluid should be examined immediately, since a decrease in motility of the organism occurs within minutes, and this would hamper their detection in darkfield microscopy.[1]

Serological tests include TTs and non-TTs (NTTs). NTTs such as VDRL test and RPR become reactive 1–2 weeks after the onset of primary syphilis; but become non-reactive in 25–30% of late latent syphilis. NTTs usually become non-reactive with adequate treatment. The time taken for the results to be non-reactive after adequate treatment varies with the stage of syphilis. A treated primary syphilis shows

Table 2: Evaluation of syphilis in pregnancy.

Specimen		Investigation	Remarks
Lesions of primary or secondary syphilis	Immediate examination possible	Darkfield microscopy	Detects the motile treponemes When negative, need to repeat daily for 3 days, especially if there is history of application of topical steroids or antibiotics
	Immediate examination not possible	Direct fluorescent antibody test (DFAT-TP)	Biopsy or necropsy specimens can also be used, the test has >90% sensitivity
		Multiplex polymerase chain reaction	-
Serum		Non-treponemal tests - venereal disease research laboratory test, rapid plasma regain test	To screen for syphilis infection or to follow-up treated patients
		Treponemal tests — enzyme immunoassay, fluorescent treponemal antibody absorption assay, *Treponema pallidum* particle agglutination assay, *Treponema pallidum* heme agglutination assay	To confirm the diagnosis
Amniotic fluid		Darkfield microscopy	Amniocentesis can be done from second trimester onwards *Treponema pallidum* in the amniotic fluid indicates severe fetal disease
		Multiplex polymerase chain reaction	78-86% sensitivity and 100% specificity
Fetal blood		Fetal blood analysis	To detect anemia, abnormal liver transaminase, thrombocytopenia, fetal anti-treponemal IgM
Umbilical cord blood		Percutaneous umbilical cord blood sampling (cordocentesis)	

When maternal syphilis is diagnosed after 20 weeks of gestation, fetal ultrasound examination is recommended

non-reactive serology within 1 year of treatment, while this takes about 2 years in secondary syphilis. The results may become non-reactive after a few decades even in untreated. Titer of antibodies reflects the disease activity. After treatment, a four-fold decrease on follow up suggests effective and adequate treatment while fourfold increase indicates an active disease. Seropositive pregnant women are considered infected, unless she has clearly documented evidence of having received adequate treatment.[27]

A reactive NTT at a low titer may be a biological false positivity due to pregnancy. It should be confirmed with TTs. A pregnant women with biological false positivity (a positive NTT and a negative TT) is advised follow-up testing 4–6 weeks after delivery to confirm the biological false positivity. Refrigerated cold sera may produce negative result, so refrigerated sera must be warmed before testing.[29]

Among TTs, EIA (enzyme immunoassay) detects both IgG and IgM antibodies against *T. pallidum*. IgM EIA (Captia IgM EIA) gives positive result 2 to 3 weeks after infection. It is the first test to become positive in a syphilitic infection and has a sensitivity of 93% in primary syphilis. Reactivity decreases with increasing duration of syphilis. IgM reactivity in a new born confirms prenatal infection since IgM antibodies do not cross placenta.[14] Captia IgM test is increasingly used as a screening test. Tests based on IgG yields a positive result 4–5 weeks after infection. Hence, IgM test is more useful as far as early diagnosis is concerned.[14]

Fetal ultrasound examination is recommended when maternal syphilis is diagnosed after 20 weeks of gestation. A large and edematous placenta is a characteristic feature of fetal infection. Other findings are hydrops placenta, chorionic villitis (plasma cells with inflammatory infiltrate), perivillous proliferation (onion skin vessels), normoblastemia, necrotizing funisitis, acute chorioamnionitis, and plasma cell deciduitis. The initial features of fetal infection are placental involvement and hepatic dysfunction, followed by infection of amniotic fluid, hematological abnormalities, ascitis, and hydrops fetalis.[30] Other ultrasonogram signs of fetal infection are hepatomegaly, polyhydramnios, ascitis, hydrops fetalis, and abnormal

Doppler findings of middle cerebral artery (elevated peak systolic velocity in the middle cerebral artery, indicative of fetal anemia).[30]

Rac *et al.,* in a retrospective study that assessed the serial ultrasound findings and infant outcomes in 235 seropositive women after 18 weeks of gestation and who underwent an initial ultrasound before treatment, reported that the ultrasound findings that resolved first after treatment were middle cerebral arterial Doppler abnormalities, ascitis, and polyhydramnios followed by placentomegaly and finally hepatomegaly.[31] The authors had information on infant outcomes for 173 deliveries. Thirty-two infants (18.5%) had congenital syphilis. Congenital syphilis was more common in those with antenatal ultrasound abnormalities (39% vs. 12%; $P < 0.001$). Among infants with congenital syphilis, hepatomegaly was the most frequent antenatal ultrasound finding. Hepatomegaly developed early and was the last ultrasonogram finding to resolve after antepartum treatment. The authors concluded that sonographic signs of fetal syphilis indicated a higher risk for congenital syphilis.[31]

TREATMENT

Table 3 shows the treatment of syphilis in pregnant women.[27]

A pregnant woman, who had received adequate treatment for syphilis previously and showing stable, serofast, low non-treponemal titers might not require additional treatment, if she is not a high-risk person for re-infection. High antibody titers or a rising antibody titers in a pregnant woman (even if previously treated) might indicate re-infection or treatment failure.[27]

Table 3: Treatment of syphilis in pregnant women.

Clinical scenario	Treatment
Early syphilis	Benzathine penicillin G 2.4 million units administered intramuscularly in a single dose, an additional dose repeated 1 week after the first dose may be beneficial to prevent congenital syphilis
Late syphilis	Benzathine penicillin G 2.4 million units administered intramuscularly in a single dose every week for 3 weeks
Late syphilis	
Does not return for the next dose on 7th day	All efforts should be made to contact the patient and offer treatment before 9th day
Could not give next dose before 9th day	To repeat the whole treatment
Neurosyphilis, ocular syphilis or otosyphilis	Aqueous crystalline penicillin G 18-24 million units per day (3-4 million units intravenously every 4 hours) for 14 days
Patient with a history of an allergic reaction to penicillin	Desensitize and treat with penicillin

Women treated for syphilis with penicillin during the second half of pregnancy may develop Jarisch-Herxheimer reaction. The reaction can cause contractions, fetal heart rate abnormalities, and even stillbirth. The risk is higher in the pregnant woman who has early syphilis due to a high load of treponemes. The reaction is not an adverse reaction to penicillin and should not be a contraindication to treatment. Antipyretics may offer symptomatic relief in Jarisch-Herxheimer reaction, but may not prevent it.[27]

If syphilis is diagnosed and treated at or before 24 weeks of gestation, a repeat NTT should not be carried out before 8 weeks after treatment, since a rise in non-treponemal titer may be noted soon after treatment which is considered as indicative of treatment response. Hence, unless signs of primary or secondary syphilis exist (suspected cases of re-infection or treatment failure), follow-up titer should not be attempted before 8 weeks after treatment. The non-treponemal titer should be repeated at delivery if the affected pregnant woman had received treatment after 24 weeks of gestation.[27]

A four-fold decrease in titer may not be achieved at delivery and does not indicate treatment failure. However, a four-fold rise in titer after treatment and that persists for 2 weeks or more indicates treatment failure or re-infection.[27]

Maternal treatment is likely to be inadequate if the pregnant woman was treated with erythromycin instead of penicillin (since erythromycin has only poor to fair ability to cross placenta), or if delivery occurred within 30 days of treatment or clinical signs of infection are present at delivery or the non-treponemal titer at delivery is four-fold higher than the pre-treatment titer.[14,27] The infant should be thoroughly evaluated at birth.[14,27] If the evaluation that includes complete blood count, long bone radiograph and CSF analysis is within normal limits and if follow-up is certain, the infant may be treated with single dose of benzathine penicillin G 50,000 units/kg body weight administered intramuscularly. If any component of the evaluation is abnormal or could not be performed or CSF analysis could not be interpreted due to contamination with blood or if follow-up is uncertain, the infant should receive crystalline penicillin G 100,000–150,000 units/kg body weight/day (50,000 units/kg body weight/dose 12th hourly for first 7 days of life and every 8 hours thereafter) for a total of 10 days.[27]

CONCLUSION

Prevention of congenital syphilis can go a long way in reducing child mortality and improving maternal health.

Healthcare workers and public should be educated regarding the importance of early diagnosis and treatment to ensure prevention of transmission of syphilis from mother to child. Centers for Disease Control and Prevention recommends that all pregnant women should receive a non-treponemal serology screening test for syphilis at the first antenatal visit. Among population where prenatal care is not optimal, screening for syphilis has to be carried out at the time of pregnancy test itself and those found infected (after confirmation with TT) should be treated.[29] Serology testing is to be repeated twice during the third trimester (at 28 weeks of gestation and at delivery) for women, who are at high risk of acquiring the infection in pregnancy and those who live in communities that show a high rate of syphilis infection.[27]

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

Dr. Melathil Sadanandan Sadeep and Dr. Kunjumani Sobhanakumari are on the editorial board of the Journal.

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