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Review Article

Syphilis in Pregnancy - Revisted

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Abstract

Introduction: Syphilis continues be prevalent the world over even during this millennium. The global burden of syphilis infection is high, with an estimated 10.6 million cases occurring annually; and this is not only a health and pubic hazard; but is known to affect the pregnancy, fetus, newborn and children. Ten to 70% of the infected mothers, if untreated, give birth to children with congenital syphilis. Treatment of the infected mother during pregnancy can significantly reduce the chances of congenital syphilis and identifying and treating pregnant women with syphilis is a public health priority.

Materials and Methods: This prospective study was conducted by the departments of Obstetrics and Gynecology at three different institutes; one an Indian Armed Forces hospital and two medical colleges over a period of three years. The study was primarily for antenatal cases and newborn babies; but known or diagnosed cases of syphilis from dermatology departments were also included in the study. The data related to pregnancy and syphilis were collected.

Results and Observations: 8733 cases were registered as antenatal cases during this period. 3847 (43.8%) cases were primigravida's and remaining 4886 (55.9%) were multigravidas. 7 cases were found to be positive by non-treponemal tests. The spouses of positive cases were also tested. One newborn baby had congenital syphilis and one mother had frank secondary syphilis, but her baby did not have any sign of congenital syphilis.

Discussion: Syphilis is one of the sexually transmitted diseases; the causative organism being bacterium Treponema pallidum. Its transmission is possible from mother to baby during pregnancy or at birth, resulting in congenital syphilis. The Centers for Disease Control and Prevention recommend all pregnant women be tested. Screening for syphilis during pregnancy is an ideal time to detect the disease early and prevent fetal affection.

Conclusion: Syphilis is easily diagnosed with non-expensive tests available. Syphilis is completely curable by Penicillin, and transmission to baby is prevented. Efforts should be made at every level of health care to increase the awareness about the seriousness of syphilis in pregnancy.

Keywords: *Congenital Syphilis; Pregnancy; Penicillin; Treponema*

Introduction

Syphilis continues be prevalent [1,2] the world over even during this millennium. The global burden of syphilis infection is high, with an estimated 10.6 million cases occurring annually; and this is not only a health and pubic hazard; but is known to affect the pregnancy, fetus, newborn and children. Present exists despite many public health programs, means to prevent transmission and treat the disease effectively with antibiotics. The disease may be transmitted sexually, via blood and blood products, organ donation and above all by vertical transmission from mother to child [3]. Most cases of syphilis transmission during pregnancy are thought to occur in utero trans placentally; although transmission during birth is possible [2].

It is a known fact that nearly all pregnant women with untreated primary or secondary syphilis will experience adverse outcomes, with half experiencing premature births, neonatal deaths and stillbirths, and half giving birth to infants with congenital syphilis (CS) [4]. Almost 70% of infected women will have untoward outcomes without antenatal screening and treatment [5]. Ten to 70% of the infected mothers, if untreated, give birth to children with CS [6] Treatment of the infected mother during pregnancy can significantly reduce the chances of congenital syphilis [7,8] and identifying and treating pregnant women with syphilis is a public health priority. Treatment of syphilis in mother will not only prevent fetal transmission but will also treat fetal infection.

Center for Disease Control (CDC) recommends that all pregnant women should be tested for syphilis serologically at the very first antenatal visit and, those who have high risk factors should be tested again in third trimester and in labour. Screening women for syphilis during pregnancy and providing proper treatment are the cornerstones of congenital syphilis prevention [9]. An early diagnosis of syphilis in antenatal period facilitates proper management and initiation of therapy to prevent transmission of congenital infections and anomalies of newborns [1]. Hence all women should be screened during pregnancy and treated if required.

A prospective study was conducted at three different hospitals for a period of three years to find out the incidence of syphilis in pregnancy and pregnancy outcomes where serological tests for syphilis were positive.

Materials and Methods

This prospective study was conducted by the departments of Obstetrics and Gynecology at three different institutes; one an Indian Armed Forces hospital and two medical colleges over a period of three years. The study was primarily for antenatal cases and newborn babies; but known or diagnosed cases of syphilis from dermatology departments were also included in the study. The following data were collected:

- Antenatal registration
- Timing of registration
- Standard tests for syphilis and follow up of antenatal cases if detected positive
- Treatment instituted to positive cases
- The newborn babies of positive cases were examined and followed for congenital syphilis; treatment to the babies was instituted as per standard guidelines.
- Newborn babies with suspicion or diagnosis of congenital syphilis were also included in the study

- Number of times the screening tests were done
- Screening tests done for unbooked and unregistered cases who were admitted at the time of labour
- Confirmatory tests of the cases detected to be positive on screening tests
- Testing of partners of positive cases
- Examination and testing of newborn babies of positive cases
- Positive cases from dermatology department
- Screening tests of mothers of all still birth cases
- HPE examination of placentae of still born cases to find out any evidence of syphilis.

All antenatal cases were tested for HIV as a standard practice; and those who were detected to have positive serological tests; their HIV status was compared. The demographic and clinical data of all the cases were collected, compiled and compared with literature.

Results and Observations

The study was conducted at three large institutes for a period of three years. 8733 cases were registered as antenatal cases during this period. 3847 (43.8%) cases were primigravidas and remaining 4886 (55.9%) were multigravidas. Of the 8733 cases registered with three institutes only 8234 (94.2%) delivered in the hospital where they were registered rest 499 (5.7%) had gone to other places for the delivery.

1945 (22.2%) were registered in first trimester, 6026 (69%) reported in second trimester and rest 762 (8.7%) reported in third trimester. 254 cases were admitted directly during labour. 42 (17.3%) cases were primigravida's and remaining 212 were multigravidas (83.4%). Of these 254 cases 212 were registered in some other hospital and 42 were admitted directly in labour without any registration anywhere. The age range was from 19 to 37 years which is comparable to other studies [10].

All registered cases had undergone standard tests for syphilis and 07 (0.08%) cases were detected to be positive. The spouses of these 07 cases were counselled for testing, 05 cases underwent testing, one case refused, and one was out of station hence could not come for testing. Of the 05 spouses who were tested; 2 were positive and three turned out to be negative. All the cases had undergone testing once only, none of the cases was counselled or tested for second test during third trimester of pregnancy. The cases who turned out to be positive underwent confirmatory test for syphilis, only one case was confirmed case of syphilis.

All the cases, antenatal and their spouses; who were detected to be positive were administered one dose of Benzathine Penicillin 2.4 mega units irrespective of confirmatory tests. Those who had confirmatory test positive were given three weekly doses. One positive case whose confirmatory test was negative but was administered three doses as her titres were very high. The newborn babies of positive cases were examined and followed for congenital syphilis; treatment to the babies was to be instituted if indicated. None of the babies whose mothers were positive had a positive test or signs of syphilis.

One newborn baby was diagnosed and treated as congenital syphilis. The mother was tested during first trimester and the test was negative. The baby was born at 35 completed weeks of pregnancy by vaginal route normally. Birth weight was 1.88 kg; baby was shifted to neonatal intensive care unit (NICU) due to prematurity and reduced movements of all four limbs. Other vital parameters and colour were normal. Baby had swollen wrists too. Provisional diagnosis of congenital quadriparesis was made keeping one of these causes like

Birth Trauma, Congenital Infections, Congenital Guillian Barre Syndrome, Spinal Cord Tumor, Spinal Cord Injury, Spinal Muscular Atrophy or Congenital Myopathy. The investigations done were PBS for Sepsis, CRP/Procalcitonin, RFT/LFT, Electrolytes, X-ray - Long Bones, MRI spine and cranium, TORCH Test and CSF examination. VDRL on CSF was positive. Blood examination showed lymphocytic leukocytosis. MRI brain features were suggestive of focal areas of altered signal intensity in the right tentorium cerebelli probably due to calcification. MR spine, eye and hearing examination and urine for metabolic screen were normal. Both the parents were VDRL and TPHA positive. X-ray long bones showed periosteal reaction. Baby was started on Inj Piperacillin for 21 days and injection Inj Benzathine Penicillin 50000 IU/Kg stat dose was given. Breast feeding and routine immunization were done. The parents were treated with three weekly doses of Benzathine Penicillin as the standard practice is. Old documents of the mother were reviewed; she had some skin lesions during 33 weeks of gestation and had shown to dermatologist, biopsy of the lesions too was performed with provisional diagnosis of secondary syphilis. She did not come for review as her lesions had disappeared spontaneously. She never had oral, vaginal or anal lesions. Skin biopsy showed evidence of secondary syphilis. The baby made a complete recovery and was discharged at the age of three weeks.

One antenatal case had vulval and anal lesions (Figure 1) and was referred to antenatal OPD for antenatal care. All her routine investigations were done which were normal except VDRL which was strongly positive. Her confirmatory test also was positive, and she was administered three weekly doses of Benzathine Penicillin. She made a remarkable recovery (Figure 2) and delivered a healthy baby vaginally at term; the baby did not have any clinical or laboratory manifestation of congenital syphilis. Baby was administered single dose of Benzathine Penicillin as the mother had evidence of syphilis during third trimester of pregnancy. Her husband's blood test showed positive screening and confirmatory tests, was treated on similar lines. Clinically he had no local lesions and denied history of extramarital sexual exposure.

Figure 1: *Anal and vulval lesions - condyloma.*

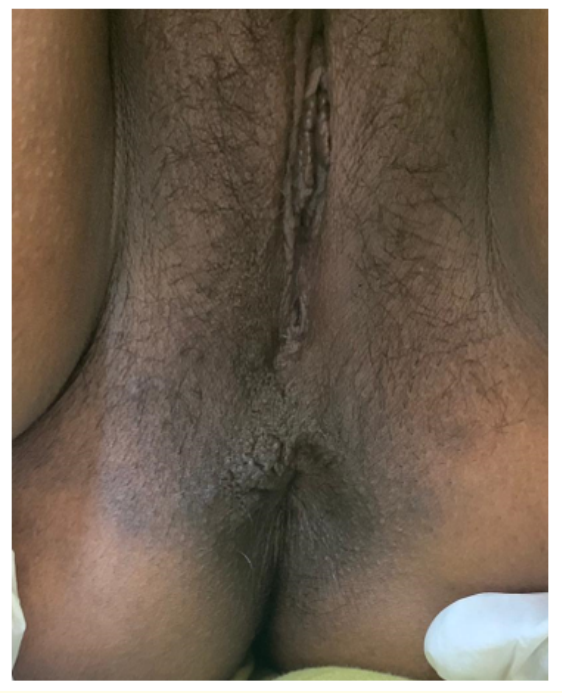

Figure 1: *Lesions after three penicillin injections.*

Screening tests were done for all unbooked and unregistered cases who were admitted at the time of labour; none of the cases was detected to be positive. Examination and testing of newborn babies of positive cases was done; no baby showed any clinical or laboratory evidence of syphilis.

Two cases were referred from dermatology department. One man and one woman-woman had clinical syphilis; as mentioned above. Man was married; the confirmatory tests were negative, and his wife was negative. He was counselled and treated with single dose of Benzathine Penicillin.

Tests were not repeated in any of the cases except those who delivered stillborn babies. 03 stillborn babies were delivered in the study group; one was from VDRL positive mother. HPE examination of placentae of these three babies was done which was unremarkable. Only one case of STS positive was HIV positive.

History of blood transfusion was inquired in all cases; 38 cases had been transfused blood in the past. Only one case had history of blood transfusion in STS positive cases.

Discussion

Syphilis is one of the sexually transmitted diseases; the causative organism being bacterium Treponema pallidum [10]. Maternal syphilis infection may be transmitted to baby during pregnancy or at birth [1,11]. The clinical presentation of the disease depends on the stage of syphilis whether primary, secondary, latent, or tertiary [3]. The primary stage typically presents with a single ulcer called chancre, but

sometimes multiple sores may be there. Secondary syphilis is characterized by a diffuse rash, which many times involves the palms and soles. Sores may be present in the mouth or vagina. Latent syphilis can last for many years when there are no clinical manifestations. Latent syphilis means a positive serologic test but without any signs and symptoms of the disease. It is defined as early when it is less than 1 year after secondary syphilis or late when more than 1 year. In tertiary syphilis, there are gummas, neurological problems, or heart symptoms. Syphilis has been known as "the great imitator" as it may cause symptoms similar to many other diseases [12]. Clinical manifestations of syphilis are not apparently altered by pregnancy. But chances of contacting syphilis and spirochaetaemia increase in pregnancy due to the cervical changes like hyperemia, eversion, and friability [13]. The bacteria can cross the placenta and infect the fetus from about 14 weeks' gestation, and the risk of fetal infection increases as pregnancy advances [12].

Congenital syphilis is very distressing manifestation of syphilis in pregnancy. The manifestations of congenital syphilis depend on many factors; gestational age, stage of maternal syphilis, maternal treatment and immunological response of the fetus [14]. Pregnancies complicated by syphilis may result in intra-uterine growth restriction, non-immune hydrops fetalis, stillbirth, preterm delivery and spontaneous abortion [3]. Placental involvement results in reduction of blood flow to the fetus there by causing fetal death. One third of the babies affected with CS are born alive. At times low birth weight may be the only manifestation of infection at birth. A large number almost to the extent of 60% are asymptomatic at birth [15,16].

The Centers for Disease Control and Prevention (U.S.) recommend all antenatal cases be tested for syphilis. Screening for syphilis during pregnancy is an ideal time to detect the disease early and prevent fetal and neonatal affection. Those who attend antenatal care but are not offered syphilis testing have been shown to have adverse outcome of the disease. The recommendations in Malaysia for antenatal screening include a non-treponemal serology test on first visit and subsequently again at 28 weeks of pregnancy [17]. Prenatal test for syphilis is important for the diagnosis, as it is very well-known fact that the timing of interventions in pregnancy can make a remarkable difference in the risk of having an untoward outcome [18].

Two types of blood tests are available; nontreponemal and treponemal. Venereal Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR) tests are the commonly performed. At times the results are false-positive; which may be due to pregnancy, autoimmune disorders, and infections [19]. False positives results may occur with some viral infections, such as varicella, measles, lymphoma, tuberculosis, malaria, endocarditis, connective tissue disease. All nontreponemal positive tests must be confirmed with a treponemal test, such as treponemal pallidum particle agglutination (TPHA) or fluorescent treponemal antibody absorption test (FTA-Abs) [12]. It takes about two to five weeks for Treponemal antibody tests to become positive after contacting the infection [20]. Nontreponemal antibody levels correlate with disease activity and are used for following up after treatment to find out the response hence quantitative results are necessary. Four times change in level; equivalent to a change of two dilutions is considered mandatory to show a clinically significant difference between two results obtained using the same serologic test. Nontreponemal test levels reduce after medication and might not be detectable later; however, in some antibodies can remain for a long time, a response called "serofast reaction." Many remain reactive for the rest of their lives, irrespective of treatment or disease activity. 15% - 25% of patients if managed during the primary stage become serologically nonreactive after 2 - 3 years. Treponemal antibody titers are not resorted to for finding out the response to treatment.

Incidence of seropositivity has been reducing over the last few decades [21]. Syndromic management of venereal diseases may also have played a role in the reported reduction in the prevalence of syphilis during pregnancy [22].

Prevalence in our study was detected to be 0.08%. The incidence of seropositivity in pregnancy was reported to be between 0.02 - 4.5% in northern Europe and the United States after accounting for biological false reactive tests [5,23,24]. The seroprevalence of syphilis during pregnancy ranged from 0.57% to 0.78% during the studies done in India [9,21]. In Nigeria two independent studies were conducted in 2009 which showed that the seropositivity of Syphilis in pregnant women was 0.4% (01 out of 231 pregnant women) and 1.5%

(157 out of 10680) in year when screened for Syphilis infection by RPR method [25,26]. Studies from Saudi Arabia in year 2000 and 2007 have reported a rate of 0.7% and 0.02% of syphilis among prenatal women respectively [27]. Reduction in the prevalence of syphilis during pregnancy and the incidence of congenital syphilis are indicators of successful syphilis control programs. There have been few studies of the prevalence of syphilis in pregnant women and congenital syphilis in India [21,28,29].

The neonates with congenital syphilis may be symptomatic at birth or may manifest disease later, before age 2, or even later [29,30]. Even if there is lack of signs and symptoms of the disease in the mother; it still can be transmitted to fetus [32]. Mental retardation, hydrocephalus, convulsive disorders, cranial nerve abnormalities (including blindness and deafness), and juvenile general paresis [33] are neurological manifestations of LCS.

The chances of antenatal fetal infection or congenital syphilis are related to the stage of syphilis during pregnancy, highest risk being during primary and secondary stage. High nontreponemal levels at the time of diagnosis is associated with increased chances of mother to fetus transmission [34]. The case in our study of congenital quadriparesis too was infected during secondary stage of maternal syphilis when she had skin rash. It has been seen that those who remain negative in non-treponemal tests will not transmit syphilis to the fetus or newborn [35]. A commonly held belief though not right that infection of the fetus does not occur before 18 weeks. Some tests like silver and immunofluorescence staining of the fetal tissues, or polymerase chain reaction and rabbit infectivity testing of amniotic fluid showed that the spirochetes can gain access to the fetus as early as 9 - 10 weeks.

The figures on the outcome of pregnancy in untreated syphilis is derived from the findings in the times prior to availability of Penicillin or present-day syphilis control programs came into operation in the Western world. Prenatal diagnosis of fetal syphilis includes noninvasive and invasive tests. Ultrasonographic fetal examination for findings of CS should be performed before initiation of therapy after 20 weeks' gestation. Sonographic findings of fetal hydrops, abnormally large abdomen, hydramnios, and thick placenta in the presence of maternal syphilis can be presumed to be due to syphilis involving the fetus [36]. Amniocentesis and percutaneous umbilical blood sampling are the invasive diagnostic procedures where tests can be performed and fetal anti treponemal IgM can be detected.

Treatment: it is an established and known fact that Penicillin is the most effective drug for treatment of syphilis; proven through clinical experience and randomized controlled trials. The effective levels of the drug are maintained for weeks; only drawback being its inability to cross blood brain barrier. Syphilis is highly sensitive to Penicillin, and Benzathine Penicillin is the drug of choice [37] as blood levels are maintained for a long period of time. Pregnant women should be treated with Penicillin regimen appropriate for their stage of infection as recommended by CDC [38] in all clinical stages of syphilis like primary, secondary, and early latent syphilis, Benzathine Penicillin G 2.4 million units IM in a single dose is recommended [38]. Evidence is suggestive of additional therapy being more advantageous during pregnancy [39]. For women who have primary, secondary, or early latent syphilis, a second dose of Benzathine Penicillin 2.4 million units IM can be administered 1 week after the initial dose. Failure of treatment has been documented though very rarely, especially in patients having concurrent HIV infection, but there is no documented Penicillin resistance in *T. pallidum* [40]. Treatment of the infected mother during pregnancy can significantly reduce the chance of congenital syphilis, and identifying and treating pregnant women with syphilis is a public health priority [7,8]. There is no need for further treatment in women who have been adequately treated in the past and do not have any current high-risk factor. Women without treatment history should be assessed; staged and managed accordingly with a recommended Penicillin regimen. Treatment of syphilis during the latter half of gestation is a risk for premature labor and/or fetal distress if the treatment precipitates Jarisch-Herxheimer reaction. The Jarisch-Herxheimer [41,42] reaction is known to occur in almost half of pregnant women after medication for acquired early syphilis; manifesting as fever, chills, myalgia, headache, hypotension, tachycardia, and transient exaggeration of the skin lesions. Jarisch-Herxheimer reaction can precipitate uterine contractions and initiate labour probably due to release of prostaglandins [43]. Serological titres should be checked every month for finding out the adequacy of the treatment and prevention of fetal infection. Fourfold decrease in titre occurs after one year in early latent infection but the fall may be more gradual

in late latent or tertiary syphilis. Persistently low but stable titres may remain in approximately 50% of these patients after 5 years [44]. Almost all women treated during pregnancy will deliver before their serological response can be evaluated with certainty. Newborn babies of these women must be assessed for congenital syphilis. Penicillin is the drug of choice in pregnancy even in presence of history of allergy, these women should be desensitized as Penicillin is hundred percent effective without any resistance reported.

Despite recommended Penicillin regimen to the pregnant women, 14% will have an intrauterine fetal death, or deliver babies affected with congenital syphilis [45-47]. This occurs when the treatment is done late in pregnancy (especially in secondary stage); the fetal affection may have already occurred.

The newborn babies born to syphilis-positive women should be tested by RPR. The babies detected to have four-fold rise in titre in comparison to that of mother's titre must be hospitalized to initiate Penicillin treatment for 10 days. Newborn babies should be treated with Penicillin who are born to mothers with clinical evidence of syphilis, with a reactive syphilis IgM antibody test, born to mothers who did not complete the recommended course of Penicillin during pregnancy or born to mothers whose RPR/VDRL titres had not dropped four-fold. Aqueous crystalline Penicillin G 100,000 - 150,000 million units/kg/day should be given intravenously (IV). The other option being 50,000 units/kg/dose IV twice a day for the first 7 days, and thereafter 8 hourly for 3 days to complete a total of 10 days of treatment. Intramuscular (IM) treatment regimen is Procaine Penicillin 50,000 units/kg as a single daily dose for 10 days or Benzathine Penicillin G 50,000 units/kg in a single dose. Babies should always be hospitalized to ensure the full course of treatment. If the treatment is missed for more than one day then the entire course should be restarted. Follow-up of the baby is required during postnatal care (PNC) visits and at 6 months and 24 months after completion of treatment.

Conclusion

As early as 1917, it was seen that syphilis was responsible for 20% of all stillbirths and 18 - 22% of the infant deaths in the United States [48] as reported by Osler. It can be diagnosed by simple screening tests which are cheap and easily available, Syphilis is completely curable by Penicillin, and transmission to baby is prevented. Efforts should be made at every level of health care to increase the awareness about the seriousness of syphilis in pregnancy. Women at high risk for contacting syphilis, or those residing in high prevalence areas, those with past adverse outcome or those who were not tested earlier, should be screened again in the third trimester or at the time of delivery. Testing of spouse/partner of syphilis-positive women must be done and treatment instituted as per protocol if found positive. The partner should be managed as if the concerned case was suffering from early syphilis. Cuba was the first country to eliminate mother-to-child transmission of syphilis completely as reported in 2015.

It is a known fact that those who attended antenatal care but were not offered syphilis testing have been shown to have adverse outcome of the disease hence all antenatal cases should be offered testing for syphilis. Screening women for syphilis during pregnancy and providing proper treatment are the cornerstones of congenital syphilis prevention [9]. Blood tests should be performed again at 28 to 32 weeks and at the time of labour. It should be done every month in women at high risk for reinfection or for those living in high prevalence areas.

An early diagnosis of Syphilis in antenatal period facilitates proper patient management and initiation of therapy to prevent transmission of congenital infections and anomalies to newborns. Breast feeding is permitted as breast milk does not transmit the disease unless there is infectious lesion on the breast.

Vaccine is not available till date for prevention of syphilis [49]. Many vaccines based on treponemal proteins have been found to reduce lesion formation in animals, but research still continues [50]. It is unfortunate that congenital syphilis is still a cause of perinatal morbidity and mortality in the present era [50].

Disclosure

Author reports no conflict of interest in this work.

Bibliography

1. Wahab AA., *et al*. "Syphilis in pregnancy". *Pakistan Journal of Medical Sciences* 31.1 (2015): 217-219.
2. Juliet ES and Stephanie EC. "Syphilis transmission: a review of the current evidence". *Sex Health* 12.2 (2015): 103-109.
3. De Santis M., *et al*. "Syphilis infection during pregnancy: fetal risks and clinical management". *Infectious Diseases in Obstetrics and Gynecology* 20 (2012): 12-16.
4. Spangler A., *et al*. "Syphilis with a negative blood test reaction". *The Journal of the American Medical Association* 189 (1964): 87-90.
5. S Hawkes., *et al*. "Effectiveness of interventions to improve screening for syphilis in pregnancy: a systematic review and meta-analysis". *The Lancet Infectious Diseases* 11.9 (2011): 684-691.
6. Singh AE and Romanowski B. "Syphilis: Review with emphasis on clinical, epidemiologic and some biologic features". *Clinical Microbiology Reviews* 12 (1999): 187-209.
7. Hollier LM., *et al*. "Fetal syphilis: clinical and laboratory characteristics". *Obstetrics and Gynecology* 97 (2001): 947-953.
8. Peeling RW and Hook EW. "The pathogenesis of syphilis: The Great Mimicker-revisited". *The Journal of Pathology* 208 (2006): 224-232.
9. Archana BR., *et al*. "Maternal and Congenital Syphilis in Karnataka, India". *Southeast Asian Journal of Tropical Medicine and Public Health* 45.2 (2014): 430-432.
10. Nair N., *et al*. "Incidence of Syphilis among pregnant women attending a tertiary care hospital in Navi Mumbai, India". *International Journal of Current Microbiology and Applied Sciences* 2.8 (2013): 79-84.
11. Woods CR. "Congenital syphilis-persisting pestilence". *The Pediatric Infectious Disease Journal* 28.6 (2009): 536-537.
12. Kent ME and Romanelli F. "Re-examining syphilis: an update on epidemiology, clinical manifestations, and management". *Annals of Pharmacotherapy* 42.2 (2008): 226-236.
13. Wendel G. "Gestational and congenital syphilis". *Clinics in Perinatology* 15 (1988): 287-303.
14. Oswal S and Lyons G. "Syphilis in pregnancy". *Continuing Education in Anaesthesia, Critical Care and Pain* 8.6 (2008): 224-227.
15. D. Watson-Jones., *et al*. "Syphilis in pregnancy in Tanzania. I. Impact of maternal syphilis on outcome of pregnancy". *Journal of Infectious Diseases* 186.7 (2002): 940-947.
16. JS Sheffield., *et al*. "Congenital syphilis after maternal treatment for syphilis during pregnancy". *American Journal of Obstetrics and Gynecology* 186.3 (2002): 569-573.
17. Belani GH., *et al*. "Malaysian guidelines in the treatment of sexually transmitted infections". Ministry of Health Malaysia (2008).
18. Hawkes SJ., *et al*. "Early antenatal care: Does it make a difference to outcome of pregnancy associated with syphilis? A systemic review and meta-analysis". *PLOS ONE* 8.2 (2013): 1-7.

19. SA Larsen., *et al*. "Laboratory diagnosis and interpretation of tests for syphilis". *Clinical Microbiology Reviews* 8.1 (1995): 1-21.

20. Eccleston K., *et al*. "Primary syphilis". *International Journal of STD and AIDS* 3 (2008): 145-151.

21. Sethi Sunil., *et al*. "Declining trends in syphilis prevalence among antenatal women in northern India: a 10-year analysis from a tertiary healthcare centre". *Sexually Transmitted Infections* 83.7 (2007): 592-597.

22. Sharma VK and Khandpur S. "Changing patterns of sexually transmitted infections in India". *The National Medical Journal of India* 17 (2004): 310-319.

23. Sisin CD., *et al*. "The resurgence of congenital syphilis; a cocaine-related problem". *The Journal of Pediatrics* 130 (1997): 289-292.

24. G Mehmet and William J Ledger. "Syphilis in pregnancy". *Sexually Transmitted Infections* (2000): 213-216.

25. Olokoba AB., *et al*. "Syphilis in Pregnant Nigerian Women: Is it Still Necessary to Screen?" *International Journal of Tropical Medicine* 3.3 (2008): 70-72.

26. Ibadin KO., *et al*. "Serodynamics of *Treponema pallidum* in Serum of Pregnant Women in Benin City". *Benin Journal of Postgraduate Medicine* 11 (2009): 9-14.

27. Zimmo SK., *et al*. "Prenatal Screening Syphilis: Is Universal Screening Necessary in Saudi Arabia?" *Derm Androl* 20.2 (2008): 71-76.

28. Mathai E., *et al*. "Audit of management of pregnant women with positive VDRL tests". *The National Medical Journal of India* 14 (2001): 202-204.

29. Parveen SS., *et al*. "Declining seroprevalence of syphilis among pregnant women in rural area". *Journal of Microbiology and Biotechnology Research* 2 (2012): 305-307.

30. Mabey D and Peeling RW. "Syphilis, still a major cause of infant mortality". *Lancet* 11 (2011): 654-655.

31. Malakar M and Choudhury M. "Syphilis in the Goalpara district of Assam, India". *International Journal of Scientific and Engineering Research* 5.3 (2014).

32. D Ingall and P J Sánchez. "Syphilis in Infectious Diseases of the Fetus and Newborn Infant". JS Remington and JO Klein, Eds. W.B. Saunders, Philadelphia, 5th edition (2001): 643-681.

33. Bulova S I., *et al*. "Hydrops fetalis and congenital syphilis". *Pediatrics* 49.2 (1972): 285-287.

34. Kingston M., *et al*. "UK National guidelines on management of syphilis 2008". *The International Journal of STD and AIDS* 19 (2008): 729-740.

35. Peterman TA., *et al*. "Do women with persistently negative nontreponemal test results transmit syphilis during pregnancy?" *Sexually Transmitted Diseases* 40.4 (2013): 311-315.

36. L M Hill and JB Maloney. "An unusual constellation of sonographic findings associated with congenital syphilis". *Obstetrics and Gynecology* 78.5 (1991): 895-897.

37. Workowski KA and Berman S. "Sexually transmitted diseases treatment guidelines, 2010". *MMWR Recommendations and Reports* 59 (2010): 1-110.

38. J M Blandford and T L Gift. "The cost-effectiveness of single-dose azithromycin for treatment of incubating syphilis". *Sexually Transmitted Diseases* 30.6 (2003): 502-508.

39. FT Fischbach. "Syphilis detection tests". A Manual of Laboratory & Diagnostic Tests, Lippincott, Philadelphia, 6th edition (2000): 581-583.

40. J M Alexander., *et al*. "Efficacy of treatment for syphilis in pregnancy". *Obstetrics and Gynecology* 93.1 (1999): 5-8.

41. Klein V., *et al*. "The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy". *Obstetrics and Gynecology* 75 (1991): 375-380.

42. Myles T., *et al*. "The Jarisch-Herxheimer reaction and fetal monitoring changes in pregnant women treated for syphilis". *Obstetrics and Gynecology* 92 (1998): 859-864.

43. YP Singh and G Jalpota. "Jarisch-Herxheimer reaction in early syphilis". *Indian Journal of Dermatology, Venereology and Leprology* 61 (1995): 386.

44. Fiumara N. "Serologic responses to treatment of 128 patients with late latent syphilis". *Sexually Transmitted Diseases* 6 (1979): 243-246.

45. McFarlin B., *et al*. "Epidemic syphilis: maternal factors associated with congenital infection". *The American Journal of Obstetrics and Gynecology* 170 (1994): 535-540.

46. Mascola L., *et al*. "Inadequate treatment of syphilis in pregnancy". *The American Journal of Obstetrics and Gynecology* 150 (1984): 945-947.

47. Conover C., *et al*. "Congenital syphilis after treatment of maternal syphilis with a Penicillin regimen exceeding CDC guidelines". *Infectious Diseases in Obstetrics and Gynecology* 6 (1998): 134-137.

48. Osler W. "The anti-venereal campaign". *Transactions of the Medical Society of London* 40 (1917): 290.

49. Stamm LV. "Global challenge of antibiotic-resistant Treponema pallidum". *Antimicrobial Agents and Chemotherapy* 54.2 (2010): 583-589.

50. Cameron CE and Lukehart SA. "Current status of syphilis vaccine development: need, challenges, prospects". *Vaccine* 32.14 (2014): 1602-1609.

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