REVIEW

Maternal Syphilis: Variations in Prenatal Screening, Treatment, and Diagnosis of Congenital Syphilis

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Abstract

Syphilis is a sexually transmitted infection that, if left untreated, can impact fetal development. In this systematic review of syphilis in pregnancy, we attempt to better understand worldwide discrepancies regarding its diagnosis and management. OVID MEDLINE and PubMed databases were searched for keywords and 74 relevant articles were identified. Twenty-nine articles were ultimately included in our review. In the literature spanning from 1944—2014, we identified several variations in maternal syphilis screening and treatment, as well as a spectrum of gestational outcomes. Even following the publication of universal guidelines by the World Health Organization, the Centers for Disease Control and Prevention, and scientific investigators, practice patterns have continued to vary. Greater adherence to these guidelines could improve the quality of research in this area and promote earlier detection and thus prevention of maternal and congenital syphilis.

Introduction

Syphilis is caused by infection with a spirochete, *Treponema pallidum*, which can be passed to the mother during sexual contact and subsequently from mother to child during pregnancy.[1,2] Untreated syphilis can progress through multiple stages (Table 1) and can be characterized by painless papules in the mouth, genitals, rectum, or skin, body rash, headache, fever, fatigue, and lymphadenopathy.[3] Progression to tertiary syphilis can result in damage to the heart, eyes, brain, and nervous system.[1]

Patients can also have latent syphilis with a positive serological test and no clinical signs of syphilis.[1,3] Early latent syphilis typically manifests one year after infection. Late latent syphilis is clinically described as an infection of unknown duration. Although *T. pallidum* cannot be transmitted sexually in late latent stage syphilis, pregnant women can transmit the treponeme to their fetuses.[1,2,3]

Table 1: Stages of Syphilis

Stage	Time Period	Symptoms
Primary	21 days after initial infection	Painless ulcer in mouth, genitals, rectum or skin
Secondary	4 – 8 weeks after primary infection ulcer appearance	Body rash, headache, fever, fatigue, lymphadenopathy
Tertiary	1 – 10 years after initial infection	Aortic insufficiency, aortic aneurysm, tabes dorsalis, loss of cortical function, altered mental status
Latent		
Early	First year after resolution of the primary or secondary lesions	Signs & symptoms usually disappear
Late	Unknown Duration	Cardiovascular syphilis, neurosyphilis, syphilitic meningitis

Adapted from Hook et al., 2012.

In 2008, more than 1 million pregnant women worldwide were newly infected with syphilis,[4] and it is estimated that 12 million new infections occur each year.[3] Syphilis in pregnancy results in

Table 2: Recommended Treatment Guidelines for Pregnant Patients

Stage	CDC STD Treatment Guidelines	WHO STI Guidelines
Primary/Secondary	2.4 MU benzathine penicillin G IM x1 once	2.4 MU benzathine penicillin G IM x1 once
Early Latent	2.4 MU benzathine penicillin G IM x1 once	2.4 MU benzathine penicillin G IM x1 once
Late Latent/Unknown Duration	2.4 MU benzathine penicillin G IM x1 per week for 3 weeks	2.4 MU benzathine penicillin G IM x1 per week for 3 weeks
Tertiary without evidence of neurosyphilis	2.4 MU benzathine penicillin G IM x1 per week for 3 weeks	No set recommendation

Adapted from Centers for Disease Control and Prevention, 2015; World Health Organization, 2016; IM=intramuscular, MU=million units.

many complications, the most deadly of which is congenital syphilis. Newman et al. estimate that 520,000 adverse outcomes occurred in 2008 as a result of maternal syphilis infection.[4] Due to these adverse outcomes, the World Health Organization (WHO) recommends that all pregnant women be tested for syphilis early in antenatal care (ANC) and begin treatment if infected.[2 World Health Organization, Department of Reproductive Health and Research. The global elimination of congenital syphilis: rationale and strategy for action. Geneva, Switerland: WHO Press; 2007.] The Centers for Disease Control and Prevention (CDC) and WHO both recommend maternal penicillin therapy (Table 2); although, in practice, there is considerable therapeutic heterogeneity.

Maternal syphilis infections are preventable and treatable. However, the global burden of this disease in pregnancy persists. The broad variation in the diagnosis and management of maternal syphilis could be a contributing factor.[5] In this review, we discuss variations in the delivery of antenatal care, treatment of maternal syphilis, and diagnosis of congenital syphilis in an effort to better understand these variations and potential avenues for achieving greater therapeutic homogeneity.

Search Strategy and Selection Criteria

A systematic search of peer-reviewed published articles was performed using OVID MEDLINE. The MeSH terms applied were "Syphilis, Congenital", "Pregnancy Complications" and "Pregnancy Outcome" in combination. Search results were limited to English language studies using human subjects published through June 2014 to identify the most up-to-date information regarding worldwide clinical practice. This search yielded seventy-four articles, which were reviewed by a subset of the authors. Five more articles were reviewed by suggestion of the senior author. Twenty-nine were selected for further review and were grouped together based on their emphasis of syphilis screening practices, treatment, and gestational outcomes.

Prenatal Screening
Antenatal Care

Syphilis screening in conjunction with antenatal care (ANC) is strongly recommended by the WHO and CDC. While it is estimated that each year 2 million pregnant women are infected with syphilis, only 85% of pregnant women worldwide access antenatal care at least once. Even fewer, 58%, have access to four or more visits with an ANC provider.[6,7] Of the women who receive ANC, only two thirds are tested for syphilis.[8]

Even if ANC is sought, earlier screening, and thus earlier treatment, has the greatest impact on maternal and fetal health.[9] Hawkes et al.[10] found that an infant born to a mother who was not screened early in pregnancy is nearly three times as likely to present evidence of infection. Furthermore, screening and treatment during late pregnancy does not reliably reduce fetal transmission rates since the intervention period is shorter and the likelihood of fetal transmission is increased.[11]

Screening Tests
Screening tests for syphilis are categorized as non-treponemal or treponemal. A non-treponemal test indirectly identifies infected individuals by detecting the presence of non-specific IgG or IgM antibodies, which are elevated in syphilis.[12] These antibodies are present as a result of either direct production from treponemes or as debris from cellular damage of host cells.[12] The first mass-produced, non-treponemal test was the Venereal Disease Research Laboratory (VDRL) (Table 3). Other non-treponemal tests include Rapid Plasma Reagin (RPR) and Toluidine Red Unheated Serum Test (TRUST).[12] Despite their high sensitivities (86% and 85%, respectively), these screening tools are prone to false positives because they are not specific to *T. pallidum*.[13]

Contrary to non-treponemal tests, treponemal tests directly identify the presence of T. pallidum. The most common tests include the Fluorescent Treponemal Antibody-Absorption test (FTA-ABS), the Serodia Treponema Pallidum Passive Particle Agglutination test (TP-PA) and the Treponema Pallidum Hemagglutination Assay (TPHA). A recent development in treponemal testing is the immunochromatographic strip (ICS) test, in which a test strip indicates the presence of treponemal antibodies. Tucker[14] found that ICS is rapid, simple to perform, and boasts a high specificity (99%).

Point-of-care (POC) tests may more effectively address syphilis infections because diagnosis and prompt treatment can prevent vertical transmission. Rapid diagnosis also presents an opportunity to engage women in conversations regarding sexual behavior and minimizes loss to follow-up. Still, barriers exist with some tests, such as availability in rural areas and reduced accuracy which disproportionately impacts pregnant women specifically in areas such as Sub-Saharan Africa and South Asia where less than 50% of women receive antenatal care.[15][16]

Table 3: Diagnostic & Screening Tests for Syphilis

Test	Assay Format	POC	FDA Cleared
Abbott Determine Syphilis	Non-Treponemal ICT	Yes	No
Arlington Scientific Antigen test	Non-Treponemal VDRL	No	No
New Horizons Diagnostics TRUST	Non-Treponemal TRUST	Yes	Yes
SCIMEDX FTA-ABS Test	Treponemal FTA-ABS	No	No
Fujirebio Serodia TP-PA	Treponemal TP-PA	No	No
Arlington Scientific TPHA Test	Treponemal TPHA	No	Yes
Omega VisiTect Syphilis	Treponemal ICT	Yes	No
Trinity Syphilis Health Check	Treponemal ICT	Yes	Yes
Qualpro Syphicheck-WB	Treponemal ICT	Yes	No
Standard SD Bioline Syphilis 3.0	Treponemal ICT	Yes	No
Chembio DPP Syphilis Screen & Confirm	Dual Non-Treponemal and Treponemal ICT	Yes	No
Diesse Diagnostica Syphilis Fast	Treponemal TP-PA	Yes	No

Adapted from United States Food and Drug Administration Cleared Diagnostic Serologic Tests for Treponema Pallidum (Syphilis), 2013.

Recent technological advances have given rise to new treponemal tests. Rapid POC tests typically require blood from a fingerstick, a procedure that can be performed with minimal training in a resource-limited setting. In the United States only one POC test, Trinity Health CheckTM (Diagnostics Direct, LLC, Stone Harbor, NJ), is FDA-cleared.

The "traditional" testing algorithm has been to first administer a non-treponemal test, with a confirmatory treponemal test in the case of a positive.[17] However, this algorithm poses some challenges. The stage of disease often affects the sensitivity of both non-treponemal and treponemal tests. According to Peterman et al.[18],

15% of individuals with latent syphilis could have negative non-treponemal test results. Additionally, the high rate of positive results from treponemal tests underscores the fact that previous infections can cause positive test results potentially for years following successful treatment. For this reason, treponemal tests are not appropriate indicators for measuring treatment success.[17, 18]

The CDC now recommends a reverse sequence algorithm to detect infections that might otherwise be missed by the traditional screening method.[19] The reverse sequence utilizes a treponemal test and, if positive, is followed by a quantitative non-treponemal test. In cases of negative treponemal tests, an RPR is repeated several weeks later for patients considered at risk for syphilis. Advantages of switching to the reverse algorithm include high throughput, cost savings in high volume settings, and the detection of chronic, untreated syphilis.[20] However, it is possible that reverse sequence screening will produce a higher rate of false positives due to the lower sensitivity of some treponemal tests. Future studies could further investigate this caveat.

Testing Implementation
Despite the wide variety of tests, cost is still the prevailing factor determining worldwide use. Because treponemal tests generally require expensive laboratory equipment and materials, they are often difficult to perform in resource-poor areas where infection rates are usually the highest.[17] Even though the reverse algorithm is now recommended, this has only shown to be economically beneficial in developed nations; the opposite may hold true in developing countries.[20] For example, Wiwanitkit[21] found that treponemal screening in blood centers in Thailand would cost 2-2.5 times that of non-treponemal screening, and Binnicker et al.[22] found that in the U.S., costs for six different treponemal tests range from $1.73 to $18.75 compared to $0.51 for an RPR test. Thus, in a resource-limited setting, rapid and POC syphilis tests may be the most efficient and cost-effective option.

Though widely-recognized guidelines for screening have been in place since 1988, in practice there is great variability in antenatal screening for maternal syphilis[23]. We found screening protocols ranging from 1) RPR and FTA-ABS[24], 2) RPR and TP-PA[25], 3) RPR and ICS[17], 4) RPR and either FTA-ABS or TP-PA[26], 5) VDRL and FTA-ABS[27], and 6) TRUST and TP-PA confirmed with FTA-ABS.[11] Overall, a multitude of factors, such as cost, setting, and disease stage at presentation likely impact whether prenatal screening can be carried out according to guidelines.

Treatment of Maternal Syphilis
Current Recommendations
The CDC's 2015 Sexually Transmitted Diseases Treatment Guidelines specify that only parenteral penicillin G (PCN) has documented efficacy for syphilis in pregnancy and should be used to prevent maternal-fetal transmission (Table 2).[19] Before benzathine PCN was widely used, fetuses of mothers with syphilis had a 70% risk of contracting congenital syphilis.[28] After its widespread use, treatment of maternal syphilis prevented 98% of congenital infections.[29] Today, the CDC guidelines outline a specific treatment regimen appropriate for a patient's stage of infection (Table 2). The WHO has similar guidelines and also recommends treatment of all sero-reactive pregnant women with benzathine PCN therapy.[30] However, until recently, the WHO had only specified a single dose of benzathine PCN and did not provide treatment regimens according to disease stage. In the face of antibiotic resistance and in effort to update national guidelines for the treatment of syphilis, the WHO released new recommendations for the first time in over a decade which now correspond with the CDC's treatment of primary, secondary, and latent syphilis. Interestingly, though, these new guidelines include a conditional recommendation that ceftriaxone or macrolides may be used as an alternative treatment for pregnant women allergic to PCN when desensitization is not possible or unavailable, which is in contrast to the CDC's

recommendations which firmly support desensitization alone.

Treatment of syphilis in pregnancy should be completed at least 30 days before delivery in order to avoid increased risk of adverse outcomes associated with late treatment.[12] Cheng et al.[11] found that treatment close to the delivery date is less effective in reducing risk for congenital syphilis because the intervention time period is shorter compared to normal treatment courses. Women who have their first serological screening test for syphilis at 28 weeks gestation or later are nearly twice as likely to deliver an infant with congenital syphilis as those whose first test occurred earlier[9]. The risk of vertical transmission from an infected mother is reduced with treatment at earlier stages of pregnancy.[11] Regardless of timing, treatment at any stage reduces the risk of transmission.

Variations in Treatment Timeline
Within the literature, there are notable variations from the aforementioned CDC/WHO treatment guidelines. The primary of these concerns benzathine PCN dosage schedules that may have differed from the recommended guidelines. While both guidelines, until recently, suggested different dosages per stage of the disease, it is unclear from the studies that were reviewed if that is what dictated treatment plans in practice. Many studies did not report the exact dosage of benzathine PCN used, but stated that CDC/WHO guidelines were followed. Others did not record or report the disease stage of their subjects. For example, Owusu-Edusei et al.[17] treated every subject with a single dose of 2.4 MU of PCN and thus may have undertreated pregnant women with late latent syphilis. Casal et al.[31] took disease stage into consideration, but perhaps over-treated women with early latent syphilis. Uniform adherence to CDC/WHO treatment guidelines in both developed and resource-poor regions may substantially minimize these discrepancies.

Alternative Therapies
Although PCN therapy is the most effective treatment, some studies in Asia have documented use of other antibiotics. In a prospective study conducted by Sangtawesin et al.[32], erythromycin was used to treat maternal syphilis in approximately 15% of cases. The authors did not provide a clear rationale for the clinical use of erythromycin; however, concluded that it is probably adequate for treating maternal syphilis but not in utero syphilis. Similarly, Cheng et al.[11] reported use of both erythromycin and azithromycin for seropositive pregnant women allergic to PCN, differing starkly from the CDC guidelines. Interestingly, the study did find a 99.1% success rate in preventing maternal-to-fetal transmission. Although the authors note that diagnosis and management followed CDC Guidelines for Prevention and Control of Congenital Syphilis, it is unclear which criteria dictated the use of alternative antibiotics. Further exploration is necessary to assess both the context for alternative therapies and the degree to which variations in treatment practice impact gestational outcomes.

Congenital Syphilis

Syphilis in pregnancy increases the risk of adverse outcomes, including pre-term delivery, low birth weight, non-immune hydrops fetalis, intrauterine growth restriction, stillbirth, and congenital syphilis.[26, 33, 34]. While 20% of infants born to untreated mothers are without any adverse outcomes, the chance of having an infant with global delay (40%), stillbirth (30%), and neonatal death (40%) is significantly higher for untreated versus treated mothers.[34] Watson-Jones et al.[35] also found that women with high-titer active syphilis had an 18-fold increased risk of stillbirth and a 4-fold increased risk of any adverse outcomes to the infant. The study also found that women treated for high- and low-titer active syphilis experienced no increased risk in adverse outcome compared with women who were seronegative for syphilis.

Women who do not receive ANC have consistently given birth to the highest proportion of infants with congenital syphilis.[9, 11] In China, infected mothers who never underwent prenatal examinations and only received care during

delivery contributed the largest share (63%) of infants born with congenital syphilis.[11] In Russia, a study by Tikhonova et al.[9] found that among women without ANC, 86% delivered an infant with congenital syphilis. Jones et al.[36] found that four out of five cases of congenital syphilis were associated with mothers who did not receive ANC.

While the gestational outcomes of syphilis have been well described, the specific pathophysiologic changes occurring in utero have not been clearly elucidated. It is unclear whether these adverse outcomes are attributable to maternal syphilis, congenital syphilis, or both. It remains unclear whether these outcomes are due to maternal infection resulting in a less favorable intra-uterine environment for the developing fetus or whether these outcomes are the result of fetal transmission and subsequent pathogenicity.

Definitions of Congenital Syphilis

A complete standardization of diagnostic criteria for congenital syphilis remains to be established. Based on the number of screening test options alone, there are at least 21 different ways to diagnose congenital syphilis.[37] Kaufman et al.[37] were the first to organize specific criteria, classifying several cases of congenital syphilis as "definite", "probable", or "unlikely". In 1988, the CDC established a new set of diagnostic criteria, expanding the classifications to "confirmed", "compatible" or "probable," and "unlikely". In addition, contrary to the CDC recommendations, Kaufman et al.[37] suggest a variety of non-treponemal and treponemal tests to confirm a diagnosis. These substantial differences represent the significant variation that exists among the prevailing classification systems worldwide.

Still, investigators continue to utilize variable diagnostic criteria. For example, Southwick et al.[24] focused on laboratory results and considered a case of congenital syphilis to be laboratory-confirmed if the infant was born to a seropositive mother and had either a positive direct fluorescent antibody test, immunohistochemistry test, or IgM western blot assay. However, even these authors acknowledge possible sources of variation in their own testing because either whole spirochetes or bacterial fragments could constitute a positive result. Other groups have made diagnoses based on criteria that covered a wider range of tests.[38] In Russia, as cited by Tikhonova et al., infants must be symptomatic, have persistent serological abnormalities, or be diagnosed with syphilitic stillbirth in order to be reported as a case of congenital syphilis.[9] Furthermore, while WHO criteria define "syphilitic stillbirth" as fetal death after 20 weeks, the Russian Federation requires a gestational age of at least 28 weeks.[9] These two requirements therefore likely underestimate the prevalence of congenital syphilis in the Russian Federation. Physical diagnosis can also be difficult as clinical manifestations may not be present at birth[39], and even if there are signs in symptomatic infants, they may be subtle and nonspecific, making diagnosis difficult.[12] Overall, variations in outcomes based on different diagnostic criteria could justify a need for universal criteria.

Discussion

While syphilis is preventable and curable, it continues to be a worldwide public health concern, especially among women of reproductive age. Through our review, we found significant worldwide variation in maternal and congenital syphilis diagnosis and treatment. Specifically, we observed continued deviation from the CDC/WHO's recommended guidelines many years after they were first published. Aligning practice with recommended guidelines could significantly improve maternal health and fetal outcomes. Timely ANC interventions, as previously discussed, are a critical element underlying initiatives to reduce syphilis in pregnancy.

Unfortunately, many women do not receive ANC or are not screened for syphilis.[4, 8, 10] Often, if ANC is pursued, it is at a stage too late for effective treatment or prevention. Low rates of ANC may be due in part to the cost of screening and diagnostic tests. While automated

treponemal tests are preferable for their high throughput and automated process, these methods are more expensive and less realistic for application in resource-poor areas. In these areas, syphilis rapid and point-of-care tests are likely the most pragmatic option for diagnosis.

Challenges remain if untreated maternal syphilis gives rise to congenital syphilis. The range of definitions and diagnostic criteria for congenital syphilis greatly impacts the delivery of timely and successful treatment. Even though many standardized criteria have been put forth, the literature indicates that these are only partially followed. Given the often understated and diverse constellation of symptoms in neonates, it is imperative to follow established criteria in order to accurately diagnose more cases of congenital syphilis. As a result, standardized diagnostic criteria could better estimate the true prevalence of congenital syphilis. Hence, a consensus on diagnostic criteria for congenital syphilis should be considered.

Our review is subject to some limitations. While the OVID MEDLINE and PubMed databases were searched to maximize a variety of results, other sources outside of the journal articles in the databases could be explored. Unpublished trials, conference proceedings, and manufacturers' reports could be potentially valuable sources, and experts and primary authors from primary studies could be contacted for additional relevant information. As for the extent of the review, an even more thorough review of the literature could include investigation into clinical differences in patient selection or characteristics, conditions of measurements, and covariate variables.

Reducing maternal and congenital syphilis is a global priority. By bringing attention to variations in global practices concerning maternal syphilis infection, we hope to promote action towards a more standardized, financially feasible, and socially adaptable model of screening and treatment.

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Conflicts of Interest
These authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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