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Review

Reemergence of Congenital Syphilis in the United States: A Narrative Review

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Abstract: Congenital syphilis, a preventable and deadly disease, has witnessed an alarming resurgence in the US in recent years, posing a vital public health challenge. Historically, effective prevention and treatment strategies led to a decline in congenital syphilis, and some believed that it could be eradicated. However, inadequate prenatal care, limited access to healthcare services, and gaps in syphilis screening programs have led to a resurgence of congenital syphilis. In this narrative review, we aim to highlight the key factors contributing to the reemergence of congenital syphilis and its implications on maternal and child health.

Keywords: congenital syphilis; syphilis in pregnancy; congenital syphilis treatment; congenital syphilis epidemiology

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1. Introduction

Congenital syphilis (CS) is a life-threatening condition where *Treponema pallidum* is vertically transmitted from a mother with untreated or inadequately treated syphilis to the fetus. CS can cause stillbirth, miscarriage, and early infant death and infected infants can experience lifelong complications [1]. According to the CDC's surveillance case definition, congenital syphilis is classified as probable under the following conditions: (1) an infant whose mother had untreated or inadequately treated syphilis at delivery, regardless of signs in the infant or (2) an infant who has a reactive non-treponemal test for syphilis (Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR]) and evidence of congenital syphilis on physical exam, radiography of long bones, or cerebrospinal fluid [2]. Cases are considered confirmed when there is a positive confirmatory laboratory diagnostic test which includes: (A) Demonstration of *T. pallidum* by darkfield microscopy of lesions, nasal discharge, or body fluids or (B) A positive molecular test on fetal or neonatal tissue or umbilical cord or (C) Positive histochemical or immunohistochemical identification of *T. pallidum* in fetal or neonatal (lesional) tissue, placenta, or umbilical cord.

Despite our understanding of the disease, the available treatments, and preventive measures, congenital syphilis is a major cause of fetal and neonatal mortality [3]. The rise of CS since 2013 in a highly developed country raises concerns of health disparities [4]. A main cause of the rise in CS cases in the US is due to a lack of adequate maternal treatment despite appropriate diagnosis and a lack of timely prenatal care [1].

2. Epidemiology

Globally, congenital syphilis was found to be 425 cases/100,000 cases in 2020, which was much higher than the WHO's 2007 target of 50 cases/100,000 cases. There has been a significant surge of reported cases of congenital syphilis in the United States. The rate of congenital syphilis in 2013 (9.2 cases per 100,000 live births) marked the first increase in congenital syphilis in several years and the rate has risen since. In 2021, 2855 cases of

congenital syphilis were reported—220 of those cases being congenital syphilis-related stillbirths and infant deaths. Historically, most congenital syphilis cases have been reported from less than 40 states, but in 2021, 48 of 51 states reported at least one case of congenital syphilis [5]. States in the southern region of the United States disproportionately experience higher rates of congenital syphilis, with Arizona, New Mexico, Texas, and California ranking among the top four [6].

The incidence of congenital syphilis in the United States in 2021 has seen a significant rise, reaching 77.9 cases per 100,000 live births. This marks a notable increase of 30.5% compared to 2020 and an alarming rise of 219.3% compared to 2017. This trend aligns with the growing rates of syphilis among women of reproductive age. During the span of 2020 and 2021, there was a considerable 52.3% increase in the rate of primary and secondary syphilis among women aged 15–44 years. In 2012, only three states reported over 100 cases of primary and secondary syphilis among women aged 15–44 years. In contrast, by 2021, this number had escalated to 29 states [7]. Higher rates of congenital syphilis in younger women (<30 years) is due to a rise in newborn syphilis, poor access to healthcare, and a decline in prevention care and resources.

3. Review

3.1. Brief Overview of Syphilis

Syphilis can be transmitted through contact of a chancre or condyloma lata or through vertical transmission [4]. It is a multistage disease characterized into four distinct stages: primary, secondary, latent, and tertiary. Neurosyphilis can manifest at any point [4]. Primary syphilis results from an inoculation of *T. pallidum* into dermal lesions or mucous membranes, causing a large, painless cutaneous lesion called a chancre and regional lymphadenopathy [8]. Secondary syphilis is characterized by a nonpruritic plantar and palmar rash and lymphadenopathy, and can include condylomata lata, leukoplakia, and alopecia [8]. If disseminated symptoms are left untreated within 3 months of appearance, then symptoms disappear and the patient becomes asymptomatic, marking the latent phase. The first year after infection is classified as early latent syphilis. Late latent syphilis is defined as being asymptomatic for longer than one year [8]. Tertiary syphilis is extremely rare in the era of antibiotics. However, if syphilis is left untreated for 20 to 40 years after initial infection, the infection may come out of latency and patients will present with tissue and bone destruction, cardiovascular manifestations such as aortitis and aortic regurgitation, and neurological symptoms [8].

T. pallidum can be transmitted through placental blood flow or direct contact with an infected lesion during childbirth [4]. Congenital syphilis occurs when maternal syphilis goes untreated or inadequately treated and may result in fetal death, but most newborns of mothers with untreated syphilis are asymptomatic [9]. The risk of maternal to neonatal transmission is related to the stage of maternal infection. Studies show that the earlier the stage of maternal disease (during gestation), the higher the risk of transmission. Additionally, the risk of transmission becomes higher as pregnancy progresses [4].

Congenital syphilis is also divided into stages: Early congenital syphilis is the manifestation of disease within the first 2 years of life. Symptoms include hepatomegaly, rhinitis ("snuffles"), long bone lesions, generalized lymphadenopathy, and a maculopapular rash involving the palms and soles [9]. Late syphilis is seen in children older than 2 years old and is not contagious [4]. The clinical manifestations of late syphilis comprise dental abnormalities such as Hutchinson teeth, which are small, widely spaced, notched teeth, and Mulberry molars, which is an eponym for numerous small cusps in the first molars [3]. Facial changes include prominent maxilla, frontal bossing, and saddle nose. Other features involve intellectual disability and sensorineural hearing loss [9]. Congenital syphilis is associated with a significant fetal loss rate (30%); however, it can be asymptomatic in newborns [9].

3.2. Review of Pathological Findings

Congenital syphilis can occur even in mothers who receive screening, because infection can occur between the time of screening and labor [10]. Up until its recent re-emergence, congenital syphilis was almost a forgotten disease in high-income countries and so may be difficult to recognize clinically. In addition, its clinical presentation is variable. The pathologist may have the opportunity to make the diagnosis when unsuspected by the clinical team, and so pathologists should be familiar with the tissue manifestations of congenital syphilis. Relevant pathology specimens may include: lesional tissue, placenta, or stillbirth examination. In clinical practice, if a pathologist suspects congenital syphilis, they should communicate with the clinical team and ensure that serological tests be performed on the mother and neonate (if applicable). Additional testing of the neonate such as darkfield microcopy of nasal discharge, if applicable, can also be carried out. The pathologist should endeavor to obtain a diagnostic test on the tissue even if it is not locally available, by consulting a regional or tertiary center. Histochemical silver staining is considered a diagnostic test (per the CDC, see above) but the sensitivity is not well established, and the slide may be difficult to interpret. More specific tests include immunohistochemistry of tissue sections or molecular tests that can be carried out on formalin-fixed paraffin-embedded tissue; however, while specific, these tests may not be sensitive, and so results should be interpreted accordingly.

In any delivery where syphilis is suspected, whether liveborn or stillborn, the placenta should be submitted for pathological examination. Russel and Altshuler noted that macroscopically, placentas in cases of congenital syphilis are large and pale. They defined a triad of placental pathology findings associated with congenital syphilis: histiocyte predominant villitis, proliferative endovasculitis, and necrotizing periphlebitis [11]. Proliferative endovasculitis is seen as concentric sclerosis around stem villous vessels. Necrotizing umbilical periphlebitis is an admixture of necrotic debris and eosinophilic precipitate around the umbilical vein. Qureshi et al. added acute villitis to this triad [12]. Sheffield et al. showed an increased incidence of erythroblastosis, and this in turn suggests that anemia is the cause of hydrops, when seen [13]. In general, the trend in the literature suggests that if a series of placentas in cases of confirmed congenital syphilis is studied, then the proportion of placentas with pathology will be high [11,12], whereas if a series of cases of maternal gestational syphilis is looked at, then the proportion of placentas with pathology will be low [14]. This makes sense because in the latter, the mother will invariably be treated prior to delivery [14].

The recent literature on how to diagnose congenital syphilis in a stillbirth autopsy is sparse and more literature on this topic is needed. Placental examination as part of a stillbirth autopsy may be very helpful in this regard. A recent review looked at a series of 21 stillbirth autopsies in cases of congenital syphilis [13]: No fetal or placenta feature was pathognomonic—fetal hydrops was seen in 13/21 cases, hepatomegaly in 13/21 cases, metaphyseal abnormalities on fetal radiographs in 6/21 cases, and placental villitis in 5/21 cases. Immunohistochemistry of tissue was positive in under half of specimens tested. One of the implications of this study is that when congenital syphilis manifests as a fatal embryopathy, the mechanistic cascade of anemia leading to hydrops is etiological in a substantial amount, but not all cases. As congenital syphilis can be difficult to recognize in a stillbirth autopsy, we would suggest that maternal serology performed to test for syphilis be added to clinical post-loss workup panels, even when the mother has been previously screened—especially in areas were the rates of congenital syphilis are high or rising.

3.3. Review of Clinical Findings, Clinical Care, and Treatment

Clinically, congenital syphilis in a fetus is assumed in all cases of maternal syphilis in pregnancy [15]. Positive ultrasound findings represent a higher severity of infection in the fetus and an increased likelihood of developing CS. The most common ultrasound findings are hepatomegaly, placentomegaly, polyhydramnios, ascites, and nonimmune hydrops [15]. Middle cerebral artery doppler studies can also be used to detect fetal anemia.

Abnormal ultrasound findings can be identified at 18–20 weeks of gestation, and once present, initial treatment and monitoring in an inpatient setting is recommended [15]. Treatment should occur as soon as possible, as studies show that there is a lower rate of CS when maternal syphilis is treated early in the pregnancy [16]. Optimal treatment during pregnancy also reduces the risk of stillbirths, preterm births, and neonatal mortality [15]. Benzathine Penicillin G (BPG) is the only effective antimicrobial for pregnant patients. The antibiotic regimen is dependent on the stage of infection [17]. For early-stage syphilis (primary, secondary, and early latent), one dose of 2.4 million units of intramuscular BPG is recommended. Some experts recommend a second dose of BPG within 9 days of the first dose because there is certain evidence that indicates that additional therapy is beneficial in preventing CS. For late latent syphilis or an unknown duration of syphilis, three weekly doses of 2.4 million units of intramuscular BPG is recommended [16]. If one dose is missed (>9 days), the course must be restarted. Potential side effects of treatment include the Jarisch–Herxheimer reaction, which increases the risk of premature labor or fetal distress in the second half of the pregnancy [17]. The Jarisch–Herxheimer reaction is an acute febrile reaction with associated headache and myalgia due to the release of enormous amounts of lipopolysaccharides by dying spirochetes [17]. As fetal distress and preterm labor may occur, inpatient treatment and monitoring is recommended at a facility that is capable of emergent delivery and care [17].

All neonates born to a mother diagnosed with syphilis should be screened with a quantitative nontreponemal serologic test (RPR or VDRL) and examined for evidence for CS [18]. For any neonate with physical findings consistent with CS, a serum quantitative nontreponemal serologic titer that is fourfold higher than maternal titers at delivery, a positive darkfield test or PCR of the placenta, cord, lesions, or body fluids, or a positive silver stain of the placenta or cord can be classified as confirmed or highly probable CS [18]. Patients that fall in this classification require aqueous crystalline penicillin G 100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose by IV every 12 h during the first 7 days of life and followed by administration every 8 h for a total of 10 days, or Procaine penicillin G 50,000 units/kg body weight/dose IM in a single daily dose for 10 days [18].

3.4. Health Disparities

Syphilis screening in pregnant women is essential for preventing congenital syphilis. The CDC recommends screening with a non-treponemal test at the first prenatal visit for all patients, and repeat screening in the third trimester and at delivery in patients in areas with high rates of syphilis or patients with risk factors such as multiple sexual partners, drug use, or house insecurity [18]. Unfortunately, gaps in the healthcare system have led to ineffective screening or treatment. These gaps disproportionately affect certain subgroups of women. A higher rate of CS in the U.S. came from mothers who lacked prenatal care or had late initiation of prenatal care, used substances during pregnancy, or received inadequate testing or inadequate treatment of syphilis during pregnancy [19]. These missed opportunities of prevention were the most prevalent in the southern states [6]. In 2018, the CDC preformed a review and found that a lack of adequate maternal treatment despite a timely diagnosis of syphilis was the most common missed opportunity for the prevention of congenital syphilis [1]. Other very common gaps in care that were found include a lack of timely prenatal care with no timely syphilis testing, a lack of timely syphilis testing despite timely prenatal care, and the late identification of seroconversion during pregnancy (identified <30 days before delivery) [16]. Racial disparities also exist, and studies show that African Americans are disproportionally impacted by CS. In 2018, Blacks accounted for 40.4% of reported CS cases, Hispanics accounted for 32.6%, and Whites accounted for 22.7% [19]. A recent analysis of common missed prevention opportunities for congenital syphilis identified some variation across regions and demographic groups. In the West, the most common missed prevention opportunities (no timely prenatal care and inadequate treatment despite receiving a timely diagnosis) were similar among Black,

Hispanic, and White mothers. However, in the South, White mothers more commonly reported a lack of timely prenatal care, whereas Black and Hispanic mothers reported a lack of adequate maternal treatment [1]. Other socioeconomic factors that increased the risk for congenital syphilis in the U.S. include a low household income, lack of insurance or reliance on public health insurance, and low educational levels [19].

3.5. Screening

There have been multiple screening strategies for the prenatal screening of syphilis. Some studies have suggested that third-trimester syphilis screening could prevent CS in regions where syphilis transmission is high. Partnering with health insurance agencies to evaluate the cost-effectiveness of screening recommendations may improve the accuracy of the estimate of potential cost savings by using insurance agency-specific data for populations at risk for CS. In a study carried out in Louisiana and Florida, the women who were screened both early and in the third trimester had more favorable outcomes in terms of having a baby with congenital syphilis than those who were screened only in the first trimester [20]. In 2007, the World Health Organization launched a program for the prevention of Mother-to-Child transmission of Syphilis, citing the worldwide prevalence of this problem [21]. Congenital syphilis can be managed by routine antenatal screening, treatment with penicillin, and health education programs which positively focus on effective safe sex practices and drug use control. Neonatal management should be carried out while keeping in mind the syphilis history of the mother, proper screening and evaluation of blood, CSF and long-bone analysis, and follow-up treponemal testing. Repeat and serial testing is important for people with risk factors like being from specific minority ethnicities, a prior history of STIs, drug users, and sex workers (US Centers for Disease Control and Prevention Syphilis during pregnancy: sexually transmitted infections treatment guidelines) [17]. In addition, screening the partners of all pregnant women would be a good approach to minimize the risk of syphilis infection in the women.

4. Methods

4.1. Data Sources and Search Strategy

We conducted a systematic literature search using PubMed, Scopus, and EMBASE between 1 June 2023 and 1 September 2023. Our search strategy was designed to retrieve all published articles on congenital syphilis in the United States reporting its prevalence, prevention, and epidemiology. We applied various combinations of Boolean operators and thus used the following keywords for our search: ((Congenital Syphilis OR Congenital syphilis in USA OR Pregnancy and syphilis) AND (prevalence OR prevalent OR rise OR increasing rates OR prevention) AND ("severity" OR "secondary infection" OR "critical care" OR "Mortality")). We also checked the references of the articles we selected to retrieve any additional articles we might have missed in our initial search. Authors (OA, SC, and PD) reviewed all articles to ensure no duplicates.

4.2. Study Selection

Our narrative review consisted of only those studies which met the following criteria: (1) originally published in the English language; (2) included confirmed diagnosis of congenital syphilis; (3) had data on humans; (4) provided information about comorbidities, prevalence, and prevention; (5) contained information on the disease outcomes; and (6) studies published for data in the United States only. Studies outside of the US and those that were abstracts only were excluded from the analysis.

4.3. Quality Assessment

SANRA—a scale for the quality assessment of narrative review articles—was used for the quality assessment of the study [22]. Two authors (OA and SC) independently graded the quality of the included studies using Baethge et al. [22]. Consensus discussions were carried out between the three authors to resolve any disagreements.

5. Conclusions

Congenital syphilis has resurfaced as a significant public health concern, posing a high risk of mortality and severe morbidity among affected children.

The management of congenital syphilis involves several key recommendations: First, it is important to conduct routine antenatal screening for syphilis in both the first and third trimesters to effectively identify and treat the infection in pregnant women. The standard best practice for screening and diagnosis involves using quantitative nontreponemal serologic tests such as RPR or VDRL. After a positive RPR or VDRL test for syphilis, follow-up tests typically involve confirming the diagnosis and assessing the stage of the infection. This may include additional treponemal tests such as FTA-ABS and MHA-TP to confirm the diagnosis, as well as other tests to assess the extent of the infection, such as a physical examination, dark field microscopy, direct fluorescent staining, and PCR of the placenta, cord, lesions, or body fluids. Additionally, there is a need for more research on the optimal combination of tests, especially in relation to placenta and stillborn specimens, to improve the diagnosis and management of congenital syphilis.

The re-emergence of syphilis in the United States is attributed to multiple factors. Studies show that there is a difference in rates of congenital syphilis depending on region, socioeconomic level, and race. Addressing these health disparities requires a comprehensive approach. It involves improving access to quality prenatal care, implementing targeted interventions in high-risk communities, enhancing health education and awareness programs, and addressing social determinants of health such as poverty and discrimination. Ultimately, this should reduce the occurrence of congenital syphilis and promote equitable health outcomes.

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