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Congenital syphilis

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ABSTRACT

Congenital syphilis remains a major public health problem worldwide, and its incidence is increasing in the United States. This review highlights the ongoing problem of this preventable infection, and discusses vertical transmission and clinical manifestations while providing a practical algorithm for the evaluation and management of infants born to mothers with reactive serologic tests for syphilis. Every case of congenital syphilis must be seen as a failure of our public health system to provide optimal prenatal care to pregnant women, as congenital syphilis can be prevented by early and repeated prenatal serologic screening of mothers and penicillin treatment of infected women, their sexual partners, and their newborn infants.

Congenital syphilis, a result of fetal infection with *Treponema pallidum*,[1] is an ancient disease that continues to plague infants worldwide. Despite wide understanding of the disease and optimal preventive strategies, congenital syphilis remains a major cause of fetal and neonatal mortality globally.[2] The global burden of congenital syphilis is confounded further by the high prevalence of co-infection with the human immunodeficiency virus (HIV) in adults, as syphilis is a known risk factor for acquisition of HIV.

In 1988, the surveillance case definition for national reporting of congenital syphilis was broadened by the Centers for Disease and Prevention (CDC) to include all liveborn and stillborn infants, irrespective of clinical findings, who had reactive serologic tests for syphilis and delivered to women with untreated or inadequately treated syphilis.[3] This change resulted in a fourfold increase in reported cases of congenital syphilis when compared to the previously used Kaufman criteria that included only infants with clinical, laboratory, or radiographic abnormalities. Using the revised case definition, there were 6383 cases of congenital syphilis reported to the CDC from 1999 to 2013, with a neonatal mortality of 11.6/1000 births and a case fatality rate of 6.5%.[4] Of the 418 deaths, 82% ($n = 342$) were stillbirths. Importantly, the majority of deaths occurred among infants born to mothers with untreated or inadequately treated syphilis, and 59% occurred by 31 weeks of gestation. Since 2012, there has been a steady increase in cases of congenital syphilis reported to the CDC with 628 cases (15.7/100,000 live births) reported in 2016 that included 41 syphilitic stillbirths (Fig. 1; https://www.cdc.gov/std/stats16/syphilis.htm).[5] In 2016, rates of congenital syphilis were highest among Blacks (43.1/100,000 live births), followed by American Indians/Alaska Natives (31.6/100,000 live births), Hispanics (20.5/100,000 live births), Asians/Pacific Islanders (9.2/100,000 live births), and Whites (5.3/100,000 live births).

As has been observed historically, the increase in congenital syphilis paralleled increases in primary and secondary

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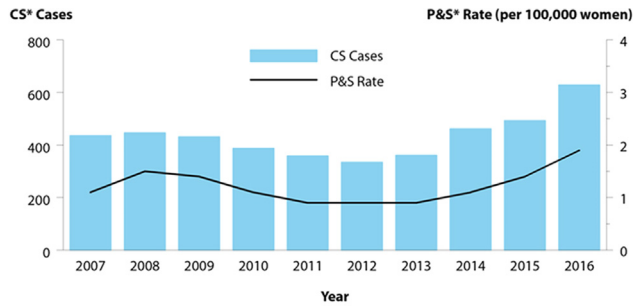

*CS = Congenital syphilis; P&S = Primary and secondary syphilis
Data from Centers for Disease Control and Prevention: 2016 Sexually Transmitted Diseases Surveillance (https://www.cdc.gov/std/stats16/syphilis.htm)

Fig. 1 – Congenital syphilis—Reported cases by year of birth and rates of reported cases of primary and secondary syphilis among woman, United States, 2007–2016.

syphilis among women.[6,7] However, the highest rates of primary and secondary syphilis in adults has occurred among men who have sex with men (MSM),[8,9] and the contribution of men who have sex with men and women (MSMW) to the congenital syphilis epidemic remains unknown.

Transmission

Syphilis is transmitted to the fetus transplacentally following maternal spirochetemia, although transmission to the newborn could occur intrapartum by contact with maternal genital lesion(s). Intrauterine transmission is supported by the isolation of the organism from umbilical cord blood and amniotic fluid by rabbit infectivity testing.[10–12] The isolation of *T. pallidum* from as many as 74% of amniotic fluid specimens obtained from women with early syphilis also suggests that the organism is capable of traversing the fetal membranes, gain access to the amniotic fluid, and result in fetal infection.[11,13] Intrauterine transmission also is supported by the finding of abnormalities consistent with congenital syphilis both *in utero* and at birth,[10] as well as by detection of specific IgM antibodies to *T. pallidum* in fetal serum obtained by cordocentesis and in neonatal serum obtained at birth.[14–16]

Vertical transmission increases as the stage of pregnancy advances but can occur at any time in gestation. The theory that the Langerhans cell layer of the cytotrophoblast forms a placental barrier against fetal infection before the 18th week of pregnancy was disproved by detection of spirochetes in fetal tissue from spontaneous abortion as early as 9 and 10 weeks' gestation[17] and recovery of spirochetes from amniotic fluid at 14 weeks of pregnancy by rabbit infectivity testing.[11] Futhermore, electron microscopy has demonstrated the persistence of the Langerhans cell layer throughout pregnancy.

Importantly, vertical transmission is related to the stage of maternal syphilis, with the highest transmission rates seen with early syphilis and specifically, secondary syphilis. In 1950, Ingraham reported that among 251 women with untreated syphilis of less than 4 years' duration, 41% of their infants were born alive and had congenital syphilis, 25% were stillborn, 14% died in the neonatal period, 21% had low birth weight but no evidence of syphilis, and only 18% were normal full term infants.[18] Among mothers with late latent infection, only 2% of their infants had congenital syphilis. In 1952, Fiumara and colleagues[19] reported that untreated maternal primary or secondary syphilis resulted in 50% of infants having congenital syphilis while the other 50% were stillborn, premature, or died in the neonatal period. With early and late latent infection, 40% and 10% of infants, respectively, had congenital syphilis. More recently, from 1988 to 1998 at Parkland Memorial Hospital, Dallas, Sheffield and colleagues reported vertical transmission rates of 29%, 59%, 50%, and 13% in mothers with primary, secondary, early latent, and late latent infection, respectively.[20]

Clinical manifestations

Syphilis during pregnancy is associated with premature delivery, spontaneous abortion, stillbirth, nonimmune hydrops, perinatal death, and two characteristic syndromes of clinical disease, early and late congenital syphilis.[21] Moreover, the placenta of infants with congenital syphilis often is large, thick, and pale. Histopathologic features include necrotizing funisitis ("barber's pole" appearance), villous enlargement, and acute villitis.[22] Placental and umbilical cord histopathology should be performed on every case of suspected syphilis. The clinical, laboratory, and radiographic abnormalities of congenital syphilis are a consequence of active infection with *T. pallidum* and the resultant inflammatory response induced in various body organs and tissues. The majority of infants born to mothers with untreated syphilis appear normal and have no clinical or laboratory evidence of infection at birth, but may develop manifestations of disease months to years later if left untreated.[23]

Early congenital syphilis refers to those clinical manifestations that appear in the first 2 years of age (Table 1). Hepatosplenomegaly secondary to either extramedullary hematopoiesis or hepatitis is frequent and may take months to resolve. The hepatitis of congenital syphilis may worsen transiently after initiation of penicillin therapy. Thrombocytopenia with petechiae and purpura also occurs frequently and may be the sole manifestation of congenital infection. Mucocutaneous lesions are prominent manifestations that occur in 40–60% of affected infants. The rash of congenital syphilis usually is oval and maculopapular but becomes copper-colored with desquamation mostly in the palms and soles (Fig. 2). A characteristic fluid-filled, bullous eruption known as *pemphigus syphiliticus* may develop with peeling and eventual crusting and skin wrinkling. Rarely, mucous patches of the lips, tongue, and palate as well as white, flat, moist, raised plaques known as *condylomata lata* in the perioral and perianal areas may occur.

Some affected infants may develop rhinitis ("snuffles"), a nasal discharge that is initially watery but may become thick, purulent, and blood-tinged. Both the nasal discharge and bullous fluid contain large concentrations of spirochetes and are highly infectious. Other less common manifestations include anemia, ocular findings (chorioretinitis, cataract, glaucoma, and uveitis), pneumonitis, pneumonia alba, nephrotic syndrome, myocarditis, pancreatitis, and inflammation and fibrosis of the gastrointestinal tract leading to malabsorption and diarrhea.