Shining the light on congenital syphilis: from TORCH to SCORTCH

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Syphilis has re-emerged as a significant public health threat in recent years. Whilst most cases of syphilis are currently diagnosed in low- and middle-income countries, the incidence of syphilis has been increasing in Western industrialised countries since the 1990s, particularly among gay, bisexual and other men who have sex with men (MSM).[1] Increased rates among heterosexuals in these countries have also been reported in more recent years, most often in marginalised populations.[2] In England, there were 7,982 diagnoses of syphilis during 2019, a 200% increase since 2010. Although three-quarters of cases were diagnosed in MSM, cases in heterosexual men and women have increased by 69% and 117%, respectively, between 2015 and 2019, and the number of cases of congenital syphilis (CS) has also increased.[3] The underlying drivers of the increase in heterosexually acquired syphilis cases in England remain unclear.

Syphilis is caused by *Treponema pallidum* subspecies *pallidum* and is typically transmitted by direct contact with an infectious lesion during sexual intercourse. The clinical presentation of syphilis is divided into three stages: primary, secondary, and tertiary, and the first two are the most infectious stages. Typically, primary syphilis presents as a painless ulcer (chancre) which usually occurs in genital sites and resolves within three to eight weeks. If left untreated, 25% of patients will develop secondary syphilis, a systemic disease characterised by fever, rash and lymphadenopathy. Secondary syphilis will resolve spontaneously in 3 to 12 weeks and all untreated cases will progress to latent (asymptomatic) infection, with one-third later developing features of tertiary syphilis.[4]

In pregnancy, syphilis can be transmitted to the foetus at any stage. The risk of transplacental infection is 60-80% and is increased during the second half of pregnancy. Mother-to-child transmission is higher in untreated maternal primary or secondary syphilis (60-90%), decreasing to 40% in early latent syphilis, and <10% in late latent syphilis. It is estimated that up to 40% of babies with congenital syphilis may be stillborn or die in the neonatal period.[5]

In England, as in most industrialised countries, vertical transmission is rare, mainly because of the consistently high (>99%) uptake of antenatal syphilis screening.[3] Additionally, early diagnosis and effective treatment of pregnant women with syphilis, especially in the first and second trimester,

significantly reduces the risk of mother-to-child transmission, which in turn reduces the risk of adverse pregnancy outcomes, including stillbirths, perinatal deaths and congenital syphilis. Consequently, the incidence of congenital syphilis in the UK is below the World Health Organization elimination threshold (≤0.5/1000 live births). However, England has not had a robust surveillance system for CS and, therefore, the number of reported cases is likely to be underestimated. During 2010-2017, 21 CS cases were identified; most were associated with mothers who were socially marginalised, had experienced difficulties accessing healthcare and had first presented to antenatal services close to the time of delivery.[2,6] However, seven of these cases were born to mothers who had had a negative first trimester antenatal screening test ('screen-negative' cases) and had, therefore, acquired syphilis later in pregnancy. Many of these mothers were UK-born and had no identifiable risk factors for syphilis. Some cases occurred in regions across England with recent increases in syphilis among women and MSM, suggesting that overlapping sexual networks may have facilitated wider dissemination.[2] Crucially, in some of these CS cases, syphilis was not considered in the differential diagnosis of the unwell infant until relatively late in the investigations, as the clinicians were reassured by a negative antenatal screen.

Current guidelines recommend that pregnant women identified as being at risk be re-screened in the third trimester, but it can be difficult to identify those at risk and routine third trimester screening for all pregnant women is unlikely to be cost-effective. It is, therefore, vital that obstetric and neonatal healthcare providers maintain a high index of suspicion throughout the antenatal and postnatal period. In one of the recent 'screen negative' cases in England, the mother presented in late pregnancy with genital ulcers, but syphilis was not considered by her healthcare provider.[7]

In infants, manifestations of syphilis are classified as early congenital (birth to 2 years) and late congenital (after 2 years) and ranges from asymptomatic to multi-organ damage. However, the clinical presentation can be non-specific, especially during the early stages of illness, and overlaps with that of several other infections. Additionally, up to two-thirds of syphilitic infants may be asymptomatic at birth.[5]

For infants with suspected congenital infection, we support the recommendation by Penner et al that the original 'TORCH' screen (toxoplasmosis, 'other', rubella, cytomegalovirus, herpes simplex) which included syphilis under 'other', should be broadened to specifically emphasise syphilis testing: 'SCORTCH' (syphilis, CMV, 'other', rubella, toxoplasmosis, chickenpox, HSV and blood borne viruses) .[8] The diagnosis of syphilis can be confirmed by identification of *T pallidum* (by dark ground microscopy or PCR) in exudates from lesions or body fluids, as well as diagnostic blood tests (**Table**). Neonatal serology can be complicated by the presence of transplacentally-acquired maternal IgG

antibodies. However, a neonatal nontreponemal antibody titre more than four times the maternal titre would support active infection because such a high ratio is unlikely to be achieved through passive transfer. Alternatively, a rising RPR titre over three months would also support a diagnosis of CS. Antibody assays for anti-treponemal IgM, which is not transferred across the placenta, are also useful.[4]

Clinicians need to be aware that the serological response in infected neonates may not always be diagnostic; among the recent 'screen-negative' CS cases, many had a negative IgM and an RPR titre lower than that of their mother.[9] This may be because the babies were infected late in pregnancy and were born prior to a mature antibody response developing, or they (or their mother prior to birth) had received empirical antibiotics which attenuated the antibody response. In such cases, a positive syphilis PCR would confirm the diagnosis; PCR of upper respiratory tract specimens such as nasopharyngeal aspirates, are particularly helpful and should be tested in all suspected CS cases.[8]

Those with clinical disease or suggestive serological test results should have additional blood tests (full blood count, liver function tests, inflammatory markers), lumbar puncture (cell count, protein and treponemal and nontreponemal antibodies), long-bone x-rays, and other investigations as clinically indicated (e,g. ophthalmological review, hearing tests, neuroimaging).[4] It is recommended that all cases of suspected CS should be discussed with a paediatrician with expertise in the diagnosis and management of congenital infection. [8]

In June 2019, Public Health England (PHE) published an Action Plan to address the increase in syphilis in England.[3] The Action Plan emphasises the importance of controlling syphilis in MSM by increasing testing frequency among high-risk men and sustaining targeted health promotion. The plan also highlights the need for enhanced efforts to prevent CS by maintaining high antenatal screening coverage and improving vigilance for syphilis throughout antenatal care. PHE has commenced surveillance of maternal and congenital syphilis through the Infectious Diseases in Pregnancy Screening Programme's Integrated Screening Outcomes Surveillance Service (ISOSS). Neonatologists and paediatricians are encouraged to report all cases directly to ISOSS.[10] A better understanding of syphilis transmission leading to CS could lead to specific interventions to protect pregnant women and their infants from this terrible disease.

Competing Interests

None declared

References

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Serology tests:	Serology tests should be performed on infant blood and maternal blood in parallel. (i) **Treponemal** tests, such as total antibody EIA and treponemal pallidum particle agglutination (TPPA) tests detect IgG as well as IgM, and may be positive due to passive transfer of maternal antibodies. A four-fold increase in titre within 3 months of birth, or positivity beyond 18 months of age, is consistent with CS. A positive IgM EIA is consistent with CS, as IgM is not transferred across the placenta. (ii) **Non-treponemal tests**, such as the VDRL or RPR, also detect both IgG and IgM antibodies. A four-fold RPR/VDRL titre above that of the mother, or a four-fold increase in titre within 3 months of birth, is consistent with CS. Tests should be performed at birth and then 3 monthly until negative.
Direct testing:	Direct demonstration of *T pallidum* by dark ground microscopy or PCR of exudates from lesions, body fluids e.g. nasal discharge, or naso-pharyngeal aspirate.

Table. Investigations to confirm the diagnosis of congenital syphilis