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Regardless of origins, syphilis has affected Europeans over many centuries. The first well-documented outbreak occurred in Naples in 1494, rapidly swept throughout Europe and was associated with a myriad of presenting signs and symptoms and a high mortality rate. The condition was once a leading cause of dementia and in the pre-antibiotic era caused one out of five of all admissions to psychiatric institutions in the USA. In 1945 Mahoney and co-workers first treated cases of syphilis with penicillin. This drug has remained the mainstay of treatment since that time.

TRANSMISSION

Horizontal transmission among adolescents and adults is primarily sexual, although anecdotal reports cite kissing, contact with infected secretions and blood transfusion as potential sources of acquisition and transmission. 4

Transmission to the fetus is usually via the placenta, but may occur during delivery in the presence of maternal genital lesions. The risk of vertical transmission of syphilis from an infected untreated mother decreases as maternal disease progresses, ranging from 70–100% for primary syphilis and 40% for early latent syphilis to 10% for late latent disease (early and late latent syphilis occurring less than or more than 1 year after initial infection in adults, respectively). 3, 5 Although unusual, transmission to newborns from mothers with tertiary syphilis has also been reported. 6 Thus, the longer the interval between infection and pregnancy, the more benign is the outcome in the infant (Kassowitz's law). 6

EPIDEMIOLOGY

Syphilis is common in the developing world with localised prevalence in pregnant women varying widely from 2.5% in Burkina Faso to 17.4% in Cameroon. 7

However, such data may be skewed by high numbers of false-positive assays. Data on sexually transmitted infections have been collected in the UK since 1917; such infections are currently reported by genitourinary medicine (GUM) clinics to the Health Protection Agency (HPA) by KC60 statutory notification in England, Wales and Northern Ireland and by ISD(D)/STISS returns in Scotland. These official figures may therefore be an underestimation of the burden of congenital syphilis if diagnoses are made outside the GUM setting. Since 1998 a sharp increase in syphilis diagnoses has been documented among heterosexual populations 8 and men who have sex with men (MSM) (fig 1). In Manchester and London, this increase resulted in the introduction of enhanced surveillance in 1999 and 2001, respectively, which was subsequently extended nationally.

Among women, syphilis primarily affects 16–34-year-olds who are also those most likely to conceive (fig 2), mandating screening for syphilis antenatally. Localised outbreaks in the UK have been associated with sex workers and cocaine usage. 9 An earlier study performed by the British Paediatric Surveillance Unit (BPSU) commented on an over-representation of pregnant women from ethnic minorities born outside the UK treated for syphilis in the Thames region. 10 Recent reports have raised concerns that current antenatal testing may be inadequate for the identification and treatment of women at risk. 11–15 These concerns are reinforced by recent data from the HPA, which identified 36 cases of congenital syphilis in the UK in 2005, the highest number in 10 years. 14

CLINICAL MANIFESTATIONS

In pregnant women untreated or inadequately treated syphilis is associated with prematurity, low birth weight, non-immune hydrops and intrauterine death. It has been estimated that at least two-thirds of all fetuses of mothers with infectious syphilis are in some way affected. 16 The WHO estimates that 1 million pregnancies are affected by syphilis worldwide. Of these 460 000 will result in abortion or perinatal death, 270 000 infants will be born prematurely or with low birth weight, and 270 000 will be born with stigmata of congenital syphilis. 16 Most affected infants are asymptomatic at birth with two-thirds developing symptoms by 3–8 weeks. Almost all exhibit symptoms by 3 months of age. 17

The early manifestations of congenital syphilis

The symptoms of early syphilis can be varied. “Snuffles” or persistent rhinitis is often the earliest presenting symptom, occurring in 4–22% of newborns. 18 This discharge can take many forms and is highly infectious. Necrotising funisitis, a deep-seated infection of the umbilical cord, was considered to be diagnostic of congenital syphilis. It almost always occurs in premature neonates and is associated with a high incidence of intrauterine or perinatal death. 19 Other common, but often non-specific, symptoms of congenital syphilis include non-tender generalised lymphadenopathy, conjunctival hyperplasia and hepatosplenomegaly (table 1). 20 21 Glomerulonephritis resulting in nephrotic syndrome may also occur. The rash in early syphilis is classically a vesiculobullous or maculopapular rash occurring on the palms and soles and may be associated with desquamation. Other rashes including erythema multiforme have been reported. 20 22 Asymptomatic cerebrospinal fluid changes (elevated protein, positive Venereal Disease Research Laboratory test (VDRL)) may be found in 80% of infants, 23 but acute syphilitic meningitis occurs rarely. 24

Bony lesions occur commonly and present in the first 8 months of life. Radiographic abnormalities may be seen in 20% of babies with asymptomatic infection necessitating prompt radiological assessment of all exposed infants. The bones most often affected include the tibia, the tubular bones of the hands and feet and, more rarely, the skull and
clavicles. Radiographic examination of bones can reveal irregular epiphyseal lines, decalcification of subchondral bone, cupping of the diaphysis, irregularity of cartilage adjacent to the epiphysis and periosteal thickening. The typical Wimberger’s lines seen during early syphilis reflect metaphyseal destruction secondary to focal erosion of the inner aspect of the proximal tibia. Osteochondritis or Parrot’s pseudo-paralysis is the most common and earliest lesion characterised by an asymmetric, painful, flaccid paralysis of the upper limbs and knees which can be confused with Erb’s palsy. Diaphyseal periostitis is asymptomatic and radiographic changes are often not seen until after 3 months of age.

Late congenital syphilis occurs in children over the age of 2, but most often presents in puberty. Late syphilis can affect many organ systems, although the sites most often involved include the bones, teeth and nervous system. A poor response to intensive treatment is often documented during the management of these late manifestations.

Some 25–33% of infants with untreated congenital syphilis have asymptomatic neurosyphilis once they are more than 2 years old. Symptomatic neurosyphilis, tabes dorsalis and cerebrovascular lesions develop rarely, with juvenile paresis developing in 1–5% of children/adolescents with congenital syphilis. When symptomatic, neurosyphilis can result in eighth nerve deafness. The onset of deafness is generally sudden and occurs at 8–10 years of age; associated with notched incisors and interstitial keratitis it forms part of the classical Hutchinson’s triad. Other ocular lesions include iridocyclitis and chorioretinitis.

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DIAGNOSIS

The gold standard for diagnosis of syphilis is the rabbit infectivity test (RIT) whereby the body fluid of a person with suspected infection is injected into a rabbit. Only one organism needs to be present to confirm diagnosis, however this test has obvious limitations and is not used routinely in clinical practice in the UK. Definitive diagnosis of syphilis more usually involves viewing the classical spirochaetes of *Treponema pallidum* on darkfield microscopy of mucosal lesions, exudates, lymph nodes or placental tissue. This test has a low sensitivity (<10⁵ organisms/ml), however, and relies on fresh, good quality specimens. In addition, it is not specific when used for examining oral lesions where treponemal species are part of the normal oral flora.

The use of polymerase chain reaction (PCR) to detect *T pallidum* in orogenital lesions and CSF offers the possibility of a more sensitive and specific means of diagnosing syphilis. Neonates have been reported to be more likely to have syphilis detectable in the blood or CSF, making PCR to detect *T pallidum* of interest for the future diagnosis of congenital syphilis, and in particular early detection of neurosyphilis.

Antenatal testing

Guidelines have recently been published relating to the diagnosis of syphilis in adults and serology remains the mainstay of laboratory testing for syphilis. Effective prevention of congenital syphilis depends on the identification of active infection in pregnant women by routine testing.
screening during antenatal visits and near the time of delivery with a non-treponemal test (VDRL or rapid plasma reagin (RPR)). These tests are quantitative and correlate with disease activity and response to therapy.

Non-treponemal tests can be falsely negative with early primary syphilis, latent acquired syphilis of long duration and late congenital syphilis. A non-treponemal test performed on serum samples containing high concentrations of antibody against T pallidum can be weakly reactive or falsely negative; this reaction is termed the prozone phenomenon. False-positive results can be secondary to viral infections (infectious mononucleosis, hepatitis, varicella, measles), lymphoma, tuberculosis, malaria, endocarditis, connective tissue disease, pregnancy, laboratory error, or Wharton jelly contamination when cord blood specimens are used.

For women treated during pregnancy, follow-up serological testing is necessary to assess the efficacy of therapy demonstrated by a fourfold decrease in non-treponemal titres. These usually become non-reactive 1 year after prompt treatment of primary or secondary infection if the initial titre is low (<1:8) and within 2 years with congenital infection or if the initial titre is high. Differentiating treated syphilis from active (re)infection may be difficult in the absence of increasing titres.

To exclude a false-positive non-treponemal test, serology should be sent for confirmatory treponemal antibody detection by fluorescent treponemal antibody absorption (FTA-ABS) or T pallidum particle agglutination (TPPA). Treatment should not be delayed while awaiting the results of the treponemal test if the patient is symptomatic or at high risk of infection. Treponemal test antibody titres remain reactive for life even after successful therapy, correlate poorly with disease activity and should therefore not be used to assess response to therapy. Treponemal tests may not be specific for syphilis, since positive reactions variably occur in patients with other spirochetal infections, including yaws, pinta, leptospirosis, rat-bite fever, relapsing fever and Lyme disease.

The combination of non-treponemal and treponemal tests provides sensitive and specific screening for all stages of syphilis but requires subjective interpretation and cannot readily be automated. With the recent commercial availability of enzyme immunoassays (EIAs), the non-treponemal and treponemal combination is increasingly being replaced in UK diagnostic microbiology laboratories by assays detecting treponemal IgG or IgM and IgM. Advantages include the production of objective results, the ability to link EIA plate readers directly to laboratory computer systems, and the facility for automation. A quantitative non-treponemal test and serology for specific anti-treponemal IgM provides a baseline for monitoring the effect of therapy. IgM becomes undetectable within 3–9 months after adequate treatment of early syphilis but may persist for up to 18 months after treatment of late disease. Although the treponemal IgG EIA has not been as widely adopted in the USA, there are published data showing that screening with recombinant antigen-based treponemal IgG and IgM has comparable sensitivity and specificity compared to the non-treponemal and treponemal combination, and may be useful for detecting treponemal antibody in HIV-infected patients.

Evaluation of newborn infants with perinatal exposure to syphilis

All infants born to seropositive mothers should be considered to be exposed to syphilis unless full investigation of the mother shows other explanations for the serological findings and/or evidence of complete treatment and response to this treatment. Where possible the placenta and/or umbilical cord should be sent for pathological examination and dark ground microscopy, if this is available. Serology should be sent for quantitative non-treponemal tests using the same assay as that performed on the mother to enable comparison of titres. Cord blood is inadequate for screening since sera can be non-reactive even when the mother is seropositive and contamination with maternal blood may occur. A guide for interpretation of the results of non-treponemal and treponemal serological tests is given in table 2. Where combinations of diagnostic tests other than those referred to above are being used, we recommend local collaboration and discussion antenatally regarding planned follow-up for the neonate.

Anti-treponemal IgG measured in the infant can be transplacentally acquired from the mother and persist for up to 18 months, and so is not of use in the initial evaluation of an infant for congenital infection. Detection of specific anti-treponemal IgM may also be useful in the diagnosis of congenital infection, but a negative result around the time of delivery does not exclude congenital infection. Serological follow-up is indicated and should include repeat IgM testing, and quantitative non-treponemal and treponemal serology to demonstrate loss of passive maternal antibody.

An exposed infant should be evaluated for active syphilis and considered at high risk for infection if:

1. The infant is symptomatic.
2. Titre of maternal non-treponemal serology (eg, VDRL, RPR) has increased fourfold.
3. Infant non-treponemal titre is fourfold greater than maternal titre.
4. Maternal syphilis was untreated or inadequately treated during pregnancy with insufficient serological follow-up.
5. Maternal syphilis was treated with a non-penicillin regimen.
6. After treatment of maternal syphilis (with an appropriate penicillin regimen), the expected decrease in non-treponemal antibody titre after therapy did not occur.
7. Treatment for maternal syphilis was commenced less than 1 month before delivery.

If the situation is unclear, then repeat maternal and infant bloods should be taken at birth, a full evaluation of the baby carried out and serious consideration given to treatment of the neonate while results are awaited. If treatment is not instituted, clinicians should be certain...
that rigorous follow-up will be possible and attendance ensured. In women who come from areas where other treponemal infections are endemic (such as pinta or yaws), babies should be treated as if they have congenital syphilis since it is impossible using standard serological tests to differentiate between these infections. If maternal HIV is present, then the risk of transmission of syphilis should be considered to be even greater and a lower threshold for treatment adopted.

In addition to blood for treponemal and non-treponemal testing, the evaluation should also include liver function tests, long bone x-rays, CSF specimen for VDRL test and analysis for the detection of white cells and elevated protein, and ophthalmic assessment. A negative VDRL on CSF does not exclude congenital neurosyphilis.

If a case of congenital syphilis is suspected, evaluation of any previously uninvestigated siblings should also be considered.

TREATMENT

Parenteral penicillin G is the only documented effective therapy for patients who have neurosyphilis, congenital syphilis or syphilis during pregnancy. Aqueous crystalline penicillin G is preferred over procaine penicillin G because adequate CSF concentrations may not be achieved with the latter. If more than 1 day of therapy is missed, it has been recommended that the entire course should be restarted, although there is no recent evidence to support this recommendation.

Newborn infants

In newborn infants, the dose for aqueous crystalline penicillin G is 100 000–150 000 U/kg per day, administered as 50 000 U/kg per dose, intravenously, every 12 h during the first 7 days of life and every 8 h thereafter for a total of 10 days. Procaine penicillin G is administered in a single dose at 50 000 U/kg per day, intramuscularly, for 10 days. These recommendations are based on chronological, not gestational, age.

Older infants and children

Infants older than 4 weeks of age who possibly have congenital syphilis or who have neurological involvement should be treated with aqueous crystalline penicillin, 200 000–300 000 U/kg per day, intravenously (administered every 6 h), for 10 days. This regimen also should be used to treat children older than 1 year of age who have late and previously untreated congenital syphilis.41

During pregnancy

UK guidelines are already available and patients should be treated with penicillin according to the dosage schedules appropriate for the stage of syphilis as recommended for non-pregnant patients.32 Penicillin-allergic pregnant women should be treated with penicillin after desensitisation. While awaiting penicillin desensitisation, erythromycin (or other non-penicillin regimes) should be used. Evidence that non-penicillin regimes are effective in the treatment of congenital syphilis is not currently available, however, meaning that infants should be treated at birth as if mother had received no treatment if such regimes are used.

FOLLOW-UP

Treated infants should be followed up at 3, 6 and 12 months of age until serologic non-treponemal tests become non-reactive or the titre has decreased fourfold. With adequate treatment or in cases where antibody is transplacentally acquired in the absence of congenital infection, non-treponemal antibody titres should decrease by 3 months of age and be non-reactive by 6 months of age. At 6–12 months of age previously treated infants with increasing or persistent titres should be evaluated, including CSF examination, and treated with a further 10-day course of parenteral penicillin G.

Treated infants with congenital neurosyphilis should undergo repeated clinical evaluation and CSF examination at 6-month intervals until their CSF examination is normal. A persistently reactive VDRL test of CSF is an indication for re-treatment.41

In untreated babies with no symptoms of congenital syphilis who are documented to have a non-treponemal antibody titre at least fourfold less than their mothers at birth and whose mother was fully treated and evaluated antenatally (including follow-up testing to confirm successful treatment), no further follow-up is required. If there is any uncertainty regarding the completeness of antenatal follow-up or neonatal serology then the baby should be reviewed and further samples sent for non-treponemal antibody testing at 3 and 6 months of age. A full re-evaluation should be carried out if titres have not decreased by 6 months of age. A sample for treponemal antibody titres should then be sent at 12 months of age; in most cases they will no longer be detectable by this age if passively acquired.

CONCLUSION

In this article we have reviewed the management of maternal and congenital syphilis. At a time when this disease has re-emerged in the UK, we hope that the review will assist clinicians in familiarising themselves again with the subtleties of this age-old affliction. Despite the introduction of effective treatment and the availability of diagnostic testing in the mid-20th century, syphilis still remains a national health issue. “...she who knows syphilis knows the more things change the more they stay the same”!

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REFERENCES


