

# Maternal syphilis: pathophysiology and treatment

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**Abstract** Despite the long history of medical interest in syphilis and its effects on pregnancy outcome, many fundamental questions about the pathophysiology and treatment of syphilis during pregnancy remain unanswered. However, understanding has been advanced by recent scientific reports such as those which delineate the complete sequence of the genome of the syphilis spirochaete, provide a more precise description of fetal and neonate infection by use of rabbit infectivity tests and describe the gestational age distribution of fetal death secondary to syphilis. It appears that fetal syphilitic involvement progresses in a rather predictable fashion, and although there is disagreement about the optimal prenatal treatment regimen, programmatic efforts to prevent fetal death must provide seropositive pregnant women with a recommended treatment early in pregnancy, and certainly before the third trimester.

**Keywords** Syphilis, Congenital/cerebrospinal fluid/physiopathology/prevention and control; Syphilis/diagnosis/drug therapy/transmission; Disease transmission, Vertical/prevention and control; Pregnancy complications, Infectious/drug therapy; Pregnancy outcome; Prenatal diagnosis/standards; Prenatal care; Treponema pallidum/genetics; Penicillin G/administration and dosage; Ceftriaxone; Fetal diseases/pathology/prevention and control; Practice guidelines (source: MeSH, NLM).

**Mots clés** Syphilis congénitale/liquide céphalorachidien/physiopathologie/prévention et contrôle; Syphilis/diagnostic/chimiothérapie/transmission; Transmission verticale maladie/prévention et contrôle; Complication infectieuse grossesse/chimiothérapie; Issue grossesse; Diagnostic prénatal/normes; Soins prénataux; Treponema pallidum/génétique; Pénicilline G/administration et posologie; Ceftriaxone; Fœtus, Maladies/anatomie pathologique/prévention et contrôle; Ligne directrice pratique médicale (source: MeSH, INSERM).

**Palabras clave** Sífilis congénita/líquido cefalorraquídeo/fisiopatología/prevención y control; Sífilis/diagnóstico/quimioterapia/transmisión; Transmisión vertical de enfermedad/prevención y control; Complicaciones infecciosas del embarazo/quimioterapia; Resultado del embarazo; Diagnóstico prenatal/normas; Atención prenatal; Treponema pallidum/genética; Penicilina G/administración y dosificación; Ceftriaxone; Enfermedades fetales/patología/prevención y control; Pautas prácticas (fuente: DeCS, BIREME).

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Efforts to prevent transmission of syphilis from mother to child must be based on the best available understanding of the pathophysiology of congenital syphilis and vertical transmission. Although there is extensive literature that is helpful in this regard, there is much that is still unknown. However, several important new studies have furthered understanding and can help inform those involved in prevention.

Syphilis is neither a new disease, nor a newly-recognized one. Some of the basic facts of congenital involvement — such as Hutchinson's triad (1) and Kassowitz's observation in 1846 that the longer a woman has syphilis before pregnancy occurs, the less likely it is that her fetus will die in utero or be born with congenital syphilis (2) — have been known for over 100 years. With the rapid expansion of biomedical technological capabilities, it might be expected that by now the mysteries of congenital syphilis would have been solved and the important questions answered. Unfortunately, that is not the case. Many critical aspects of the pathophysiology of maternal syphilis

remain unexplained. In fact, much of the available information is descriptive. The diagnostic tools that are widely available remain rather primitive; there have been no important advances in the treatment of maternal syphilis in recent years, and the ability to monitor the efficacy of treatment in utero is sub-optimal.

Nevertheless, in recent years there have been some important scientific contributions that have begun to answer questions about this condition and that will help to guide further research and inform clinical management.

## The organism

One important recent advance is the complete sequencing of the genome of the *Treponema pallidum* sp. *pallidum* (3). This should allow scientists in the near future to develop additional tools and insights concerning this organism and the conditions for which it is responsible. Although *T. pallidum* is still an

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important infectious agent, little is known about its mechanism of action or the determinants of virulence. The outer membrane of *T. pallidum* is mostly lipid and contains little protein, creating challenges for the development of accurate diagnostic tests and effective vaccines (3). One of the principal problems confronting syphilis researchers is the inability to cultivate *T. pallidum* on an artificial medium (4). The organism can only be cultivated by inoculation into rabbit testes, i.e. by rabbit infectivity testing; animals are followed over three months for evidence of orchitis and seroconversion (5).

Nevertheless, the genomic sequence has provided some important information on the organism. Although it had been known for some time that *T. pallidum* lacked biosynthetic and catabolic capabilities, the sequencing made it clear just how limited the organism is (4). Although *T. pallidum* can utilize carbohydrates, it cannot synthesize fatty acids, and has few enzyme sets for building complex molecules; to survive it acquires what it needs from its host (6).

Like Gram-negative bacteria, *T. pallidum* sp. *pallidum* has an outer membrane, but its inner membrane contains only rare integral membrane proteins, some of which are surface exposed (7). This characteristic may provide some understanding of how the organism elicits such a vigorous inflammatory and immunological response, but manages to evade immunological clearance, although a paucity of surface proteins means that its cell surface presents few targets for a host immune response. The organism has genes for 22 different lipoproteins, which may elicit strong inflammatory responses (6). However, many questions remain unanswered because despite the genomic sequencing the functions of more than 40% of the genes in the sequence are as yet unknown (4).

Some other known basic properties of the treponeme help to determine biological effect and have influenced decisions about management. For example, the organism replicates slowly; the doubling time for *T. pallidum* has been calculated to be 30–33 hours in early disease (8). On this basis, Idsoe (9) suggested that effective treatment of early syphilis required maintenance of a minimal serum concentration for 7–10 days without interruption. In addition, the fact that no penicillin-resistant strains of *T. pallidum* have ever been isolated may reflect the organism's limited metabolic and biosynthetic capabilities.

## Transmission

Fetal infection is a result of haematogenous spread from an infected mother, although transmission at the time of delivery can result from direct contact with infectious genital lesions of the mother. Haematogenous spread is dependent upon the occurrence of maternal spirochaetemia. Since the early stage of syphilis is characterized by spirochaetemia, the probability of transmission to the fetus is nearly 100% if the mother has early syphilis (10). Following secondary syphilis, the probability of recurrence of spirochaetemia diminishes over time; the probability of sexual transmission two years after acquisition of syphilis is low (5). Although the probability of transmission to a fetus can be up to 70% four years after the acquisition of disease by the mother (11), most infants born to mothers with late latent syphilis are uninfected (12). The main factors that determine the probability of fetal transmission are stage of maternal syphilis and duration of exposure in utero. Therefore, in considering fetal transmission, the following are pertinent: if a woman with syphilis becomes pregnant, what is the stage of

syphilis at conception? If a pregnant woman acquires syphilis, what was the gestational age at acquisition? As discussed below, these factors are also relevant with regard to manifestations of fetal involvement.

It was assumed in the past that treponemes did not cross the placenta until after 20 weeks of gestation. Early researchers believed that the Langhans' cell layer of the cytotrophoblast was an effective placental barrier; fetal involvement had not been identified at earlier stages of gestation (13). However, this theory had to be discounted once it was discovered that the Langhans' cell layer persisted throughout pregnancy (14). Moreover, in 1974, Harter & Benirschke examined fetal tissue from spontaneous abortions among women with syphilis. Using silver stains and immunofluorescence techniques, they identified spirochaetes in abortuses after 9 and 10 weeks of gestation (15). Some questions about early fetal infection remained because placental disruption, rather than actual transmission, could have been responsible for the presence of spirochaetes in the abortuses. However, definitive evidence demonstrating the ability of treponemes to cross the placenta early in pregnancy was recently provided by Nathan et al. (16). They performed amniocenteses between 14 and 19 weeks (average 16.8 weeks) on 11 pregnant women who had untreated syphilis. Using rabbit infectivity testing, they identified living treponemes in the amniotic fluid of four of the 11 women tested. However, this study raised numerous questions that have not yet been answered; for example, how do the treponemes get into the amniotic fluid? Is it by direct passage through the placenta (perhaps permitting fetal infection by ingestion) or via the fetus?

## Fetal involvement

Although it is now clear that treponemes cross the placenta early in gestation, there is little evidence of any adverse effect at this time. It is useful to review the manifestations of fetal involvement and to note that the microscopic appearance of syphilitic lesions is similar whether manifested in the fetus, adult or infant. Lesions are characterized by perivascular infiltration by lymphocytes, plasma cells and histiocytes, with endarteritis and extensive fibrosis (5). These typical lesions reflect an inflammatory response, and have suggested to some researchers an important role for cytokines in the pathophysiology of disease secondary to syphilis (17). Additional work has suggested that the interaction of *T. pallidum* with vascular endothelium may be an important early event in the host immune response, resulting in initiation of an inflammatory cascade. Purified 47-kDa lipoprotein can activate vascular endothelial cells to upregulate expression of intermediaries causing perivascularitis and/or fibrin deposition (18, 19).

A review of the pathology of the lesions associated with congenital syphilis shows a clear similarity between them (Table 1). The pathology suggests multi-organ involvement, with an extensive inflammatory response. The manifestations reflect, in part, the immunological maturity of the fetus — an observation made by Silverstein 40 years ago (25). In general, it is not until the age of 22 weeks that the fetus is capable of consistently mounting an immune response to infection (5, 26). Levels of interleukins, interferons and of tumour necrosis factor are much lower in preterm infants than in those born at term — an important finding given the central role that cytokines may play in the pathophysiology of congenital syphilis. However, other components of the immune system — such as T-cell function — are also far from competent earlier in gestation (27).

Table 1. Pathology of fetal involvement with syphilis

Organ	Characteristics
Placenta (20)	Thickened placenta; villitis with endovascular and perivascular proliferation (it has not been determined whether these cells are of maternal or fetal origin)
Liver (21)	Inflammation in interstitial stroma and perivascular network
Lungs (22)	"Pneumonia alba" is the classic lesion; organ is yellowish white, heavy, firm and grossly enlarged. Connective tissue is increased
Gastrointestinal tract (21)	Mucosal and submucosal inflammation and mononuclear infiltration
Pancreas (21)	Perivascular inflammatory infiltrate
Kidneys (21, 23)	Damage secondary to deposition of immune complexes (similar to glomerulonephritis in adults); perivascular inflammatory infiltrate involving interstitial tissues
Central nervous system (5)	Meningeal involvement with thickening of basilar meninges and endarteritis; neuronal injury dependent upon extent of this blood vessel involvement
Skeletal system (24)	Osteochondritis, periostitis and osteomyelitis may all be present. The basic process of osseous disturbance is the failure to convert cartilage to bone. These findings may reflect non-specific trophic changes, resulting from severe generalized infection, rather than a direct effect of treponemal infection; this possibility is supported by evidence that lesions can heal without specific treatment

Although it is not yet clear why some fetuses are more affected than others and there is limited information to explain the pattern of involvement, recent work provides a better understanding of the sequence of involvement. Hollier et al. (28) studied 24 pregnant women with untreated syphilis at 24–37 weeks of gestation (mean: 30 weeks) with the following battery of tests: amniocentesis (rabbit infectivity testing, polymerase chain reaction for syphilis and darkfield microscopy); funi-puncture (venereal disease research laboratory (VDRL) test, haematocrit, platelet count, liver function tests and syphilis-specific immunoglobulin (Ig) M; and ultrasound (for evaluating placental thickness, hepatic size, gestational age, fetal blood pressure and presence of ascites). Six women had primary, 12 secondary, and six early latent syphilis; their mean VDRL titre was 1:32. The authors confirmed infection in the fetuses of 16 of these women — 14 women had fetuses with detectable *T. pallidum* and two others, who delivered soon after evaluation, had infants with clinical evidence of infection. Among these 16 women, 87.5% (14) had an abnormal ultrasound scan 68.5% (11) had hepatomegaly alone and three had hepatomegaly with ascites) and 94% (15) had abnormal results of liver function testing (gamma-glutamyl transpeptidase). The authors suggested that these findings indicate that abnormal liver function may represent an early manifestation of true infection, preceding liver enlargement. Placental enlargement became more likely as duration of maternal infection increased, followed by haematological abnormalities which also became more likely with longer duration of maternal infection. Antitreponemal IgM was detectable in only three fetuses, two of which had hepatomegaly with ascites — suggesting an association with severity of infection.

However, such work still fails to address the involvement of the central nervous system (CNS), a critical question that has influenced recommendations for treating congenital syphilis. The diagnosis of CNS involvement has been challenging; the interpretation of the results of conventional tests (cerebrospinal fluid (CSF) VDRL, CSF protein/white blood cell count) is problematic in the neonate. Although in 1949 Platou suggested that 60% of infants with congenital syphilis

had CSF involvement (29), it is only recently that conclusive evidence has become available. Michelow et al. (30) evaluated 148 infants born to mothers with syphilis, 64% of whom had not been treated prior to delivery. In addition to conventional studies (e.g. physical examination, long-bone radiograph, CSF VDRL, white cell count and protein), infants were evaluated using rabbit infectivity testing, polymerase chain reaction, and syphilis-specific IgM tests of CSF and serum or blood. Among those infants who had not been exposed to antibiotics ( $n = 76$ ), 22% had a positive result of the rabbit infectivity test on CSF. The evidence suggested that CSF involvement was more likely if maternal syphilis was categorized as secondary or early latent (29%) than with other classifications (11%). In addition, among those infants who were not exposed to antibiotics and who had conventional evidence of congenital syphilis, 41% had treponemes detected in their CSF, providing evidence for the prevalence of CSF involvement among infants with congenital syphilis.

## Maternal treatment

Although there is clear historical evidence that treatment of maternal syphilis with penicillin is effective in preventing congenital syphilis, several questions remain. Health agency recommendations for treatment vary — the Centers for Disease Control and Prevention (CDC) (31) recommends treating early syphilis (primary, secondary or early latent) with a single dose of 2.4 million units of benzathine penicillin G (7.2 million units over three weeks if duration of syphilis is at least a year), as does WHO (32). However, in the United Kingdom, the recommendation is for daily injections of procaine penicillin (0.6–0.9 million units) for 10–14 days (33); various authors have made other recommendations for treatment (34). Unfortunately, there are few data available from randomized clinical trials that directly compare the effectiveness of the various therapeutic regimens. The point was underlined in a recent review addressing the efficacy of penicillin for treating maternal syphilis; 26 studies met the criteria for detailed scrutiny but none met criteria that permitted comparison of treatment regimens and in none were

treatments randomly allocated (35). The authors concluded that although there was no doubt that penicillin was effective in treating maternal syphilis and in preventing congenital syphilis, there was uncertainty about the optimal treatment regimen. A recently published paper described the considerations behind the CDC recommendations; an expert panel concluded that the available evidence did not indicate that any regimen was more effective than 2.4 million units of benzathine penicillin G for treating early syphilis (36).

Recently-published data are available that describe the effectiveness of the regimens recommended by the CDC and WHO. Watson-Jones et al., working in the Mwanza region of the United Republic of Tanzania, studied a cohort of 1688 pregnant women, 133 of whom had high-titre (i.e.  $\geq 1:8$ ) active syphilis, shown in that population to be associated with adverse outcomes of pregnancy (relative risk, 4.4; 95% confidence interval (CI), 2.8–6.9) and with stillbirth (relative risk, 18.1; 95% CI, 5.5–59.6) (37). The women with syphilis were treated with a single dose of benzathine penicillin. There was no increased risk of adverse pregnancy outcome in these women (2.3% had stillbirths and 6.3% had low-birth-weight infants) when compared with seronegative women (2.5% had stillbirths, 9.2% had low-birth-weight infants) (38). This was an important observation, since other work had suggested that pregnant women with syphilis who receive more than two or three doses of benzathine penicillin have better pregnancy outcomes than women who receive only one such dose (39, 40). However, the women who received two or three doses generally presented to prenatal care and received treatment earlier in gestation than women who received only one injection, which could be an important source of bias (39).

Alexander et al. (41) also evaluated the CDC/WHO regimen, in a study on 340 pregnant women with syphilis. They reported that treatment effectiveness was as follows: primary syphilis – 100% (27 out of 27); secondary syphilis – 95% (71 out of 75); early latent syphilis – 98% (100 out of 102); late latent – 100% (136 out of 136). In this study, treatment failure required evidence of congenital syphilis and was based on physical examination, lumbar puncture, long-bone radiographs and results of liver function tests. These data provide reassurance about the effectiveness of the CDC/WHO recommendations. The data from Alexander et al. suggest that improvements in treatment of secondary syphilis would be useful, but also indicate how challenging it would be to demonstrate the greater effectiveness of an alternative regimen. A randomized clinical trial in which half of the subjects are assigned to a group treated with 2.4 million units benzathine penicillin G (assumed effectiveness of 95%) and the other half to treatment with an alternative regimen (assumed effectiveness of 98%), would require the enrolment of over 1300 women with secondary syphilis (assuming 80% power and an alpha error of 0.05).

Other studies have demonstrated that screening pregnant women for syphilis and providing benzathine penicillin treatment is not only effective, but inexpensive and safe. Terris-Prestholt et al. found that on-site antenatal screening in Mwanza and provision of a single dose of benzathine penicillin cost US\$ 1.44 per woman screened, and US\$ 20 per woman treated. The authors demonstrated that screening and treatment for syphilis was at least as cost-effective as prevention of mother-to-child transmission of human immunodeficiency virus (HIV) (42).

In terms of safety, allergy to penicillin poses the greatest risk associated with maternal treatment. Although 5–20% of

patients may consider themselves allergic to penicillin (43), many of the reactions recalled are localized rashes; only 1% of reactions are type-1 hypersensitivity reactions (i.e. generalized itchy rash associated with breathing difficulties) (44). Treatment of maternal syphilis may also be complicated by the Jarisch–Herxheimer reaction, an acute febrile reaction frequently accompanied by headache and myalgia that usually occurs within 24 hours after any therapy for syphilis. This can affect approximately 40% of pregnant women treated for syphilis and is associated with uterine contractions and variable decelerations in fetal heart rate, but usually resolves without incident (36). Nevertheless, women treated for syphilis in early pregnancy should stay well hydrated and rest; acetaminophen may help with uterine cramping, pelvic pain and fever. Women beyond 20 weeks of gestation should be evaluated if they experience fever, decreased fetal movement, or regular contractions within 24 hours of treatment (36).

A critical challenge appears to be clinical management when the fetus has severe manifestations of disease; unfortunately, in this situation, there is no evidence that any approach is distinctly superior (36). It may be that improvements in outcome depend on the provision of treatment early in gestation, before significant fetal involvement has developed. (In the Alexander series, four out of six failed treatments had been conducted at 31 weeks of gestation or later (41).)

The importance of treating maternal syphilis early in gestation was demonstrated by Gust et al. (45). Using surveillance case reports, the authors reviewed the mortality associated with congenital syphilis in the United States. From 1992 to 1998, there were 942 deaths among the 14 627 cases of congenital syphilis reported. In the overwhelming majority of instances (87.4%), mothers were untreated or inadequately treated; few of the mothers (3.8%) whose infants died had received appropriate treatment (i.e. treatment consistent with the CDC guidelines) at least 30 days before delivery. Fifty-two per cent of the deaths occurred among infants at less than 30 weeks of gestation and few severely affected infants were delivered at term. Assuming that maternal treatment must be provided at least 28 days prior to delivery, the authors concluded that, to reduce perinatal mortality by 70%, all pregnant women with syphilis must be treated before 21 weeks of gestation.

Although it is clear that penicillin G is the drug of choice for treating maternal syphilis, there is less agreement about appropriate alternative antibiotics. The application of the CDC guidelines, which do not offer any alternative to penicillin and advise desensitization, may be problematic in many settings where such care is not available. Although erythromycin has been recommended by some agencies (32), its effectiveness is questionable (46). This is consistent with evidence that the transplacental passage of erythromycin is limited (47) and although there are no clinical outcome data evaluating the use of azithromycin during pregnancy, this antibiotic also has limited transplacental passage. Ceftriaxone has been suggested as an alternative treatment for syphilis in non-pregnant adults who are allergic to penicillin, and pharmacokinetic studies among pregnant women have indicated that serum levels of ceftriaxone can be treponemicidal; the levels in fetal serum and amniotic fluid may also be treponemicidal (36). However, the optimal dose and duration of this treatment have not been defined; some specialists recommend 1 g daily either intramuscularly or intravenously for 8–10 days as treatment for early syphilis (31). Unfortunately there are few data describing the effectiveness of such treatment among pregnant women.

Lastly, there is insufficient information available to evaluate the effectiveness of treatments for pregnant women who are



co-infected with syphilis and HIV. Some authors have questioned the effectiveness of standard therapeutic regimens for syphilis among HIV-infected populations (48) and there have been anecdotal reports of treatment failure among co-infected pregnant women (41). However, no studies so far have demonstrated the superiority of alternative approaches for treatment of syphilis among patients with HIV co-infection (49); both the CDC and WHO (31, 32, 36) advise that syphilis treatment need not be changed because of HIV co-infection. Clearly, this is an issue that needs additional evaluation.

## Conclusion

There is much to be learned about pathophysiology of syphilis during pregnancy. A better understanding of the processes involved may help to improve clinical management. However, current knowledge suggests that, regardless of the penicillin regimen used, efforts to prevent severe fetal involvement and death must focus on treating pregnant women with syphilis sufficiently early in pregnancy. ■

**Conflicts of interest:** none declared.

## Résumé

### Syphilis maternelle : physiopathologie et traitement

Malgré l'intérêt que l'on porte depuis longtemps à la syphilis et à ses effets sur l'issue de la grossesse, de nombreuses questions fondamentales concernant la physiopathologie et le traitement de la syphilis pendant la grossesse restent sans réponse. Des travaux récents ont cependant apporté quelques éclaircissements, avec par exemple le décryptage complet du génome du spirochète de la syphilis, une description plus précise de l'infection chez le fœtus et le nouveau-né au moyen de tests d'infectiosité sur le lapin, et l'établissement de la distribution par âge gestationnel

des morts fœtales secondaires à la syphilis. Il ressort de tous ces travaux que l'atteinte syphilitique chez le fœtus progresse de façon assez prévisible et, même s'il existe des désaccords quant au meilleur schéma thérapeutique anténatal, les programmes visant à empêcher les morts fœtales doivent recommander à l'intention des femmes enceintes séropositives pour la syphilis un traitement administré suffisamment tôt pendant la grossesse, en tout état de cause avant le troisième trimestre.

## Resumen

### Sífilis materna: fisiopatología y tratamiento

Pese al interés médico que desde hace tiempo suscita la sífilis y sus efectos en los resultados del embarazo, siguen sin resolverse muchos interrogantes básicos sobre la fisiopatología y el tratamiento de dicha enfermedad durante la gestación. Sin embargo, los conocimientos en este terreno se han visto impulsados por diversos informes científicos recientes, como los relacionados con la secuenciación completa del genoma de la espiroqueta de la sífilis, la más precisa descripción de la infección en el feto y el recién nacido mediante el uso de pruebas

de infectividad en conejos, y la distribución por edad gestacional de los casos de muerte fetal por sífilis. Parece que la sífilis evoluciona en el feto de forma bastante predecible, y aunque hay discrepancias en cuanto a la pauta óptima de tratamiento prenatal, las actividades programáticas destinadas a prevenir la muerte fetal deben ofrecer a las mujeres embarazadas seropositivas un tratamiento recomendado para las primeras fases del embarazo, sin duda antes del tercer trimestre.

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