Infection in the foetus and neonate

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Abstract
Neonates, particularly when premature, are relatively immunocompromised and are therefore prone to more infections, more severe disease, and infection with unusual organisms. Almost all foetal and many neonatal infections are caused by organisms acquired from the mother. Transmission may be transplacental *in utero*, perinatal during the birth process or postnatal. Neonates can also acquire infections horizontally. This review provides an overview of the epidemiology, clinical features, diagnosis, prevention and treatment of infections in the foetus and neonate with updates on new developments including the identification of risk and management of maternal hepatitis B and HIV infections, the role of molecular diagnosis, new vaccines under development and the role of emerging infections.

Keywords CMV; foetal; group B streptococci; hepatitis B; HIV; *in utero*; infection; neonatal; sepsis

What's new?

- PCR is increasingly being used in the diagnosis and management of congenital and perinatally acquired infections
- A CMV vaccine is under development and initial results from phase 2 trials are promising
- The likelihood of perinatal transmission of HIV and hepatitis B infection can be dramatically reduced through preventive measures. All pregnant women should be routinely screened for HIV and hepatitis B and provided with a risk-based management plan

Neonates, particularly when premature, are relatively immunocompromised and are therefore prone to more infections, more severe disease, and infection with unusual organisms. Almost all foetal and many neonatal infections are caused by organisms acquired from the mother; that is, they are vertically transmitted. Transmission may be transplacental *in utero*, perinatal during the birth process or postnatal (including transmission via breastfeeding). Neonates also acquire infections horizontally, including nosocomially. Several infections, including HIV, may be transmitted by more than one of these routes, but, because diagnosis and management differ between routes, it is convenient to consider transplacental infection separately from perinatal and postnatal infection.

Transplacental infections of the foetus

Most infections in women during pregnancy remain localized (e.g. to the respiratory or gastrointestinal tract) and do not affect the developing foetus. However, if bloodstream invasion occurs, the foetus may be infected transplacentally. The most well-recognized agents are rubella, cytomegalovirus (CMV), *Toxoplasma gondii* and *Treponema pallidum*. It is important to remember that transmission of subclinical maternal infection may be as damaging to the foetus as transmission of overt infection. Infected infants may be asymptomatic at birth, manifesting symptoms only much later in life.

Clinical features (Table 1)

Most maternal bloodstream infections are cleared by the mother's immune system. Placentitis can occur without infection of the foetus (e.g. tuberculosis — TB, malaria, syphilis, CMV, rubella) and may cause foetal growth retardation. Even in the absence of foetal and placental infection, the foetus can be affected indirectly by fever, anoxia, circulating toxins and metabolic derangement, which can result in abortion, stillbirth or premature delivery (e.g. malaria, trypanosomiasis). When an embryo or foetus is infected, there is a range of possible outcomes.

Embryonic death and resorption — the incidence of early pregnancy loss has been estimated at one-third. It is not known what proportion of these losses results from infection.

Abortion, stillbirth and early neonatal death — early death may result from overwhelming foetal infection or major interference with organogenesis. A wide variety of organisms can cause this, notably erythrovirus (formerly parvovirus) B19, *Listeria*, herpes simplex virus (HSV), hepatitis E and enteroviruses, particularly Coxsackie viruses.

Developmental anomalies and teratogenesis — CMV, rubella virus and varicella-zoster virus (VZV) cause developmental anomalies in the foetus that appear to result at least partly from the ability of these viruses to cause cell death, changes in cell growth and chromosomal damage. In contrast, inflammation and tissue destruction rather than teratogenesis appear to be responsible for the structural abnormalities caused by congenital syphilis, transplacental HSV infection and toxoplasmosis. VZV infection carries a 3–5% risk of embryopathy, including scarring (Figure 1).

Intrauterine growth restriction may be a marked feature of foetal and placental infection, typically affecting both head and general growth. (More common causes of foetal growth failure, such

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Important examples of clinical features and management in transplacental infections

Organism/disease	Investigation and management	Clinical features
Rubella	*In pregnancy* • Serology (IgG and IgM) • Counsel parents about possible termination before 18 weeks' gestation *In newborn* • Viral culture, serology (IgM), reverse transcription PCR analysis, audiology, ophthalmology, long-bone radiography *Prevention* • By vaccination in susceptible groups • Vaccination should not be given in pregnancy — attenuated virus has been found in aborted foetuses	• Risk of foetal infection decreases — 90% in first trimester, 50% in second, 37% in third • If infected, risk of significant defects decreases — 80% < 12 weeks' gestation, 35% 13—16 weeks, 1% > 17 weeks • Clinical manifestations are variable — two-thirds of infants are asymptomatic at birth but may develop immunological problems, blood dyscrasias and neurological problems • Developmental anomalies — intrauterine growth restriction, congenital heart disease, sensorineural deafness, ocular, neurological and genitourinary defects • Late-onset manifestations — encephalitis, lymphadenopathy, hepatosplenomegaly, interstitial pneumonitis, thrombocytopenia and osteitis
Cytomegalovirus	*In pregnancy* • Seldom diagnosed (asymptomatic) • If seroconversion found, invasive foetal diagnosis and termination not indicated *In newborn* • Throat and urine cultures (must be within first 21 days to exclude perinatal/postnatal acquisition), serology (IgM) and PCR analysis, audiology and ophthalmology, CT or MRI of head • Ganciclovir for symptomatic infection (under evaluation) *Prevention* • None available currently — vaccine under development	• The most common cause of congenital infection in high-income countries (incidence 0.2—2.2%) • Transmission rate 20—50%, 90% asymptomatic • Transmission and sequelae can also occur during reactivation of maternal cytomegalovirus infection, but less commonly • Most survivors suffer long-term sequelae, including microcephaly and intracerebral calcification, deafness and neurodevelopmental problems • Of asymptomatic infants, 5—15% develop long-term sequelae, principally deafness
Toxoplasma gondii	*In pregnancy* • Serology and PCR analysis targeting the *B1* gene of *Toxoplasma gondii* in amniotic fluid, foetal cord and maternal blood • Spiramycin until definite foetal infection confirmed, then alternate with pyrimethamine, sulfadiazine and folinic acid *In newborn* • IgM, enzyme-linked immunofiltration assay, PCR analysis of blood and (if neurological symptoms) cerebrospinal fluid, ophthalmology, skull radiography or CT • Spiramycin alternating in 3—4-week cycles with pyrimethamine, sulfadiazine and folinic acid for 12 months *Prevention* • Pregnant women should avoid eating under-cooked meat and unwashed vegetables, and exposure to cat faeces	• Transmission occurs in primary maternal infection — often asymptomatic • Occasionally, an infectious mononucleosis-like illness with cervical lymphadenopathy is present • Transmission after reactivated infection occurs only in severely immunocompromised individuals • Incidence of foetal infection — 25% in first trimester, 65% in third • 10% of cases are symptomatic at birth • Classic triad of chorioretinitis, intracranial calcification and hydrocephalus is rare; also jaundice, hepatosplenomegaly, lymphadenopathy, purpura, anaemia and hypothermia • Initially asymptomatic children may develop late-onset, sight-threatening chorioretinitis

CT, computerized tomography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

Table 1