Review Prenatal diagnosis and management of fetal infections

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Key content:

- The risks of transplacental transmission and fetal damage are pathogen- and gestation-specific.
- Amniocentesis is the mainstay of diagnosis of fetal infection.
- Ultrasound surveillance is the primary tool for the detection of an affected fetus.
- Therapeutic options are restricted to intrauterine blood transfusion in parvovirus infection and maternal antibiotic therapy in toxoplasmosis infection.

Learning objectives:

- To gain an overview of prenatal diagnosis of the commonest congenital infections.
- To appreciate that optimal care involves a multidisciplinary approach.

Ethical issues:

- Detection of virus alone is not synonymous with fetal damage; a negative result does not completely exclude the possibility of fetal infection.
- Presence or absence of sonographic markers of fetal infection may not accurately predict long-term outcome.

Keywords cytomegalovirus / human parvovirus B19 / *toxoplasma gondii* / rubella / varicella-zoster

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Introduction

This is a review of the current approach to the prenatal diagnosis and management of the common and most clinically relevant congenital infections: cytomegalovirus (CMV), human parvovirus B19, *toxoplasma gondii*, rubella and varicella-zoster virus. Testing is usually carried out as a result of maternal exposure to an infectious pathogen, finding sonographic markers of fetal infection during a routine ultrasound scan or, more rarely, symptomatic maternal infection. There is a wide range of laboratory tests available; however, interpretation of the results can be complex. An accurate assessment of the risk of transplacental transmission following maternal infection must take into consideration the clinical presentation, the timing of the test in relation to exposure to the infectious agent and a detailed knowledge of the limitations of each test. In cases of suspected fetal infection, clinicians need to be familiar with the risk and spectrum of associated fetal damage, the benefits and limitations of prenatal diagnosis and the effectiveness of potential treatment in order to determine an appropriate management plan. Care in such cases is optimally provided by a multidisciplinary team involving obstetricians, virologists, neonatologists and fetal medicine specialists.

Cytomegalovirus

Congenital CMV infection is one of the most common congenital infections, with a reported incidence of 0.5–2%.[1] It is one of the leading causes of childhood deafness.[2] Primary infection is usually asymptomatic or a mild illness characterised by fever, lethargy and malaise. Approximately 50–70% of women in Europe and the USA have evidence of previous CMV infection, as determined by the presence of immunoglobulin G (IgG) serum antibodies.[3]

Congenital CMV is mainly related to primary maternal infection, where the risk of vertical transmission is 40% in the first and second trimesters; fetal damage occurs in about 10% of these cases. Transmission occurs in about 80% of cases in the third trimester but it is usually asymptomatic after 27 weeks of gestation.[4] In recurrent infection (reactivation of an existing infection or reinfection with a different strain), the transmission rate is in the region of 1–2.2%.[5,6]

Sequelae of fetal infection

The spectrum of problems associated with neonatal congenital CMV comprises the following: ocular defects, including chorioretinitis, microphthalmos, cataracts and optic atrophy; sensorineural deafness; hepatosplenomegaly; jaundice; thrombocytopenic purpura; pneumonitis; fetal growth restriction; microcephaly; and neurodevelopmental consequences such as cerebral palsy, learning disability and epilepsy.

The overall risk of damage in fetuses infected as a result of primary maternal infection is about 25%. Approximately 10% of infected fetuses are clinically symptomatic at birth and a further 10–15% of those asymptomatic at birth will develop some long-term sequelae, primarily sensorineural hearing loss.[7] The expression of disease tends to be worse the earlier the fetus is affected. A recent study[8] suggested that children with congenital CMV infection following first trimester maternal infection are more likely to have central nervous system sequelae, especially sensorineural hearing loss, than those affected later in gestation.

The presence of maternal antibody before conception appears to provide some protection against damaging congenital CMV in the newborn. In a study[6] that included 64 infants infected as a result of recurrent maternal infection, one or more sequelae were seen in only 8% and these were of a less severe nature than in those infants affected as a result of primary maternal infection.

Diagnosis of maternal infection

Maternal diagnosis is traditionally based on serology testing for CMV-specific immunoglobulin M (IgM) and IgG. It is most helpful if paired samples are available, particularly if the woman's serostatus can be confirmed prior to conception or at the time of booking. Results must be interpreted in conjunction with an accurate record of maternal history and consultation with a virologist. A summary of the most commonly used tests is shown in **Box 1**.

Diagnosis of fetal infection

Since infection in immunologically competent adults is often asymptomatic, testing for CMV during pregnancy is usually precipitated by the discovery of a fetal marker during sonographic examination. If CMV infection of the fetus is suspected, the maternal infection status is usually established in the first instance. Once primary infection or reactivation of maternal CMV is confirmed, prenatal diagnosis can be offered to determine the risk of fetal infection.

Fetal diagnosis is based on the detection of CMV in amniotic fluid. There are several available methods for the detection of virus but the most commonly used are described in **Box 2**.

Amniocentesis should be delayed for a minimum of 6 weeks after maternal seropositivity is confirmed to allow accumulation of CMV to detectable levels in amniotic fluid. Since fetal diuresis is not established until approximately 18–20 weeks of gestation, negative results from amniocentesis

Box 1
Commonly used serological tests for maternal CMV infection

CMV IgM enzyme immunoassay (EIA)

This may be positive in primary infection and in reinfection or reactivation (although the strength of reactivity in the test is usually lower). It is usually present within 2 weeks and it persists for 3–4 months after primary infection; however, it may persist at low levels for many years. The false positive rate of the IgM test is about 2% and, hence, this result alone should not be used to make a definitive diagnosis.

CMV IgG EIA

This is usually present within 2–3 weeks of primary infection and is lifelong. Primary infection is suggested by seroconversion from IgG negative to IgG positive. Whilst IgG levels may be boosted by reinfection/reactivation, only a four-fold rise would be considered good evidence.

CMV IgG avidity

This test is based on the observation that antibodies bind less avidly to antigens during the early stages than in the chronic stages of infection. Avidity <30% indicates infection within the preceding 3 months, whilst avidity >40% indicates infection more than 6 months previously. This test may help to distinguish between primary infection and reactivation/reinfection where there is a low or equivocal IgM response and a positive IgG and no previous sample to look at for seroconversion.

Box 2
Commonly used tests for the detection of CMV in amniotic fluid

CMV DNA by polymerase chain reaction (PCR)

A highly sensitive technique for detection of viral genomes. It has correspondingly high positive and negative predictive values for fetal infection.

CMV detection of immediate–early antigen fluorescent foci (DEAFF)

An immunofluorescence test designed to detect CMV after limited growth in cell culture. It is not very sensitive but it has a high specificity for transplacental infection.

carried out before this time should be treated with caution and a repeat procedure and laboratory diagnosis considered.[9] Fetal blood sampling can also be used for the detection of CMV or CMV-specific IgM but it appears to have lower sensitivity in the detection of fetal infection.[10,11]

Management of the infected fetus

If CMV is detected in amniotic fluid, transmission to the fetus is assumed. There are no established prognostic indicators; the role of CMV glycoprotein B genotype and CMV DNA load in amniotic fluid remains uncertain, as studies show conflicting results.[12,13]

Patients should be counselled about the risk of fetal damage in relation to the gestational age at which infection occurred and a detailed ultrasound examination of the fetus should be carried out. The sonographic features include microcephaly, cerebral atrophy, ventriculomegaly, intracerebral calcification, periventricular cyst formation, leukomalacia, fetal growth restriction, echogenic bowel and hepatic calcifications. Further fetal surveillance using serial ultrasound scanning should be arranged, as some of these features may manifest later in pregnancy. It is important to note that, whilst the absence of sonographic findings is reassuring, it cannot exclude the presence of neurological abnormalities at birth. A recent study[14] of 50 pregnancies with confirmed vertical transmission of CMV reported postnatal neurological abnormalities in up to 19% of cases where there were no prenatal sonographic defects. Furthermore, several manifestations of congenital CMV are not detectable by prenatal ultrasound.

There are no licensed antiviral agents and none proven to be effective for use in pregnancy; however, a recent nonrandomised study[15] suggested that treatment of pregnant women with CMV-specific hyperimmune globulin may be effective in the treatment and prevention of congenital CMV infection.

Human parvovirus B19

Human parvovirus B19 has a predilection for rapidly dividing cells, mainly the erythroid cell precursors, thereby interrupting red cell production. Adult infections are frequently subclinical but may present as erythema infectiosum (fifth disease), which consists of transient fever, malaise and arthralgia. In children it is a mild illness characterised by fever and a typical facial rash ('slapped cheek'). In contrast, congenital B19 infection can cause profound fetal haemolytic anaemia, leading to cardiac failure, hydrops and intrauterine death.

Approximately 60% of adults have serological evidence of prior infection[16] and the presence of human parvovirus IgG appears to confer lasting immunity. The primary infection rate in pregnant women, as measured by the frequency of seroconversion, is about 1.1% per year. Transplacental transmission occurs in 15% of cases before 15 weeks of gestation and 25% between 15–20 weeks: this rises to 70% towards term.[17]

Testing for parvovirus B19 during pregnancy is most commonly the result of a history of recent maternal exposure or the finding of fetal hydrops during sonographic examination. The incubation period is 5–7 days following exposure and women are infectious for 3–10 days post-exposure or until the rash appears. Symptoms peak around day 9 and the rash may appear up to 18 days after exposure.

Sequelae of fetal infection

These include miscarriage, anaemia, nonimmune hydrops and intrauterine death. There is no

evidence of teratogenesis. There is a 9% excess fetal loss rate before 20 weeks of gestation. The risk of hydrops is low (3%) but it has a fatality rate of 50%. It usually occurs about 5 weeks after maternal infection (range 2–12 weeks) and spontaneous resolution may occur 1–7 weeks after diagnosis. The risk of intrauterine death in parvovirus B19 IgM-positive mothers is <10% and most deaths occur 4–6 weeks following the onset of maternal symptoms but they can occur up to 3 months later.[17] There is no reliable epidemiological evidence of adverse long-term effects in babies who were hydropic and mothers should be reassured that, following resolution, no long-term problems are expected.

Diagnosis of maternal infection

Maternal infection is diagnosed mainly by serological means, but detection of the parvovirus genome by PCR may be helpful in some cases (see **Box 3**). Once again, it is useful if paired samples are available from prior to and after the infection. Results must be interpreted in conjunction with an accurate maternal history and consultation with a virologist. **Box 3** contains a summary of the most commonly used tests.

Diagnosis of fetal infection

Fetal infection can be diagnosed by detection of human parvovirus B19 IgM or viral DNA as described above, using amniotic fluid or fetal blood. In the absence of signs of fetal anaemia, however, the value of testing is of uncertain clinical importance.

Once maternal infection has been confirmed, monitoring of the fetus using serial ultrasound examinations should be undertaken. These should start 4 weeks after the onset of illness or date of seroconversion and then be done at 1- to 2-weekly intervals for up to 12 weeks. The aim of monitoring is to identify signs of potential fetal anaemia, which include ascites and hydrops. Recently, measurement of fetal middle cerebral artery peak systolic velocity (MCA-PSV) was shown to be useful in identifying cases of moderate or severe anaemia.[18–20] In a study[18] of 111 fetuses at risk of anaemia, an increased MCA-PSV had 100% sensitivity for moderate and severe anaemia, with a false positive rate of 12%. In well-trained operators, the intra- and interobserver variability of this measurement is small.[21]

Management of the infected fetus

Fetal hydrops secondary to parvovirus B19 infection can resolve spontaneously in up to one-third of cases; however, there do not appear to be any clinical or ultrasound criteria that will differentiate these cases from those that will progress to intrauterine death.[22,23]

Fetal blood sampling may be indicated when the MCA-PSV is >1.5 multiples of the median or where there is ascites or hydrops. Intrauterine blood transfusion may be indicated if the fetal haemoglobin is below the gestational age mean, as there is evidence to suggest that this is associated with a reduction in the risk of fetal death (OR 0.14; 95% CI 0.02–0.96).[24] Fetal transfusion carries a number of potential benefits for the alleviation of B19-induced nonimmune hydrops. Firstly, mature erythrocytes are not susceptible to parvovirus infection and, therefore, the oxygen-carrying capacity of the fetal circulation can be restored and stabilised to improve the fetal heart function. Secondly, the half-life of formed erythrocytes is approximately 120 days, which should provide sufficient cover for the intrinsic fetal immune system to develop or for maternal antibodies to cross the placenta and assist in the resolution of viral infection. Finally, some passive transfer of antiparvovirus antibody can be expected along with the red cells from a seropositive donor, which could further aid recovery of the fetus.

Fetal blood sampling and transfusion can be carried out from 18 weeks but, ideally, are performed after 22 weeks. Cordocentesis is associated with a 1% procedure-related loss rate.[25,26] Possible transfusion sites include the placental insertion of the umbilical cord, the cardiac ventricles or the straight portion of the intrahepatic umbilical vein. At later gestations the risks of intrauterine therapy should be balanced against the risks of premature delivery and extrauterine transfusion.

Resolution of hydrops should occur following transfusion, although the time taken for this varies. Data from the Society of Perinatal Obstetricians[27] showed that, of 137 cases of hydrops related to

Box 3
Tests commonly used for the detection of parvovirus infection

Parvovirus B19 IgM EIA

Detected 10 days after infection but may be extremely short lived (<4 weeks, compared with the usual 12 weeks in other infections). If rash is present, IgM should be detectable because the rash is immune-mediated. Failure to detect parvovirus IgM probably excludes infection in the previous 4 weeks but not if the sample is taken more than 4 weeks after the rash.

Parvovirus B19 IgG EIA

Usually detectable 12–14 days after infection. It provides lifelong immunity. Primary infection is confirmed by seroconversion from IgG negative to IgG positive from paired samples, comparing a blood sample from before with a sample taken after illness.

Parvovirus DNA by PCR

This is particularly useful when clinical suspicion is high yet there is no history of rash, or where IgM is negative and IgG seroconversion is not demonstrable (for example, when no previous sample is available).

parvovirus B19 infection, 94% had resolved within 6 weeks of intrauterine blood transfusion.

Toxoplasmosis

Toxoplasma gondii is a parasitic infection that can be acquired by ingestion of toxoplasma tissue cysts in undercooked or cured meat such as Parma ham, or from infectious oocysts which are excreted by cats or which are present in contaminated soil/water.

In Europe, improvements in hygiene have led to a general fall in the incidence of infection during recent years. The prevalence of toxoplasma antibodies in women of childbearing age varies with country of residence and age of group studied but ranges from 10–96%.[28] In the UK, 90% of women of childbearing age are susceptible to toxoplasma infection and the incidence of maternal infection is approximately 2 per 1000 pregnancies.[29] The cumulative incidence of congenital toxoplasmosis in England and Wales was estimated to be 3.4 per 100 000 live births in the years 2002–04. Primary infection is often asymptomatic (60–70%) but some women suffer malaise, fever or lymphadenopathy.

Fetal transmission risk increases with gestational age at seroconversion (from <1% before 4 weeks, between 4–15% at 13 weeks, to >60% at 36 weeks).[28,30] Conversely, the risk of congenital abnormality is inversely related to the gestation at maternal infection, such that the severity is greatest when infection occurs during the first trimester.[31] Thus, the combined risk of having an affected fetus, given proven maternal primary infection, is highest in the middle of pregnancy, at 13–28 weeks.

Sequelae of congenital infection

Toxoplasmosis mainly affects the central nervous system and eyes and can cause microcephaly, ventriculomegaly, hydrocephalus and chorioretinitis. The child may experience the following: learning difficulty; convulsions and spasticity; and chorioretinitis and blindness. Any organ can be affected, however, and other consequences of congenital toxoplasmosis include hepatosplenomegaly, anaemia, rash, pneumonitis and jaundice.

Diagnosis of maternal infection

This is now documented as a National Standard Method (Health Protection Agency, 2006).[32] The approach is mainly serological and based on testing for toxoplasma-specific IgG and IgM. Again, analysis of paired samples from before and after infection is very useful. A combination of tests will help determine the timing of infection; the interpretation of these should be made in conjunction with a virologist and with an accurate record of maternal history. **Box 4** contains a summary of the most commonly used tests.

Diagnosis of fetal infection

Cases of confirmed primary maternal infection should be referred to a fetal medicine unit. Fetal diagnosis is based on the detection of *toxoplasma gondii* DNA in amniotic fluid. Amniocentesis should be considered from 16 weeks of gestation, as a positive result would lead to a change from treatment with spiramycin to a pyrimethamine/sulfadiazine regimen. It must, however, be appreciated that, since fetal diuresis is not fully established until 18–20 weeks of gestation and accumulation of toxoplasma to detectable levels may not occur for up to 6 weeks after maternal seroconversion, a negative result prior to this may necessitate a repeat procedure. Cordocentesis to detect fetal immunoglobulin M (IgM) has been used but has significantly lower sensitivity for the detection of fetal infection.[33,34]

Management of the infected fetus

Studies[35] report that spiramycin administered to the mother reduces the risk of fetal infection by 60–70%; however, there is no good evidence that it reduces the severity of disease.[36] Spiramycin therapy does not appear to have any maternal or fetal toxicity. In cases, therefore, where primary maternal infection is confirmed before 16 weeks of gestation, it is sensible to begin treatment empirically rather than delay starting until after amniocentesis can be undertaken, as the longer the interval between maternal seroconversion and the start of treatment, the greater the likelihood of fetal transmission.[37] In cases where amniocentesis is not possible, spiramycin should be started and continued throughout pregnancy with the aim of reducing transmission to the fetus.

Box 4
Commonly used serological tests for toxoplasmosis

Toxoplasma IgM EIA/IgM immunosorbent agglutination assay (ISAGA)

IgM usually appears within 2 weeks of exposure and it can persist for up to 18 months but the length of time that IgM is detectable varies between individuals and with the assay used. IgM measured using EIA can be detectable for 3–6 months; when measured using ISAGA it is detectable for 12–15 months. The false positive rate is approximately 2% and, therefore, positive tests on a sample should be repeated.

Toxoplasma IgG EIA/ISAGA

IgG usually appears approximately 2 weeks after exposure and is lifelong. Measurement of IgG reactivity on sequential samples may be informative. IgG measured using EIA/latex is moderately sensitive and specific and by dye test very sensitive and specific.

Toxoplasma IgG avidity

This uses the same principles as CMV avidity testing. Avidity <30% indicates infection within the preceding 3 months, whilst >40% indicates infection >6 months previously.

Since the negative predictive value of PCR is not 100%, monthly ultrasound follow-up should be initiated even in cases of negative amniocentesis. In cases where the amniotic fluid is positive for toxoplasma DNA, transmission to the fetus is assumed. The risk of an affected fetus should be assessed in conjunction with timing of maternal infection, although it should be seen as an evolving risk that can only be influenced by spiramycin administration. In cases of confirmed fetal infection, the options include maternal drug therapy with a pyrimethamine/sulfadiazine regimen **(Box 5)** throughout pregnancy, with ultrasound surveillance for evidence of fetal damage, or termination of pregnancy.

Ultrasound features described include ventriculomegaly, hydrocephalus, microcephaly, intracerebral calcification, cataract formation and ascites. Magnetic resonance imaging (MRI) of the fetal brain when the ultrasound is inconclusive or incomplete, or even to rule out brain lesions definitively in the presence of a normal ultrasound, is advocated by some authors.[38,39]

The prediction of outcome in fetal infection is controversial. Daffos *et al.*[40] reported that the best predictor was gestational age at seroconversion, whereas Berrebi *et al.*[41] concluded that, in cases of first and second trimester infection where treatment was instigated, if there was no evidence of hydrocephalus on antenatal scans the outcome was normal in children followed for up to 71 months of life. The presence of intracranial calcifications was not predictive of poor outcome. A further study by the same author[42] demonstrated that in 36 cases of congenital toxoplasmosis, where primary infection occurred in the first trimester and where ultrasound findings during pregnancy were normal, 78% had subclinical toxoplasmosis and 19% suffered chorioretinitis without major vision loss. All children had normal intellectual development. One child (3%) developed severe congenital toxoplasmosis. Whilst the risk to the fetus is low in the absence of ultrasound abnormalities, parents should, therefore, be counselled that there remains a small risk of symptomatic congenital toxoplasmosis.

Rubella

In the UK, the rubella virus has become less of a problem since the introduction of routine vaccination. Following the adverse publicity that falsely linked the measles/mumps/rubella (MMR) vaccine to the development of autism, however, coverage has fallen and some areas have seen a rise in cases of rubella. Infection in pregnancy is rare but the proportion of women of childbearing age thought to be susceptible to the rubella virus is in the region of 1–2%.[17]

Box 5
Drug regimen for confirmed maternal/fetal toxoplasmosis infection

Confirmed maternal infection

spiramycin 1 g, 3 times daily

Confirmed fetal infection

pyrimethamine[a] 50 mg once daily

sulfadiazine 1 g, 3 times daily

folinic acid 50 mg weekly

This regimen is alternated weekly with the spiramycin regimen.

[a]Weekly full blood counts are necessary in mothers and babies taking pyrimethamine. The drug is a folate antagonist and reactions are fairly common. This should be communicated to the consultant obstetrician or neonatologist responsible for antenatal or postnatal care, respectively.

The incubation period is 14–21 days and women are infectious from 7 days before until 7 days after the onset of the rash. Maternal rubella infection is generally asymptomatic or a mild illness of malaise, headache, coryza and lymphadenopathy, followed by a diffuse, fine maculopapular rash. In contrast, the effects on the fetus can be devastating if infected in the first trimester.

Vertical transmission occurs during maternal viraemia; the risk of fetal infection is 90% before 12 weeks of gestation, about 55% at 12–16 weeks and it declines to 45% after 16 weeks. The risk of congenital defects in infected fetuses is 90% before 12 weeks, 20% between 12–16 weeks and, thereafter, deafness is a risk up until 20 weeks.[17] Reinfection can occur and is more likely after prolonged or intense exposure and with vaccine-induced, rather than natural, immunity. It is usually subclinical, however, and the risk to the fetus is thought to be $<5\%$.[43]

Sequelae of fetal infection

The congenital rubella syndrome involves a wide spectrum of clinical features. In order of decreasing frequency, manifestations include hearing loss, learning disability, cardiac malformations and ocular defects. Multiple defects and those affecting the central nervous system, eye and heart appear only to occur when transmission takes place before 16 weeks. Other consequences include fetal growth restriction, hepatosplenomegaly, jaundice, thrombocytopenic purpura, anaemia and rash. Many infants with the congenital rubella syndrome experience late manifestations, including endocrinopathies, late onset deafness, ocular defects and neurodevelopmental problems.

Diagnosis of maternal infection

Diagnosis is serological but accurate interpretation of results is crucially dependent on appropriate timing of testing in relation to the onset of the rash. The tests commonly used are described in **Box 6**.

Diagnosis of fetal infection

The need for prenatal diagnosis will be determined by the gestation at which the infection is likely to have occurred. Given the high risk of congenital

Box 6
Commonly used serological tests for rubella

Rubella IgM EIA

IgM testing can be problematic and use should be restricted to those with a history of rash or contact with someone from an endemic area. Different assays have different sensitivities for picking up IgM and, therefore, the test must be repeated if negative and taken within 7 days of appearance of the rash. There is a false positive rate associated with IgM assays and the predictive value of a positive test has declined as a result of the low prevalence of the disease. The diagnosis of acute rubella infection from rubella-specific IgM must be made with caution and with reference to history of rash, exposure, history of vaccination and previous rubella testing.

Rubella IgG EIA

In the UK, women are screened for the presence of rubella IgG antibodies at the beginning of pregnancy. Those with a level <10 iu/ml are considered susceptible to rubella infection. IgG is usually present 1 week after the onset of rash but may be detected earlier using different assays.

Rubella IgG avidity

This may help distinguish between recent and distant infection. As with the toxoplasma and CMV antibody assays, the principle is that the presence of high avidity antibodies indicates an infection >6 months ago, whereas low avidity antibodies are found in recent infections up to 3 months previously.

infection and severe malformation in the first 12 weeks, it would be reasonable to consider termination of pregnancy. After 16 weeks of gestation, the risks to the fetus are negligible and the value of prenatal testing is questionable. Prenatal diagnosis is probably best reserved for infections occurring between 12–16 weeks, when there is a 55% risk of transmission and a 20% risk of congenital rubella syndrome.

There is no 'gold standard' for prenatal diagnosis of rubella infection but most commonly reverse transcriptase PCR (RT-PCR) is used for the detection of viral nucleic acid in amniotic fluid. Fetal blood can also be tested for RNA or rubella-specific IgM. Some studies have shown high sensitivity and specificity for viral nucleic acid in amniotic fluid but others have demonstrated the presence of RNA in fetal blood but not in amniotic fluid in the same women. These reports[44,45] also show improved sensitivities where testing was delayed for more than 6 weeks after maternal infection. For these reasons, a negative result may warrant further amniocentesis or fetal blood sampling at a later gestation. The fetus should also be monitored with serial monthly ultrasound scans.

Management of the infected fetus

If invasive testing is positive, transmission to the fetus is assumed. Risk of damage to the fetus from infection is related to gestational age as previously discussed. Options include termination of pregnancy or ultrasound surveillance to identify features of congenital rubella syndrome. Specialist fetal echocardiography should be arranged in addition to fortnightly scans to assess fetal growth. Many features of congenital rubella syndrome are not detectable by ultrasound.

Varicella

Varicella-zoster virus is endemic in the UK and >90% of the antenatal population are seropositive for varicella-zoster virus IgG. For this reason, primary infection is uncommon in pregnancy and is estimated to occur in 3 per 1000 pregnancies.[17]

Primary infection is characterised by fever, malaise and a distinctive pruritic maculopapular rash that becomes vesicular and then crusts before it heals over. The incubation period is 10–21 days and patients are infectious from 48 hours prior to the onset of the rash until the vesicles crust over. Although it is a mild illness in childhood, during pregnancy it can cause serious maternal morbidity and death in a minority. Fetal varicella syndrome does not occur at the time of initial fetal infection but is the result of herpes zoster reactivation *in utero* and appears to happen only when infection occurs before 20 weeks of gestation. In a prospective study[46] of 1373 women who had primary varicella during the first 36 weeks of pregnancy, the risk of fetal varicella syndrome was 0.4% prior to 13 weeks of gestation and 2% between 13–20 weeks. Whilst there does not appear to be any risk to the fetus when maternal infection occurs between 20–36 weeks of gestation, *in utero* infection may present as shingles in the first few years of life. After 36 weeks, or when delivery occurs within 4 weeks of maternal infection, up to 50% of babies are infected and about a quarter of neonates develop clinical varicella.[23]

Localised varicella-zoster virus infection (shingles) reflects reactivation of latent virus, which has not been shown to be of any risk to the fetus.[46]

Sequelae of fetal infection

Fetal varicella syndrome is characterised by limb defects, dermatomal skin scarring and damage to the eyes and central nervous system. In a review[47] of 96 cases of infants with fetal varicella syndrome cited in the literature, the most common symptoms were skin lesions (scars and skin loss) in 76%, neurological defects (cortical atrophy, spinal cord atrophy, limb paresis, seizures, microcephaly, Horner syndrome, encephalitis and dysphagia) in 60%, eye diseases (microphthalmia, chorioretinitis, cataracts and optic atrophy) in 51% and limb hypoplasia in 49%. Other abnormalities include fetal growth restriction, muscle hypoplasia, gastrointestinal and genitourinary defects, developmental delay and, more rarely, cardiac defects.

Box 7
Commonly used tests for the diagnosis of varicella-zoster

Varicella-zoster virus IgM EIA

Maternal IgM usually appears towards the end of the rash and persists for 3–4 months. Because of the need for rapid treatment following maternal exposure or of chickenpox itself, however, it has limited use.

Varicella-zoster virus IgG EIA

IgG usually appears within 10 days and provides lifelong immunity. If IgG is detected within 10 days of the contact, immunity is assumed. Maternal infection is confirmed by seroconversion on paired samples.

Immunofluoresence

Basal epithelial cells are scraped from a vesicle, fixed on a slide and stained with antibodies to varicella-zoster virus labelled with fluorescein dye. This test can be performed in around 2 hours.

PCR for varicella-zoster virus DNA

This is additionally useful for diagnosis when lesions are crusted over and a scrape is difficult, or when the immunofluorescence is likely to be unreliable. It has high sensitivity and specificity.

Diagnosis of maternal infection

Testing in pregnancy is most commonly done after maternal contact with a known case of chickenpox. The distinctive nature of the rash makes clinical diagnosis reliable and, therefore, where there is a definite history of previous varicella infection, protection can be assumed and testing need not be undertaken. When there is no such history and in the presence of significant contact (face-to-face for 5 minutes or in the same room for 15 minutes or more), the woman's susceptibility may be determined by testing for varicella-zoster virus IgG. Maternal chickenpox is usually diagnosed by immunofluorescence—the detection of viral antigens in skin cells from lesion scraping. Where the infection is suspected to have occurred some time ago, it can be confirmed by seroconversion. Details of the available tests are found in **Box 7**.

Diagnosis of fetal infection

Polymerase chain reaction can be used to detect varicella-zoster virus DNA in amniotic fluid; however, its presence does not necessarily imply progression to fetal varicella syndrome. In a study[48] of 9 women with positive amniocentesis following primary infection before 24 weeks, 5 delivered healthy babies with no signs of fetal varicella syndrome. The absence of viral DNA may not rule out fetal varicella syndrome; however, in this study, none of those with a negative test were affected.

The mainstay of diagnosis of fetal varicella syndrome is detailed ultrasound scanning. The key findings include microcephaly, hydrocephalus, limb deformities, fetal growth restriction and soft tissue calcifications. Prenatal ultrasound appears to have reasonably good correlation with fetal outcome at birth.[49] Hoffmeyer *et al.*[50] suggested that sonographic examination at 5 or more weeks after the initial infection should identify most cases of varicella embryopathy. Abnormalities appear to be collective, although Lloyd[51] reported a case of skin lesions as the sole manifestation. Serial ultrasound examinations should be carried out from 5 weeks after infection or 16 weeks of gestation.

Management of the infected fetus

There is no conclusive evidence that fetal varicella syndrome can be prevented or ameliorated by the maternal administration of varicella immunoglobulin or antiviral chemotherapy. In the presence of ultrasound abnormalities in a pattern consistent with fetal varicella syndrome and a confirmed diagnosis of maternal varicella prior to 20 weeks of gestation, a severely affected baby is likely and termination of pregnancy may be offered. In the absence of ultrasound abnormalities on serial ultrasound scans performed by a fetal medicine specialist, reassurance may be provided.

Conclusion

The approach to the prenatal diagnosis of congenital infection varies according to the gestational age and the likely infectious agent. An essential common step is to confirm maternal infection, most frequently serologically, by testing for pathogen-specific IgG and IgM. The interpretation of results can be difficult, particularly in the absence of a premorbid sample, such that seroconversion from IgG negative to IgG positive cannot be demonstrated. Consultation with a virologist is valuable in all cases and referral to a fetal medicine specialist for further management is appropriate once maternal infection has been confirmed. The risk of transmission to the fetus and the chance of fetal damage relate specifically to the pathogen and gestation at infection. Amniocentesis to test for the presence of RNA or DNA by PCR is the mainstay of diagnosis of fetal infection in most cases but the timing of the test in relation to the likely point at which transmission occurred is crucial. Furthermore, the detection of virus alone is not synonymous with fetal damage and a negative result does not completely exclude the possibility of fetal infection. Ultrasound surveillance is the primary tool for determining the degree of damage but it, too, has limitations in accurately predicting the outcome for the baby. There are few therapeutic options for the infected fetus and these are currently limited to intrauterine blood transfusion in cases of anaemia due to parvovirus infection and maternal antibiotic

therapy in toxoplasmosis infection to reduce transplacental transmission.

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