Fetal infection: a pragmatic approach to recognition and management

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Abstract

Viruses and parasites can be transmitted from a pregnant woman to her fetus via the placenta and can affect development of the fetus. Maternal infection is often asymptomatic or mild. The implications for the fetus are dependent on gestation, stage of organogenesis, the presence of maternal immunity and the virus type. Fetal infections are a potentially preventable cause of perinatal morbidity and mortality. Prenatal diagnosis is often initiated due to exposure of mother to an infectious contact. Management involves confirmation of maternal infection and careful consideration of the risks and benefits of fetal diagnosis, fetal surveillance, intrauterine treatment and possibly termination of pregnancy. Empathic and effective counselling of the parents is crucial and a multidisciplinary approach is important for optimal care. This review uses cases of two fetal infections to highlight a pragmatic approach to prenatal diagnosis and management. There is also an overview of three other fetal infections which can potentially cause serious morbidity and mortality.

Keywords cytomegalovirus; parvovirus B19; prenatal diagnosis

Introduction

Fetal infections are a potentially preventable cause of perinatal morbidity and mortality. Viruses such as rubella, cytomegalovirus, parvovirus, varicella-zoster virus and parasites like *Toxoplasma gondii* can be transmitted from a pregnant woman to her fetus via the placenta and can affect fetal development. The likelihood of fetal infection, and indeed the consequences of infection for the fetus, via transplacental transmission are dependent on the presence of maternal immunity and gestational age. This review discusses three fetal infections in detail, highlighting current approaches to prenatal diagnosis and management. Routine serum screening is carried out at booking for rubella, syphilis and hepatitis B. Testing is otherwise initiated, for example for cytomegalovirus, parvovirus B19 and varicella zoster, if markers of fetal infection are identified on a routine ultrasound scan or in response to maternal exposure to infection and rarely, symptoms of maternal infection. Knowledge of the methods available for prenatal diagnosis and their benefits and limitations is essential for accurate counselling and treatment of affected pregnant women.

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Case 1 (Parvovirus)

A 26-year old woman who is 22 weeks pregnant presents to you in the antenatal clinic. She has been referred by her community midwife, as she works in a nursery and two children have been diagnosed with parvovirus. She is very anxious about the well-being of her baby.

What would you do?

1. Confirm that the patient has had significant contact.

Up to 50% of women are non-immune and thus susceptible to parvovirus infection. Significant contact is defined as being in the same room for over 15 minutes, or face-to-face contact. Parvovirus is infectious prior to the development of the rash, therefore clarification is needed as to when the patient was in contact with the infected children. Transmission of parvovirus B19 most commonly occurs through respiratory secretions and hand-to-mouth contact. The incubation period is 4–14 days following exposure; the infected person generally is infectious for 5–10 days after exposure prior to the onset of the rash. The person is no longer infectious with the onset of the rash. The rash can appear up to 18 days following exposure. The transmissibility of the virus is found to be approximately 50–90% among susceptible household contacts.

2. The lady has been confirmed as having significant contact. What would you do next?

Serum should be collected as soon as possible after contact to investigate for evidence of parvovirus. The laboratory will test for parvovirus and rubella despite the clinical history. Investigation of the serum will facilitate determination of whether the patient has had a previous infection, susceptibility or has an acute parvovirus infection (Figure 1). Serum stored from booking blood can be tested for evidence of past infection to help assess the likelihood of an acute seroconversion.

Adults are frequently asymptomatic, although they may present with erythema infectiosum (fifth disease) – transient fever, arthralgia and malaise. Transient maternal aplastic crises can occur in patients with sickle cell anaemia, thalassaemia, spherocytosis and pyruvate kinase deficiency. Children have a mild illness presenting with the 'slapped cheek' facial rash and fever. Although fetal infection does not appear to cause teratogenicity it can, however, cause profound fetal haemolytic anaemia which can result in cardiac failure, non-immune hydrops and potentially intrauterine death.

The likelihood of fetal infection and damage to fetus is not dependent on whether maternal infection is asymptomatic or symptomatic. The risk of adverse outcome to the fetus may be reduced by active management of the infected fetus.

The presence of IgG is evidence of previous infection and confers lifelong immunity. Approximately 50–60% of adults will have evidence of previous infection. The seroconversion rate in pregnant women is an indirect measurement of the primary infection rate and is approximately 1% per year.

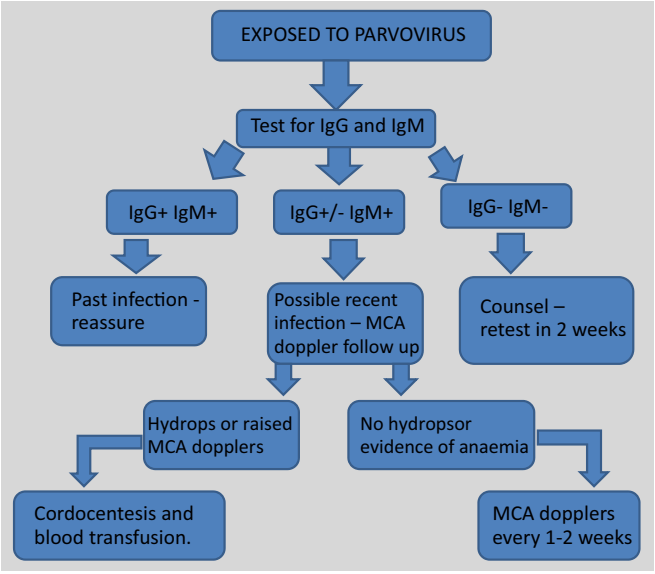

Figure 1 Serology testing for parvovirus.

Her recent serology is reported as IgG positive IgM positive parvovirus B19 infection. Her antenatal screening serology was negative for both IgG and IgM. What is your ongoing management?

3. She has an acute parvovirus infection and her care should be discussed with the Regional Fetal Medicine Unit. She may need to be managed there rather than her district hospital, depending on local scan expertise.

A multidisciplinary team including virology, neonatologists and fetal medicine specialists should be involved.

4. Counsel the woman regarding potential risks to the fetus and the management plan.

The risk of maternal infection crossing the placenta to the fetus is 15% from 5 to 15 weeks, 25% after 15 weeks, increasing up to 70% towards term. Infection before 20 weeks can lead to intrauterine death with a 5–10% fetal loss rate. However, infection after 20 weeks results in a 0.5% fetal loss rate. Hydrops usually occurs 2–4 weeks after maternal parvovirus infection. On average, there is a 3–10% risk of hydrops following parvovirus infection, which can result in fetal death in approximately 50% of cases. The suggested mechanisms include fetal anaemia as the human parvovirus B19 targets rapidly dividing cells, thereby interrupting red cell production. This, combined with a shorter half-life of fetal red blood cells, leads to the severe anaemia, hypoxia, high output cardiac failure associated with fetal hydrops. A prospective study showed that 7.5% of third trimester fetal deaths *in utero* were positive for parvovirus B19 in the placental tissues. Thus, testing for parvovirus B19 should be offered in this scenario.

5. Fetal surveillance.

Weekly ultrasound monitoring is necessary to identify fetal anaemia, ascites and hydrops (accumulation of fluid in two compartments) for up to 12 weeks after maternal exposure (Figure 2a and b).

Doppler ultrasound measurements of the middle cerebral artery peak systolic velocity (MCA-PSV) are used to help predict fetal anaemia (Figure 3). A study assessing the predictive value of MCS-PSVs reported that these Doppler studies had 100% sensitivity for predicting fetal anaemia in the presence of parvovirus.

Fetal MCAs suggest severe anaemia. What are the options?

6. Active management has been shown to improve outcome.

30% of cases with fetal hydrops will spontaneously resolve. However, there is no robust method to distinguish these cases from those that will progress to intrauterine death. Thus active management is considered in all cases.

Cordocentesis is used for fetal blood sampling to diagnose fetal anaemia. It should be done with full facilities available for immediate intrauterine blood transfusion if fetal anaemia is confirmed by the laboratory.

Cordocentesis can be performed from 18 weeks onwards. There is a 1–2% risk of procedure-associated miscarriage. The preferred transfusion site is at the umbilical vein insertion into the placenta, but the intrahepatic umbilical vein or the cardiac ventricles can be utilized. At later gestations, the risk of cordocentesis and intrauterine transfusion should be balanced against the risk of possible premature delivery and neonatal transfusion.

Fetal transfusion has been shown to improve outcome although the time taken for resolution of hydrops can vary but normally occurs within 6 weeks. The woman can be reassured that following resolution of hydrops, there is no evidence to show that there are any adverse long-term effects to be expected.

Case 2 (Cytomegalovirus)

A 27-year-old woman is 17 weeks pregnant. She is a late booker and gives a vague history of contact with someone with a rash. She cannot give any more details on the rash or when she had this contact. The booking midwife requested a TORCH screen at the time of seeing the patient who has now come to see you (the obstetrician) at 19 weeks with the following blood results: CMV IgG negative, CMV IgM positive.

How do you interpret these results?

1. She has an acute cytomegalovirus infection.

CMV infection is one of the most common congenital infections with a reported incidence of 0.2–2.2%. 50–70% of women have had previous CMV infection (IgG+). Both primary and recurrent infections can lead to fetal infection but risk of transmission and severity is greater in a primary infection. Maternal primary infection is usually asymptomatic but can present with vague symptoms of fever, malaise and lethargy.

CMV IgG is present within 2 weeks of primary infection and is life-long.

What do you do next?

2. Counsel the woman regarding potential risks to the fetus and the management plan and offer amniocentesis.

The risk of transplacental transmission to the fetus is 40% in the first and second trimesters. The risk of fetal injury is greatest after primary CMV and when maternal infection occurs in the first or early second trimester. The risk of transmission is greater (80%) in the third trimester but usually asymptomatic after 27 weeks.