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Human parvovirus B19 infection and pregnancy

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It is estimated that human parvovirus B19 infection affects 1600–2200 pregnant mothers each year in England and Wales. Vertical (transplacental) transmission occurs in approximately one-third of these maternal infections. In contrast to the relatively mild clinical effects of human parvovirus B19 in the mother, fetal infection via haematogenous transplacental spread can be severe and sometimes fatal. The infection causes a wide range of clinical syndromes. These varying clinical presentations are described, with the aim of increasing the diagnostic awareness of readers of possible exposures to human parvovirus B19 infection during pregnancy and providing an up-to-date management protocol.

Introduction

Human Parvovirus B19 was first discovered by chance in 1975 at the Central Public Health Laboratory during routine screening for hepatitis B of asymptomatic blood donors from the South London Blood Transfusion Centre.[1] For some years it remained an orphan virus with no apparent associated disease. However, in 1981 it was shown to be the causal agent of transient aplastic crisis (TAC) in patients with sickle-cell anaemia and was later associated with the common childhood exanthem, erythema infectiosum (also known as fifth disease or 'slapped cheek' syndrome).[2,3] The first case reports of human parvovirus B19 adversely affecting the fetus appeared in early 1980s.[4,5] More recently, interest has focused on the effects of persistent human parvovirus B19 infection in severely immunocompromised individuals as a cause of intractable anaemia.[6]

Human parvovirus B19 belongs to the parvovirus genus of the family Parvoviridae, which comprises the smallest and the simplest of the known DNA viruses. It has a diameter of 23 nm and contains a single stranded DNA genome (5.5 kb). The viruses in the parvovirus genus are species-specific and thus human parvovirus B19 is the only known pathogenic parvovirus in humans. Parvoviruses can replicate autonomously but only in dividing cells in the S-phase of mitosis (a feature relevant in cases of fetal B19 infection). It has been shown to replicate in, inhibit colony formation and cause lytic infection of erythroid progenitor cells from human bone marrow.[7] Intranuclear viral particles typical of human parvovirus B19 have also been discovered in fetal myoblasts.[8]

Epidemiology

Distribution

Large-scale serological testing for human parvovirus B19 in the UK indicates that infection occurs throughout the year, although there is a peak in late spring and early summer months. All age groups are affected but it is most common in younger school-age children. There are periods of increased activity every three to four years, followed by periods of relatively lower incidence. Recent epidemic years in the UK have been 1989–90, 1993–94 and 1997–98.

The outcome for fetuses infected by human parvovirus B19 and who showed ultrasonographic signs of the infection (ascites, hydrops fetalis or elevated middle cerebral artery peak systolic velocities) has been reviewed. Eleven cases were identified between October 1996 and January 2000 in the Fetal Medicine Centre at Birmingham Women's Hospital; 8 of these presented in 1998. Therefore, it seems that the last epidemic has been reflected in this study (unpublished data), as is concordant with data from the Public Health Laboratory Service Communicable Disease Surveillance Centre.

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Transmission and incubation period

Transmission is believed to be through respiratory secretions. In studies with human volunteers, serum and respiratory secretions become positive for human parvovirus B19 at 5–10 days after intranasal inoculation. However, the rash does not occur until 17–18 days after inoculation and after the confirmed disappearance of the virus from serum and respiratory secretions for at least one to five days. Thus, patients presenting with clinical features of infection are probably past the period of maximum infectiousness.

The transmissibility of the virus is found to be approximately 50–90% among susceptible household contacts. In school outbreaks, 10–60% of students may develop erythema infectiosum and 20–30% of susceptible staff develop serological evidence of B19 infection. Other mechanisms of transmission include the parenteral route (by transfusion of infected blood products) and vertical transmission from mother to fetus. The latter route will be discussed in more detail.

The healthcare professionals to whom women may turn for advice should be aware that epidemics of fifth disease pose an increased risk of fetal loss to susceptible pregnant women. Blanket decisions on exclusion from work or transfer to a lower risk area are, however, inappropriate. First, serological determination of susceptibility to human parvovirus B19 may be undertaken; women with human parvovirus B19 immuno-globulin G (IgG) but no immuno-globulin M (IgM) can then be reassured. Among patients thought to be susceptible to infection, decisions should then be made on individual basis. Women should be made aware that the risk of acquiring infection in the workplace might be similar to that in the community. For this reason, routine exclusion from the classroom of susceptible pregnant teachers who are less than 20 weeks of gestation should not be adopted as policy, since it is not likely to reduce the risk of infection. However, if there is an outbreak in the school then consideration may be given to excluding susceptible pregnant employees from the classroom until they are more than 20 weeks of gestation. An outbreak would be defined as two or more cases in the same *class* with onset date within three weeks or three or more cases in the *school* or *nursery* with onset dates within three weeks.

Clinical features

Human parvovirus B19 causes a wide range of clinical syndromes. These varying clinical presentations will be reviewed in order to raise the diagnostic awareness of likely exposures among pregnant women and of symptoms of the infection occurring in the woman herself.

Erythema infectiosum

Erythema infectiosum (fifth disease) usually presents as a mild childhood illness characterised by fever and facial rash ('slapped-cheek' appearance) and a reticulate or lace-like rash on the trunk and extremities. Erythema infectiosum is distributed worldwide and most commonly encountered in children younger than 14 years. The illness is less infectious than measles or chickenpox, although surveys show that 60% of adults have serologic evidence of prior infection.[6] In adults, the clinical presentation is more variable and diffuse: fever, malaise and, uncommonly, post-infectious arthralgia and arthritis-like symptoms may be present. Approximately 20% of human parvovirus B19 infections, confirmed serologically, may be asymptomatic.[9]

Transient aplastic crisis

Sickle-cell disease was the first haemolytic anaemia in which transient aplastic crisis was shown to be associated with human parvovirus B19. Subsequently, transient aplastic crisis in people with other hereditary anaemias (spherocytosis, thalassaemia, pyruvate kinase deficiency) and autoimmune haemolytic anaemia has also been associated with human parvovirus B19, as the causal agent.

Other clinical presentations

"Chronic anaemia" can be a feature of persistent B19 infection in severely immunocompromised individuals and has been suggested as a candidate agent in several autoimmune disorders.[10,11]

Groups 'at increased susceptibility' of infection

In a study of seroconversions among susceptible school and hospital employees during an epidemic period, the most important single factor for seroconversion was daily contact with children, either at home or in primary school settings.[12] Daily occupational contact with school-age children was associated with a five-times increased likelihood of seroconversion. In contrast, the rate of serconversion among hospital staff was low. The annual seroconversion rate for susceptible primary school employees was 5.2% compared with 2.4% among other school employees and 0.0–0.5% among hospital

employees. Having school children at home was almost as important, with seroconversion rates of 3.3–5.6%. Parous women may be at greater risk than nulliparous women for the same reason.

Infection in pregnancy

Analysis of the results of a serological survey, stratified by age, suggests that, on average, slightly less than 1% of susceptible adults are infected each year. It was estimated from this that 1600–2200 mothers are 'infected' in pregnancy each year in England and Wales; that is, one infection in every 400 pregnancies.[13] During an epidemic year there may be two or three times more cases than in an average year. In an epidemic year for human parvovirus B19 in England and Wales, 310 laboratory-confirmed infections in pregnancy were reported to the Public Health Laboratory Service Communicable Disease Surveillance Centre. This represents at most 10% of the 3000–6000 infections that are estimated to occur.[13] This demonstrates the extent to which B19 infection is underdiagnosed.

Fetal effects

Human parvovirus B19 has a predilection for rapidly dividing cells; the intense viraemia provides ample opportunity for vertical (transplacental) transmission, which is estimated to occur in 30% of infections.[14] In contrast to the relatively mild clinical effects of infection in the mother, fetal infection via haematogenous transplacental spread can be severe and sometimes fatal.

Fetal loss

In a prospective study of human parvovirus B19 infection in pregnancy, the risk of fetal death due to B19 in an infected pregnancy was estimated to be 9%, with the highest risk in the second trimester.[14] Applying this fetal death rate to the estimated number of infections suggests that 150–200 fetal deaths are caused by B19 in England and Wales each year.[13]

In a prospective study of women experiencing third-trimester intrauterine fetal death, 7.5% of these deaths had detectable human parvovirus B19 DNA in the placental tissues. Because there was no other explanation for these losses, the authors concluded that these might have been caused by B19 infection.[15] This group has gone on to investigate the detection of human parvovirus B19 in fetal material from pregnancy losses across gestation. These data indicated that detection of human parvovirus B19 DNA using polymerase chain reaction in placental and fetal tissue was more successful in making the diagnosis than immunohistochemistry and histology alone. The presence of B19 DNA in pregnancy losses (second and third trimesters) was relatively common and in many cases these babies were not hydropic.[16] Such conclusions are of great interest but are controversial.

Nonimmune fetal hydrops

Nonimmune fetal hydrops is the most frequent pathological finding in fetuses infected with human parvovirus B19. It is estimated to affect 3% of pregnancies in which B19 infection occurred at 9–20 weeks of gestation.[17] The virus binds to its cellular receptor, the P-antigen, and has a tropism for immature erythrocytes in the bone marrow and in extramedullary sites, inhibiting their multiplication.[18] In the fetus, as in chronic haemolytic anaemia, there is shortened red-cell lifespan of 45–70 days. Moreover, the fetal red-cell mass increases about 34-fold between the third and sixth months of gestation; this setting is therefore ideal for an agent whose intracellular replication depends on rapidly dividing cells. Virally induced red-cell maturation arrest at this time of increased demand causes an aplastic crisis with resultant severe anaemia and cardiac failure. The presence of inflammatory changes in the placenta and myocardium of hydropic fetuses due to parvovirus infection indicates that hydrops in these specific cases may not be due to anaemia only.[19] Indeed, the associated findings of myocardial contractile failure using fetal echocardiography and elevated cardiac enzymes in fetal blood are described and indicate the presence of a myocarditis.

In fetal medicine centres, such a diagnosis is considered in babies presenting with nonimmune hydrops fetalis (or isolated ascites), usually with significantly increased middle cerebral artery Doppler velocity indices, indicative of fetal anaemia. Fetal blood sampling usually demonstrates profound anaemia and often an associated pancytopenia. The presence of a significant reticulocytosis (greater than 20%) in fetal blood indicates that, in many cases, the fetal haemoglobin had probably reached its nadir and likely to rise in response to recovering erythropoiesis. However, the decision to treat an anaemic fetus *in utero* will depend upon the gestational age at presentation, the degree of fetal anaemia present and the associated reticylocyte count.

In a review of cases of hydrops fetalis in the West Midlands Region, UK, between September

1996 and March 1999, human parvovirus B19 infection was the most frequently identified cause of nonimmune hydrops. However, 87.5% of these severely affected pregnancies had a successful outcome.[20] Although hydrops due to B19 infection can resolve spontaneously in up to 34% of cases, there are no clinical or ultrasound criteria to specifically help the obstetrician to identify those that will resolve spontaneously.[5,17]

Diagnosis and management in pregnancy

Diagnosis of a recent human parvovirus B19 infection might be required in certain clinical scenarios. These include:

- a pregnant woman presenting with a rash illness and/or acute arthropathy
- maternal exposure (especially before 20 weeks of gestation) to definite human parvovirus B19-related infection or to a rash illness of unknown cause
- as part of the investigation of intrauterine fetal death and stillbirth
- investigation of the cause of nonimmune fetal hydrops fetalis or ascites.

Maternal diagnosis

A careful history can provide aetiological clues and may be important in devising appropriate advice on prevention. Because of the important differential diagnosis between human parvovirus B19 and rubella, it is important to measure both B19 and rubella antibodies. Recent infection can be diagnosed by detection of human parvovirus B19 IgM, either by antibody capture radioimmunoassay (RIA) or by enzyme-linked immunosorbent assays (ELISA). These methods detect human parvovirus B19 IgM in approximately 90% of cases by the third day after the onset of symptoms.[21] Titres start to decline 30–60 days after onset but low levels can persist for up to six months in some subjects. For the purpose of timing infection in relation to conception, the serological findings should be related to the clinical history of exposure or of symptoms. An exposed antenatal patient who is seronegative at the first test should have the human parvovirus B19 IgM measured again 2–3 weeks later, depending on the timing of the exposure (Figure 1).

Human parvovirus B19 IgG can be detected by RIA or ELISA. It is usually present by the seventh day of illness and persists for life. Its presence appears to convey lasting immunity to further infection. B19 DNA can be detected in serum and in respiratory secretions by polymerase chain reaction, before the IgM response develops. However, both viraemia and viral excretion are transitory phenomena and antibody assay is the recommended method of investigation.

Fetal diagnosis

If maternal infection is confirmed, the fetus should be followed up by serial ultrasound scans for the early detection of fetal hydrops. The pregnancy period for which serial ultrasound scans should be performed after a confirmed maternal infection is controversial. In a postal survey conducted by Rodis *et al.*,[22] the views of 541 members of the Society of Perinatal Obstetricians regarding the management of human parvovirus B19 infection in pregnancy were reviewed. Eight percent of the respondents followed-up their patients for 2–5 weeks, 48% for 6–8 weeks, 17% for 9–11 weeks and 24% for 12 weeks. There is some evidence that elevated maternal serum alpha-fetoprotein (MSAFP) may be a marker for fetal human parvovirus B19 infection.[23] Interestingly, the association between hydrops and B19 infection was first recognised in a patient undergoing an evaluation for elevated MSAFP.

In cases of unexplained nonimmune hydrops, human parvovirus B19 IgM and viral DNA are used to identify fetuses infected with B19. The appropriate serological tests on the mother would include human parvovirus B19-specific IgM and IgG. Fetal complications associated with B19 can occur two or more months after maternal infection, when IgM has fallen to concentrations difficult to detect with currently available assays. This may account for the inability to detect IgM-specific antibodies in both fetal and maternal sera simultaneously in these pregnancies.

Pregnant women with acute B19 infection should be treated symptomatically. If, on follow-up, fetal hydrops is detected, referral to a tertiary fetal medicine centre is prudent. Delivery and extrauterine therapy can be considered if the gestational age permits. Otherwise, a fetal blood sample should be taken to confirm fetal anaemia and intrauterine transfusion to correct it is advised.[24] Conservative management and reassessment may be appropriate (if fetal reticulocyte counts are high) as the fetal hydrops and anaemia may resolve spontaneously. Thus, the obstetrician (preferably a fetal medicine subspecialist) must carefully weigh the risks of the available forms of intervention against the condition and prognosis of the fetus.

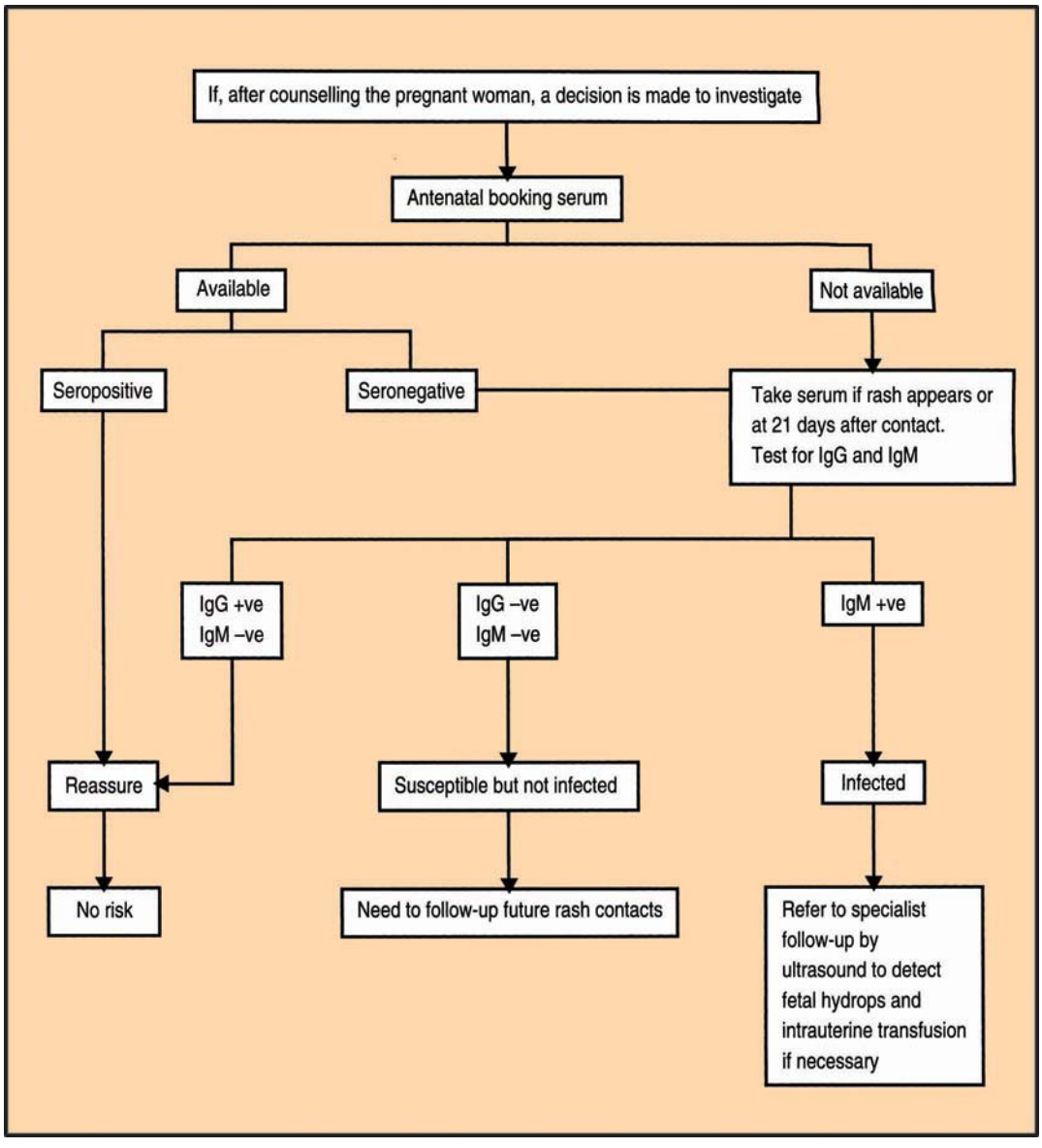

Figure 1 Flowchart for the management of pregnant women at less than 20 weeks of gestation in contact with a suspected or confirmed case of human parvovirus B19 infection (contact: in the same room for a significant period of time (15 minutes or more) or face-to-face contact during the period from seven days before the appearance of a rash to the date of appearance of the rash)

The investigation of an unexplained pregnancy loss or stillbirth should include maternal B19 antibody estimations. If human parvovirus B19 IgM is not detected, it may be possible to demonstrate seroconversion by measuring B19 IgG in paired sera if any stored blood is available from earlier in the pregnancy. Antibodies may also be measured in the fetus or stillbirth. Fetal tissues or products of conception can be examined for human parvovirus B19 DNA by dot hybridisation, even if formalin fixed. Immune electron microscopy can also be used to detect B19 virions in a variety of fetal tissues. Characteristic intranuclear inclusions of parvovirus-like particles can be detected in fetal tissues by light and by electron microscopy. The prospective collection of such data indicate that an increasing number of 'apparently unexplained pregnancy losses' are associated with human parvovirus B19 infection.[16]

Conclusion

At present, there is no role for a routine antenatal screening programme for human parvovirus B19 and infection in pregnancy is not an indication for therapeutic termination. Women, particularly those working in close contact with young children, should be given information about human parvovirus B19 infection in pregnancy. This information should not only be given in antenatal clinics but also in preconception and family planning clinics. Human parvovirus B19 is an important cause of nonimmune hydrops. A significant proportion of these fetuses might recover spontaneously. However, there are no clinical or ultrasonographic criteria to predict this. Therefore it is prudent to refer pregnancies complicated by nonimmune hydrops to fetal medicine centres with facilities for intrauterine transfusion. ■

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