Parvovirus B19 infection in human pregnancy

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Human parvovirus B19 infection is widespread. Approximately 30–50% of pregnant women are nonimmune, and vertical transmission is common following maternal infection in pregnancy. Fetal infection may be associated with a normal outcome, but fetal death may also occur without ultrasound evidence of infectious sequelae. B19 infection should be considered in any case of nonimmune hydrops. Diagnosis is mainly through serology and polymerase chain reaction.

Surveillance requires sequential ultrasound and Doppler screening for signs of fetal anaemia, heart failure and hydrops. Immunoglobulins, antiviral and vaccination are not yet available, but intrauterine transfusion in selected cases can be life saving.

**Keywords** Fetal anaemia, human, nonimmune hydrops, hydrops-fetalis, parvovirus, pregnancy.


**Introduction**

Human parvovirus (hPV) B19 infection is the most common viral agent associated with rashes in school-aged children. Approximately 65% of pregnant women in North America have evidence of past infection and, although the incidence of acute hPV B19 infection in pregnancy is approximately 1–2%, in epidemic periods this can exceed 10%. Infection with hPV B19 during pregnancy is mostly asymptomatic for the mother and causes no harm to the fetus. However, in pregnant women who are immunocompromised or suffering from pre-existing haematological conditions, or in infected fetuses where there is widespread tissue inflammation and red-cell destruction, mortality and serious morbidity may occur.

**History and nomenclature**

hPV B19 infection may manifest as erythema infectiosum (EI), or ‘fifth disease’ or ‘slapped face syndrome’. The term ‘slapped face syndrome’ exists across nations, in different languages, and describes the characteristic facial rash. The term ‘fifth disease’ was used because parvovirus B19 infection was considered to be the next example of the existing classic four childhood exanthemata: measles, scarlet fever (scarlatina), rubella and ‘fourth disease’ or Dukes’ disease.* In 1975, whilst screening blood donations for hepatitis B, a novel agent was found which could be confused morphologically and serologically with hepatitis B antigen. This was a known property of parvoviruses, but the antigen was novel and was given the name parvovirus B19 because it was found in Panel B, Sample 19 of the laboratory testing kit.4

* Dukes’ disease is eponymous with Dr Clement Dukes (1845–1925) who qualified at St Thomas’ Hospital in London (1869) and worked at the Royal Hospital for Sick Children (Great Ormond Street) in London before becoming the medical officer at Rugby School, one of England’s most famous independent schools. Rugby, from which rugby football derives its name, was, at that time, an all-boys boarding school where Dukes wrote respected books on schoolboy health and care. Following an epidemic of a rash-related illness from which he eliminated measles, scarlatina and rubella as a cause, he coined the term ‘fourth disease’, which later became known by the eponym ‘Dukes’ disease’. Up to that time, rubella was considered by many to consist of two varieties, but Dukes demonstrated that two clearly distinguishable diseases existed – rubella and ‘fourth disease’.

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**Taxonomy and description**

Parvovirus B19 is a single-stranded DNA, nonenveloped virus from the family Parvoviridae and the genus Erythroivirus, which is one of the smallest to infect mammalian tissues, hence its name (parvus, Latin: adj. = small). The genus Erythroivirus is extremely species specific, causing life-threatening diseases in both cats and dogs; yet, in humans, only hPV B19 and some adenoviruses cause disease. In comparison with other viruses, hPV B19 is physically and genetically quite stable with only a few mutations, and causes pathology through the blocking of erythropoiesis and the induction of inflammation. Other genotypes have been described, but their identification, virulence, transmission and ability to cause disease remain poorly elucidated. The morphology, genetics, capsid proteins, culture and viral life cycle have been reviewed elsewhere.

**Epidemiology**

The transmission of hPV B19 may be by respiratory droplets, transfusion of blood and blood products, or to the fetus by transplacental passage. In healthy volunteers, serum and respiratory secretions become positive for hPV B19 DNA during the prodromal phase, 5–10 days after intranasal inoculation. Transmission rarely occurs during transfusion with single-donor blood products, but is more common during treatment with blood concentrates. Similarly, transmission may also occur through bone marrow or organ transplantation. Tattooing as a source has been suspected, as well as transmission in medical research laboratories, although this may not be of relevance to hPV B19 infection in pregnancy in the 21st century.

hPV B19 infection occurs worldwide, but seroprevalence rates vary according to age and geography. Approximately 15% of preschool children, 50% of adults and 85% of the elderly are seropositive. The prevalence may be higher in developing countries and lower in isolated communities. Lifelong immunity is the norm in the immunocompetent individual; yet, despite the high prevalence of seropositivity, viraemia or detection of viral DNA in serum is rare in healthy individuals. hPV B19 infections follow a seasonal variation, with a higher prevalence in temperate climes around late winter to early spring [similar to varicella zoster virus (VZV) infection]. Epidemics occur and tend to follow a 3–6-year cycle during which time children and their domestic contacts, as well as school or nursery workers, are at greater risk. During epidemics, the secondary attack rate (number of cases in the outbreak divided by the total number of susceptible individuals in the population) is 50% in susceptible children and 25% in susceptible teachers. Nosocomial transmission in adult, paediatric and neonatal units also becomes important during outbreaks.

**Clinical findings**

The illness associated with hPV B19 evolves differently in different individuals. Some may be asymptomatic and others develop only prodromal symptoms. In some, the prodromal illness is followed by a later phase of more definable symptoms. In a few, particularly those who are immunosuppressed or suffering from related illnesses which put them at high risk, the disease may become chronic and complicated with long-term sequelae. In outbreaks, asymptomatic infection occurs in approximately 20% of children and adults exposed to the virus. hPV B19 infection has been associated with fetal loss, acute arthritis and arthralgias, as well as chronic anaemia, in immunodeficient individuals. The incubation period before the onset of mild illness with prodromal symptoms ranges from 4 to 14 days after exposure, but may be as long as 3 weeks. Serum specimens are usually negative by 7 days after the onset of illness, suggesting that patients with EI are probably beyond the period of greatest infectivity. However, the clinical course and immune response are biphasic, and a second phase of symptoms presents with rash, itchiness or arthralgia about 17–18 days after inoculation. If EI occurs, there may be the classic ‘slapped face’ appearance with a maculopapular rash of the face, and/or trunk and extremities, which may show a reticular, lattice or lace-like rash. Peripheral polyarthropathy of the hands, wrists and knees is also characteristic and, in pregnant women, this may be the only manifestation of the condition. Transient leucopenia, lymphocytopenia and thrombocytopenia have been reported in normal individuals following hPV B19 infection. Pregnant women suffering from existing haematological conditions, such as sickle-cell disease, are more likely to develop transient aplastic crisis. In addition, severe chronic anaemia associated with red blood cell aplasia related to hPV B19 has been reported in individuals suffering from HIV and other associated immunodeficiencies.

**Maternal infection and fetal disease**

Although 30–50% of pregnant women are susceptible to hPV B19, only a small percentage will be infected with the virus. The hPV B19-specific immunoglobulin G (IgG) seroconversion incidence in susceptible pregnant women may increase from 1–1.5% to 13–13.5% during epidemic periods. Up to 50% of infected pregnant women may develop transient aplastic crisis. In a few, particularly those who are immunosuppressed or suffering from related illnesses which put them at high risk, the disease may become chronic and complicated with long-term sequelae. In outbreaks, asymptomatic infection occurs in approximately 20% of children and adults exposed to the virus. hPV B19 infection has been associated with fetal loss, acute arthritis and arthralgias, as well as chronic anaemia, in immunodeficient individuals. The incubation period before the onset of mild illness with prodromal symptoms ranges from 4 to 14 days after exposure, but may be as long as 3 weeks. Serum specimens are usually negative by 7 days after the onset of illness, suggesting that patients with EI are probably beyond the period of greatest infectivity. However, the clinical course and immune response are biphasic, and a second phase of symptoms presents with rash, itchiness or arthralgia about 17–18 days after inoculation. If EI occurs, there may be the classic ‘slapped face’ appearance with a maculopapular rash of the face, and/or trunk and extremities, which may show a reticular, lattice or lace-like rash. Peripheral polyarthropathy of the hands, wrists and knees is also characteristic and, in pregnant women, this may be the only manifestation of the condition. Transient leucopenia, lymphocytopenia and thrombocytopenia have been reported in normal individuals following hPV B19 infection. Pregnant women suffering from existing haematological conditions, such as sickle-cell disease, are more likely to develop transient aplastic crisis. In addition, severe chronic anaemia associated with red blood cell aplasia related to hPV B19 has been reported in individuals suffering from HIV and other associated immunodeficiencies.
women may be asymptomatic, but vertical transmission can still occur, albeit that fetal manifestations may not become evident for weeks or even months. Fetal hydrops may be caused by cardiorespiratory congenital defects. Fetal anaemia and hydrops may be a result of immune conditions, such as red-cell or Kell alloimmunisation, or nonimmune hydrops caused by hPV B19. The diagnosis and management of fetal anaemia and hydrops, in general, have been reviewed elsewhere. Hydrops fetalis associated with hPV B19 infection was first reported in 1984. If pregnant women develop hPV B19 infection, there is a 30% chance of fetal transmission. During epidemics, there is a greater risk of vertical transmission and a 5–10% rate of fetal loss in cases of fetal infection. In the majority of cases of hPV B19 infection in pregnancy, the fetus is unaffected; however, infection may result in severe fetal anaemia, generalised oedema, congestive heart failure, myocarditis and hydropic or nonhydropic fetal death. The unpredictability of fetal infection is demonstrated by cases of discordant hPV B19 infection within twin pregnancies. hPV B19 infection is thought to account for 8–20% of nonimmune fetal hydrops yet may result in spontaneous resolution without adverse sequelae. The risk of developing hydrops fetalis among infected fetuses varies during pregnancy between 0 and 12.5%, and the peak incidence is between 17 and 24 weeks depending on the gestational age at infection. Some of the parvovirus strains that are pathogenic in animals are teratogens, and congenital malformations have been reported in humans. Nevertheless, reviews of the literature reveal that the rate of congenital anomalies associated with hPV B19 infection does not appear to exceed that which would be expected over background rates. Overall, fetal death is thought to occur in 5–10% of cases of fetal infection, and may occur with or without evidence of fetal hydrops. Detection rates vary depending on the study inclusion criteria, epidemic status and methods of detection employed. The risk of fetal death is a function of gestational age at infection. Approximately 3% of first-trimester spontaneous abortions may be caused by hPV B19 infection, although this may differ between epidemic and nonepidemic periods. According to gestational age, maternal infection in the first trimester, 13–20 weeks and after 20 weeks is associated with risks of fetal death of 19, 15 and 6%, respectively. Spontaneous fetal resolution appears to occur, as healthy neonates have been born with specific hPV B19 IgM in umbilical cord blood. hPV B19 DNA-positive tissues have been reported in a number of fetal deaths and, in cases in which pathological findings were available, all the fetuses had nonimmune hydrops.

Pathophysiology of fetal complications caused by hPV B19 infection

The pathophysiology of fetal adverse effects is mainly a result of anaemia caused by the destruction of red blood cell precursors, but may also be a result of hypoalbuminaemia, hepatitis, myocarditis and placentitis. These may culminate in cardiac failure and subsequent hydrops fetalis or fetal death. Erythropoiesis is inhibited because of the ability of the virus to produce cytotoxic apoptosis and lysis of erythroid precursors. The presence of the virus in erythroid precursors is evident by the typical intracellular inclusions seen in pathological specimens. In the second trimester, the fetus is at significantly increased risk of infection and tissue damage from hPV B19 than in the third trimester. This is because transplacental transmission is more likely to occur because of the presence of the P-antigen, which is a glycolipid (globoside) present in the trophoblast. This receptor is used by hPV B19 to achieve transplacental transfer, is highly expressed in the first and second trimester, but virtually nonexistent in the third trimester. In the second trimester, haematoipoiesis occurs in the fetal liver and, because of the increased demand from the growing fetus, there is a 34-fold increase in red blood cell mass, concomitant with a reduction in red blood cell life span to 45–70 days. These unique circumstances make the fetus especially vulnerable to any insult with respect to erythropoiesis. Severe anaemia, hPV B19 viraeemia and cytologic change in erythroid precursor cells have been described in fetuses immediately antemortem. The relatively low rate of fetal complications associated with third-trimester infection may stem from the fact that the need for a large number of red blood cells is decreased and the life span of these cells is increased.

Cardiac failure may be a result of severe anaemia, but may also be associated with myocarditis, which can cause arrhythmias or even cardiac arrest without evidence of anaemia, cardiac failure or hydrops. Direct damage to fetal myocardial cells by hPV B19 has been reported, and 15% of all myocardial biopsies obtained from dead fetuses diagnosed with perinatal cardiomyopathy were associated with hPV B19 inflammation. However, caution has been expressed about relating PCR detection of viral particles with signs of inflammation in formalin-fixed, paraffin-embedded biopsy tissues rather than freshly frozen and cryopreserved tissue. Another significant organ affected by the inflammatory response to hPV B19 infection is the placenta. Placentitis may cause placental dysfunction and adverse fetal outcome in the absence of fetal infection. In addition, the same degree of fetoplacental infection may be associated with a poorer outcome if placental function is already compromised by smoking or
hypertensive disease, and this may explain why fetal or neonatal outcome is not always related to the severity of feto-maternal disease.

**Diagnosis**

Pregnant women exposed to hPV B19 rash illness should be tested for hPV B19 IgG and IgM. Women who are IgG positive and IgM negative can be reassured that there is no evidence of recent hPV B19 infection. Those women in whom neither IgG- nor IgM-specific antibody for hPV B19 is detected should be considered susceptible, and further serological testing should be carried out 4 weeks after the last contact or if signs of the disease develop. Diagnosis and advice will depend on the results. Detection of hPV B19-specific IgM in maternal serum, irrespective of IgG serology, should initiate further serological reference testing through public health laboratory services, following the results of which the appropriate advice can be given. An algorithm for the investigation of hPV B19 in pregnant women exposed to rash illness is shown in Figure 1.

A number of studies have highlighted the problems of diagnosis of hPV B19 disease based on the characteristic facial rash, particularly in pregnant women. Commercially available assays for parvovirus B19 have high variation of sensitivity and specificity, which may contribute to the misdiagnosis of hPV B19 infection as measles or rubella. One study clearly reported the variation in specificity between five different commercially available tests for the detection of IgM antibodies to hPV B19. The specificities of the tests varied between 94% (Idea; DAKOT A/S, Copenhagen, Denmark) and 70.1% (Parvoscan; EURO Diagnostica, Malmö, Sweden).

As a fastidious virus, hPV B19 cannot be grown in continuous cell lines. As a result, viral culture is not a diagnostic option. Diagnosis requires a multi-method approach using mainly serology and PCR techniques. Histopathology and immunohistochemistry have also been employed, but have little use in routine practice. hPV B19 IgM is usually detectable 10–12 days after infection and can persist in the circulation for 3–4 months or longer, and circulating IgG persists lifelong with slowly decreasing titres unless boosted by subsequent viral exposure. In pregnant women and the immunosuppressed, serological responses are less characteristic. Molecular-based techniques may help to indicate acute or persistent infection. Fetal infection may be identified by using PCR of hPV B19 viral DNA or RNA in amniotic fluid or fetal cord blood. Currently, quantitative serum and tissue titres of hPV B19 DNA are helpful for guiding clinicians in therapeutic options, but these are not widely available and, in most countries, clinical decisions in pregnancy are normally based on qualitative PCR results. Following acute infection, bone marrow examination demonstrates an absence of mature erythroid precursors, and tissue immunohistochemistry demonstrates high specificity in cases of placental or fetal infection. As most pregnancies infected with hPV B19 have a favourable outcome, it would appear that invasive prenatal diagnostic testing should only be used if there are definitive signs of fetal anaemia or hydrops fetalis.

![Figure 1. Investigation for parvovirus B19 of pregnant women exposed to rash illness.](adapted from the 2000 Public Health Laboratory Service Working Party on ‘Rash Diagnosis in Pregnancy and Rubella Screening’, subsequently reported.)
Management

Unlike VZV infection in pregnancy, no specific antiviral therapy or vaccine is available for hPV B19 infection. Accordingly, it is important that practising obstetricians are familiar with the diagnosis, treatment and prevention of hPV B19 infection.\textsuperscript{179} Frequent hand washing is effective in preventing disease transmission, and exclusion of pregnant women from contaminated workplaces, particularly school teachers, has been recommended in some countries.\textsuperscript{2} Management involves the investigation of women exposed to rash illness who are thought to be at risk of parvovirus B19 infection and surveillance of confirmed parvovirus B19 infection in pregnancy.\textsuperscript{142}

Fetal surveillance

Following acute infection with hPV B19 in the first trimester of pregnancy, nuchal translucency measurements and ductus venosus Doppler velocimetry findings are helpful indicators of the presence of severe fetal anaemia.\textsuperscript{180} After confirmation of maternal hPV B19 infection in the first 20 weeks of gestation, fetal surveillance should be initiated no later than 4 weeks after the onset of illness or estimate of seroconversion. If the ultrasound findings are suggestive of hydrops fetalis, the mother should be referred to a tertiary referral centre. If no fetal abnormality is detected, the ultrasound should be repeated at intervals of 1–2 weeks. If there is no fetal abnormality at or later than 30 weeks of gestation, the mother can be reassured that there is unlikely to be any adverse sequelae from the hPV B19 infection.\textsuperscript{142}

Fetal therapy

The mainstay of fetal therapy is delivery. However, even if the fetus is viable, if the degree of hydrops is severe and there are concerns over neonatal resuscitation and ventilation, delay of delivery and fetal therapy may still be more appropriate.\textsuperscript{193} As most fetal adverse effects occur remote from term, a life-saving procedure may require intrauterine red blood cell transfusion which can reduce the mortality rate.\textsuperscript{89,111,189–191,194–196} Frequently, one transfusion is sufficient,\textsuperscript{51} and the risk of fetal demise is higher in hydropic pregnancies managed expectantly relative to those with active intervention with intrauterine red blood cell transfu-
sion. In a large study carried out by the Society of Perinatal Obstetricians, 30% of fetuses with hPV B19 infection and hydrops who were not transfused died in utero, compared with only 6% of those who were transfused. Although the vast majority of studies demonstrate a significant reduction in mortality with intrauterine transfusion, in a study of intrauterine transfusions between 1997 and 2005 from Leiden in the Netherlands, 25 transfusions in 24 hydropic fetuses were performed with subsequent long-term follow-up. The diagnosis of intrauterine hPV B19 infection was based on the detection of hPV B19-specific IgM and/or hPV B19 DNA in fetal blood. Of 24 hydropic fetuses that underwent transfusion, approximately 30% died and, of the survivors, approximately 30% had delayed psychomotor development at long-term follow-up.

In contrast with other causes of fetal anaemia and hydrops, fetal complications caused by hPV B19 have the potential to resolve as the fetus mounts its own immune response. Surveillance might identify those babies which, although anaemic at the time of presentation, are in the recovery phase, under which circumstances heroic intervention might be inappropriate and unnecessarily life threatening. If other signs of fetal well-being are present, it might be possible to continue with conservative measurements.

Future research

Prevalence

Further research is needed to identify the potential burden of disease among women of child-bearing age who are recent immigrants to more developed western countries. Natural immunity in such women differs from that of their western counterparts, but the proportion who would be susceptible to infection in pregnancy remains unknown.

Treatment and prevention

There are no specific antiviral agents against hPV B19 infections. Further research is necessary to develop not just antiviral therapy, but also Igs as well as a vaccine. Effective vaccines are already available for animal parvoviruses. A specific human vaccine is necessary to prevent aplastic crisis in patients with underlying disorders, and pregnancy complication in seronegative women of child-bearing age. Although no hPV B19 vaccine is currently available, a phase I study showed that a recombinant vaccine against hPV B19 was safe and demonstrated immunogenicity in 24 subjects.

Unlike varicella zoster Ig administration for VZV infection, maternal IgG administration, fetal hPV B19 IgG-rich high-titre γ-globulin therapy and human monoclonal IgG antibody therapy have limited efficacy in the management of hPV B19 infection in pregnancy, and further evaluation is necessary. In one pregnant woman infected with hPV B19, high-dose intravenous γ-globulin was used in placent al exchange transfusion, and IgG monoclonal antibodies with potent neutralising activity have been generated from individuals with high serum titres against hPV B19. It is possible that these antibodies may provide immunotherapy in those chronically infected or in pregnant women with acute infection.

Diagnosis

Despite the use of combinations of diagnostic methods, it is difficult to discriminate between acute, recent and persistent hPV B19 infection, and further research is needed in this area. In parvovirus B19 PCR-positive/IgM-negative pregnant women, measurement of parvovirus B19 antibody avidity and epitome-type specificity may help to identify acute infection versus previous infection without invasive techniques. Avidity testing is not widely available, but might be useful if maternal IgM antibodies are undetectable at the time of fetal sampling for nonimmune hydrops. In a study to evaluate the diagnostic value of supplementary molecular or serological assays following maternal hPV B19 infection at the time of hPV B19-induced fetal hydrops, B19 DNA in maternal blood showed the best diagnostic sensitivity for the identification of hPV B19 infection. However, a supplementary measure of IgG avidity improved the precision of diagnosis and the management of pregnant women infected by hPV B19. This requires further evaluation. Strict protocols for invasive testing should also be tested against standardised ultrasound and Doppler criteria to evaluate between centres whether or not invasive testing is beneficial.

Fetal therapy

Because of contradicting evidence between some studies on the use of intrauterine transfusion, indications for intrauterine transfusion should be standardised. Such interventions may need to be centralised to specific tertiary referral centres to carry out research which will address the particular problems of fetal anaemia and hydrops directly attributable to hPV B19 infection, rather than having these combined with other causes. Following such interventions, research follow-up should be long term to detect any neurodevelopmental disability.

Conclusion

hPV B19 infection during pregnancy is common. Approximately 30–50% of pregnant women are nonimmune to the virus, and this is of particular importance during epidemic years, which occur in a 3–6-year cycle. Vertical transmission to the fetus occurs in approximately 30% of infected pregnant women, although most neonates are born healthy. Although the maternal symptoms are usually transient, the
feto-placental effects of inflammation and red blood cell precursor destruction can lead to placentitis and fetal complications, such as hepatitis, myocarditis, hypoalbuminemia, severe anaemia, cardiac failure, fetal hydrops and fetal death. Accordingly, hpV B19 should be considered in any case of nonimmune hydrops. Fetal surveillance using ultrasound and Doppler to detect signs of fetal anaemia and cardiac failure, and intervention by intrauterine red blood cell transfusion, can be life saving for the fetus. In general, children having successfully survived intrauterine transfusion for hpV B19-induced fetal anaemia and hydrops fetalis have a good neurodevelopmental prognosis. Nevertheless, albeit in one small study, death and neurodevelopmental handicap in hydropic fetuses that required intrauterine red blood cell transfusion reached approximately 30%. Data concerning the relationship between the severity of the disease and viral load in maternal peripheral blood, umbilical cord blood and amniotic fluid, as well as in placental and extraplacental tissue, may contribute to the prediction of short-term and long-term fetal outcome. Diagnosis is mainly by serology and PCR, but more discriminatory diagnostic tests are essential to differentiate between acute, recent and persistent hpV B19 disease. Finally, the development of an effective vaccine, as well as treatment options such as antiviral therapy and Igs, is necessary.

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None.

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All authors have contributed.

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