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Review article

Parvovirus B19 infection in human pregnancy

RF Lamont,[a,b] JD Sobel,[c] E Vaisbuch,[a,b] JP Kusanovic,[a,b] S Mazaki-Tovi,[a,b] SK Kim,[a] N Uldbjerg,[a] R Romero[a,b,d]

[a] Perinatology Research Branch, NICHD/NIH/DHHS, Bethesda, MD and Detroit, MI, USA [b] Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI, USA [c] Department of Infectious Diseases, Wayne State University School of Medicine, Detroit, MI, USA [d] Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA
Correspondence: Prof. RF Lamont and Dr R Romero, Perinatology Research Branch, NICHD/NIH/DHHS, Wayne State University/Hutzel Women's Hospital, 3990 John R, Box 4, Detroit, MI 48201, USA. Emails: rlamont@med.wayne.edu and prbchiefstaff@med.wayne.edu

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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.

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Introduction

Human parvovirus (hPV) B19 infection is the most common viral agent associated with rashes in school-aged children.[1] 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%.[2] 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.* [3]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'.

Taxonomy and description

Parvovirus B19 is a single-stranded DNA, nonenveloped virus from the family *Parvoviridae* and the genus *Erythrovirus*, which is one of the smallest to infect mammalian tissues, hence its name (*parvus*, Latin: adj. = small).[5] The genus *Erythrovirus* is extremely species specific, causing life-threatening diseases in both cats and dogs; yet, in humans, only hPV B19 and some adenoviruses cause disease.[6] In comparison with other viruses, hPV B19 is physically and genetically quite stable with only a few mutations,[7] and causes pathology through the blocking of erythropoiesis and the induction of inflammation.[8] Other genotypes have been described, but their identification, virulence, transmission and ability to cause disease remain poorly elucidated.[9–12] The morphology, genetics, capsid proteins, culture and viral life cycle have been reviewed elsewhere.[13]

Epidemiology

The transmission of hPV B19 may be by respiratory droplets, transfusion of blood and blood products, or to the fetus by transplacental passage.[14–16] In healthy volunteers, serum and respiratory secretions become positive for hPV B19 DNA during the prodromal phase, 5–10 days after intranasal inoculation.[16,17] Transmission rarely occurs during transfusion with single-donor blood products, but is more common during treatment with blood concentrates.[4,18–22] Similarly, transmission may also occur through bone marrow or organ transplantation. Tattooing as a source has been suspected,[23] as well as transmission in medical research laboratories,[23–27] although this may not be of relevance to hPV B19 infection in pregnancy in the 21st century.

hPV B19 infection occurs worldwide,[28,29] but seroprevalence rates vary according to age and geography.[30–36] Approximately 15% of preschool children, 50% of adults and 85% of the elderly are seropositive.[25–27,37,38] The prevalence may be higher in developing countries and lower in isolated communities.[39–41] 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,[30,31] with a higher prevalence in temperate climes around late winter to early spring[25] [similar to varicella zoster virus (VZV) infection]. Epidemics occur and tend to follow a 3–6-year cycle[25,31,42–45] during which time children and their domestic contacts, as well as school or nursery workers, are at greater risk.[14,15,26,46–48] 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.[34,47–50] Nosocomial transmission in adult, paediatric and neonatal units also becomes important during outbreaks.[51,52]

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.[14,15] hPV B19 infection has been associated with fetal loss, acute arthritis and arthralgias, as well as chronic anaemia, in immunodeficient individuals.[24,53–62] 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.[26] Serum specimens are usually negative by 7 days after the onset of illness,[63] suggesting that patients with EI are probably beyond the period of greatest infectivity.[64] 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.[16,17] 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.[26] Peripheral polyarthropathy of the hands, wrists and knees is also characteristic[55,56,65] 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.[16,17] Pregnant women suffering from existing haematological conditions, such as sickle-cell disease, are more likely to develop transient aplastic crisis.[24,66–74] 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.[57–59,75,76]

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.[41,66,77–82] 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.[2,83] Up to 50% of infected pregnant

women may be asymptomatic,[84] but vertical transmission can still occur, albeit that fetal manifestations may not become evident for weeks or even months.[50,85–87] 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.[88] Hydrops fetalis associated with hPV B19 infection was first reported in 1984.[53] If pregnant women develop hPV B19 infection, there is a 30% chance of fetal transmission.[21,50,89] During epidemics, there is a greater risk of vertical transmission and a 5–10% rate of fetal loss in cases of fetal infection.[89,90] In the majority of cases of hPV B19 infection in pregnancy, the fetus is unaffected;[53,54,91–97] however, infection may result in severe fetal anaemia, generalised oedema, congestive heart failure, myocarditis and hydropic or nonhydropic fetal death.[21,27,53,54,98–101] The unpredictability of fetal infection is demonstrated by cases of discordant hPV B19 infection within twin pregnancies.[102–106] hPV B19 infection is thought to account for 8–20% of nonimmune fetal hydrops,[50,53,92,107] 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%,[79,82,89,108–110] and the peak incidence is between 17 and 24 weeks depending on the gestational age at infection.[111–114] Some of the parvovirus strains that are pathogenic in animals are teratogens,[115] and congenital malformations have been reported in humans.[116–118] 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.[13,90,119] 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.[66,89,98,111,120–123] The risk of fetal death is a function of gestational age at infection.[124] Approximately 3% of first-trimester spontaneous abortions may be caused by hPV B19 infection,[125] 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.[64] Spontaneous fetal resolution appears to occur, as healthy neonates have been born with specific hPV B19 IgM in umbilical cord blood.[78] 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.[21,25,53,92–94,117,126–129]

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,[130] 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.[131,132] Erythropoiesis is inhibited because of the ability of the virus to produce cytotoxic apoptosis and lysis of erythroid precursors.[133] The presence of the virus in erythroid precursors is evident by the typical intracellular inclusions seen in pathological specimens.[134] In the second trimester, the fetus is at significantly increased risk of infection and tissue damage from hPV B19 than in the third trimester.[132] 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.[135] In the second trimester, haematopoiesis 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.[117] These unique circumstances make the fetus especially vulnerable to any insult with respect to erythropoiesis.[136] Severe anaemia, hPV B19 viraemia and cytologic change in erythroid precursor cells have been described in fetuses immediately antemortem.[93,94,127] 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.[131,137] Direct damage to fetal myocardial cells by hPV B19 has been reported,[96] and 15% of all myocardial biopsies obtained from dead fetuses diagnosed with perinatal cardiomyopathy were associated with hPV B19 inflammation.[138] 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.[139] Another significant organ affected by the inflammatory response to hPV B19 infection is the placenta.[99,131,140,141] Placentitis may cause placental dysfunction and adverse fetal outcome in the absence of fetal infection.[72] In addition, the same degree of feto-placental 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.[142] 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,[143–146] particularly in pregnant women.[142] Commercially available assays for parvovirus B19 have high variation of sensitivity and specificity,[147–149] which may contribute to the misdiagnosis of hPV B19 infection as measles or rubella.[143,144] 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% (Ideia; DAKOT A/S, Copenhagen, Denmark) and 70.1% (Parvoscan; EURO Diagnostica, Malmö, Sweden).[147]

As a fastidious virus, hPV B19 cannot be grown in continuous cell lines. As a result, viral culture is not a diagnostic option.[150–152] Diagnosis requires a multi-method approach using mainly serology[31,37,147,153,154] and PCR techniques.[98,155–163] Histopathology[4,21,67,95,164] and immunohistochemistry have also been employed, but have little use in routine practice.[8,96,156,165–168] hPV B19 IgM is usually detectable 10–12 days after infection and can persist in the circulation for 3–4 months or longer,[23,169] and circulating IgG persists lifelong with slowly decreasing titres unless boosted by subsequent viral exposure. In pregnant women and the immunosupressed, serological responses are less characteristic.[170,171] 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.[158,172–175] Currently, quantitative serum and tissue titres of hPV B19 DNA are helpful for guiding clinicians in therapeutic options,[171,176–178] 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.[156] 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.[13]

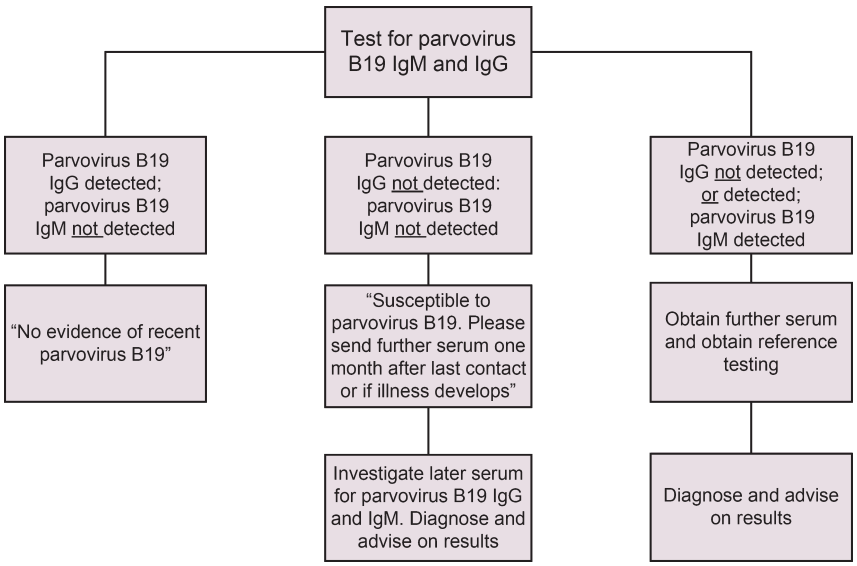

Figure 1. Investigation for parvovirus B19 of pregnant women exposed to rash illness. [Adapted from the 2000 Public Health Laboratory Service Working Party on 'Rash Diagnosis in Pregnancy and Rubella Screening', subsequently reported.[142]]

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.[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.[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.[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.[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.[142]

In those fetuses considered to be at high risk of disease, weekly Doppler examination of the middle cerebral artery peak systolic velocity and ductus venosus velocity should be performed, which are measures of the increased cardiac output and decreased plasma viscosity associated with fetal anaemia.[179–186] The early ultrasound signs of cardiac failure are cardiomegaly and ascites,[53,126,187] which may be a manifestation of hepatitis and hypoalbuminaemia as much as cardiac failure from anaemia.[53] The risk of fetal death persists for some months after maternal infection and may occur without hydrops or maternal symptoms.[66,87,122,188] Fetal thrombocytopenia is also associated with hPV B19,[189–192] such that many feto-maternal medicine units find it prudent to have compatible platelets available at the time of red blood cell transfusion. An algorithm for the management of confirmed hPV B19 infection in pregnancy is shown in Figure 2.

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.[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.[89,111,189–191,194–196] Frequently, one transfusion is sufficient,[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-

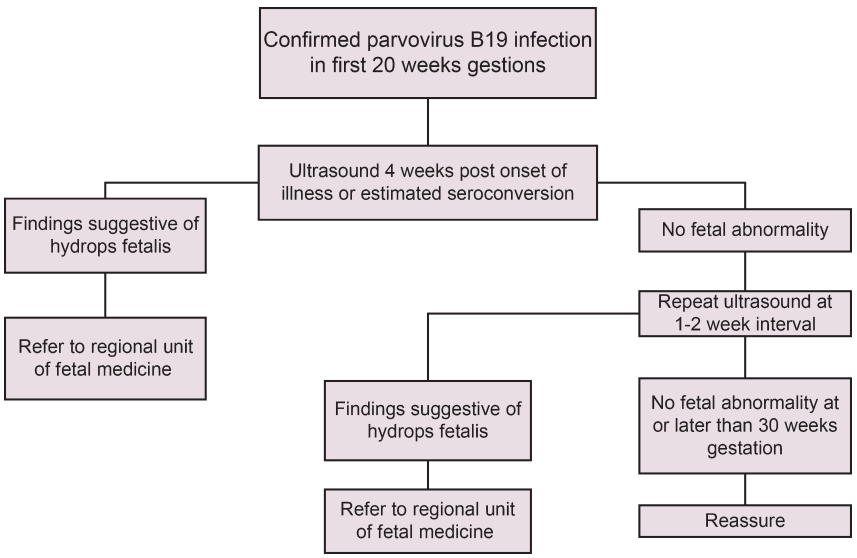

Figure 2. Management of confirmed parvovirus B19 infection in pregnancy. [Adapted from the 2000 Public Health Laboratory Service Working Party on 'Rash Diagnosis in Pregnancy and Rubella Screening', subsequently reported.[142]]

sion.[197] 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.[198] 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.[199] 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.[142]

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.[200] 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.[201]

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.[202–205] In one pregnant woman infected with hPV B19, high-dose intravenous γ-globulin was used in placental exchange transfusion,[202] 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.[204]

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.[120,206] 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.[206] 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, hypoalbuminaemia, 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.

Disclosure of interest
None.

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All authors have contributed.

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References

1 Centers for Disease Control and Prevention Rashes among schoolchildren – 14 states, October 4, 2001–February 27, 2002. *J Am Med Assoc* 2002;287:1389–91.
2 Valeur-Jensen AK, Pedersen CB, Westergaard T, Jensen IP, Lebech M, Andersen PK, *et al.* Risk factors for parvovirus B19 infection in pregnancy. *J Am Med Assoc* 1999;281:1099–105.
3 Dukes C. On the confusion of two different diseases under the name rubella (rose-rash). *Lancet* 1900;156:89–95.
4 Cossart YE, Field AM, Cant B, Widdows D. Parvovirus-like particles in human sera. *Lancet* 1975;1:72–3.
5 Cotmore SF, Tattersall P. Characterization and molecular cloning of a human parvovirus genome. *Science* 1984;226:1161–5.
6 Siegl G, Bates RC, Berns KI, Carter BJ, Kelly DC, Kurstak E, *et al.* Characteristics and taxonomy of Parvoviridae. *Intervirology* 1985;23:61–73.
7 Gallinella G, Venturoli S, Manaresi E, Musiani M, Zerbini M. B19 virus genome diversity: epidemiological and clinical correlations. *J Clin Virol* 2003;28:1–13.
8 Ozawa K, Kurtzman G, Young N. Replication of the B19 parvovirus in human bone marrow cell cultures. *Science* 1986;233:883–6.
9 Servant A, Laperche S, Lallemand F, Marinho V, De Saint MG, Meritet JF, *et al.* Genetic diversity within human erythroviruses: identification of three genotypes. *J Virol* 2002;76:9124–34.
10 Jones MS, Kapoor A, Lukashov VV, Simmonds P, Hecht F, Delwart E. New DNA viruses identified in patients with acute viral infection syndrome. *J Virol* 2005;79:8230–6.
11 Simmonds P, Douglas J, Bestetti G, Longhi E, Antinori S, Parravicini C, *et al.* A third genotype of the human parvovirus PARV4 in sub-Saharan Africa. *J Gen Virol* 2008;89:2299–302.
12 Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B. Cloning of a human parvovirus by molecular screening of respiratory tract samples. *Proc Natl Acad Sci USA* 2005;102:12891–6.
13 Ergaz Z, Ornoy A. Parvovirus B19 in pregnancy. *Reprod Toxicol* 2006;21:421–35.
14 Plummer FA, Hammond GW, Forward K, Sekla L, Thompson LM, Jones SE, *et al.* An erythema infectiosum-like illness caused by human parvovirus infection. *N Engl J Med* 1985;313:74–9.
15 Chorba T, Coccia P, Holman RC, Tattersall P, Anderson LJ, Sudman J, *et al.* The role of parvovirus B19 in aplastic crisis and erythema infectiosum (fifth disease). *J Infect Dis* 1986;154:383–93.
16 Anderson MJ, Higgins PG, Davis LR, Willman JS, Jones SE, Kidd IM, *et al.* Experimental parvoviral infection in humans. *J Infect Dis* 1985;152:257–65.
17 Potter CG, Potter AC, Hatton CS, Chapel HM, Anderson MJ, Pattison JR, *et al.* Variation of erythroid and myeloid precursors in the marrow and peripheral blood of volunteer subjects infected with human parvovirus (B19). *J Clin Invest* 1987;79:1486–92.
18 Mortimer PP, Luban NL, Kelleher JF, Cohen BJ. Transmission of serum parvovirus-like virus by clotting-factor concentrates. *Lancet* 1983;2:482–4.
19 Bartolomei CO, Azzi A, Morfini M, Fanci R, Rossi FP. Human parvovirus infection in haemophiliacs first infused with treated clotting factor concentrates. *J Med Virol* 1988;25:165–70.
20 Broliden K. Parvovirus B19 infection in pediatric solid-organ and bone marrow transplantation. *Pediatr Transplant* 2001;5:320–30.
21 Anand A, Gray ES, Brown T, Clewley JP, Cohen BJ. Human parvovirus infection in pregnancy and hydrops fetalis. *N Engl J Med* 1987;316:183–6.
22 Jordan J, Tiangco B, Kiss J, Koch W. Human parvovirus B19: prevalence of viral DNA in volunteer blood donors and clinical outcomes of transfusion recipients. *Vox Sang* 1998;75:97–102.
23 Shneerson JM, Mortimer PP, Vandervelde EM. Febrile illness due to a parvovirus. *Br Med J* 1980;280:1580.
24 Pattison JR, Jones SE, Hodgson J, Davis LR, White JM, Stroud CE, *et al.* Parvovirus infections and hypoplastic crisis in sickle-cell anaemia. *Lancet* 1981;1:664–5.
25 Anderson MJ, Cohen BJ, Schwarz T, Roggendorf M, Deinhardt F. Human parvovirus B19 infections in United Kingdom 1984–86. *Lancet* 1987;329:738–9.

26 Anderson LJ. Role of parvovirus B19 in human disease. *Pediatr Infect Dis J* 1987;6:711–8.

27 Mortimer PP, Cohen BJ, Buckley MM, Cradock-Watson JE, Ridehalgh MK, Burkhardt F, *et al.* Human parvovirus and the fetus. *Lancet* 1985;2:1012.

28 Courouce AM, Ferchal F, Morinet F, Muller A, Drouet J, Soulier JP, *et al.* Human parvovirus infections in France. *Lancet* 1984;1:160.

29 Okochi K, Mori R, Miyazaki M, Cohen BJ, Mortimer PP. Nakatani antigen and human parvovirus (B19). *Lancet* 1984;1:160–1.

30 Enders M, Weidner A, Enders G. Current epidemiological aspects of human parvovirus B19 infection during pregnancy and childhood in the western part of Germany. *Epidemiol Infect* 2007; 135:563–9.

31 Kelly HA, Siebert D, Hammond R, Leydon J, Kiely P, Maskill W. The age-specific prevalence of human parvovirus immunity in Victoria, Australia compared with other parts of the world. *Epidemiol Infect* 2000;124:449–57.

32 Nicolay N, Cotter S. Clinical and epidemiological aspects of parvovirus B19 infections in Ireland, January 1996–June 2008. *Euro Surveill* 2009;14:1–5.

33 Mossong J, Hens N, Friederichs V, Davidkin I, Broman M, Litwinska B, *et al.* Parvovirus B19 infection in five European countries: seroepidemiology, force of infection and maternal risk of infection. *Epidemiol Infect* 2008;136:1059–68.

34 Stelma FF, Smismans A, Goossens VJ, Bruggeman CA, Hoebe CJ. Occupational risk of human cytomegalovirus and parvovirus B19 infection in female day care personnel in the Netherlands; a study based on seroprevalence. *Eur J Clin Microbiol Infect Dis* 2009; 28:393–7.

35 Elnifro E, Nisha AK, Almabsoot M, Daeki A, Mujber N, Muscat J. Seroprevalence of parvovirus B19 among pregnant women in Tripoli, Libya. *J Infect Dev Ctries* 2009;3:218–20.

36 Nascimento JP, Buckley MM, Brown KE, Cohen BJ. The prevalence of antibody to human parvovirus B19 in Rio de Janeiro, Brazil. *Rev Inst Med Trop Sao Paulo* 1990;32:41–5.

37 Anderson LJ, Tsou C, Parker RA, Chorba TL, Wulff H, Tattersall P, *et al.* Detection of antibodies and antigens of human parvovirus B19 by enzyme-linked immunosorbent assay. *J Clin Microbiol* 1986;24:522–6.

38 Cohen BJ, Buckley MM. The prevalence of antibody to human parvovirus B19 in England and Wales. *J Med Microbiol* 1988;25: 151–3.

39 Schwarz TF, Gurtler LG, Zoulek G, Deinhardt F, Roggendorf M. Seroprevalence of human parvovirus B19 infection in Sao Tome and Principe, Malawi and Mascarene Islands. *Zentralbl Bakteriol* 1989;271:231–6.

40 Tolfvenstam T, Enbom M, Ghebrekidan H, Ruden U, Linde A, Grandien M, *et al.* Seroprevalence of viral childhood infections in Eritrea. *J Clin Virol* 2000;16:49–54.

41 de Freitas RB, Wong D, Boswell F, de Miranda MF, Linhares AC, Shirley J, *et al.* Prevalence of human parvovirus (B19) and rubella virus infections in urban and remote rural areas in northern Brazil. *J Med Virol* 1990;32:203–8.

42 Goldstein AR, Anderson MJ, Serjeant GR. Parvovirus associated aplastic crisis in homozygous sickle cell disease. *Arch Dis Child* 1987;62:585–8.

43 Naides SJ. Erythema infectiosum (fifth disease) occurrence in Iowa. *Am J Public Health* 1988;78:1230–1.

44 Vyse AJ, Andrews NJ, Hesketh LM, Pebody R. The burden of parvovirus B19 infection in women of childbearing age in England and Wales. *Epidemiol Infect* 2007;135:1354–62.

45 Zaaijer HL, Koppelman MH, Farrington CP. Parvovirus B19 viraemia in Dutch blood donors. *Epidemiol Infect* 2004;132:1161–6.

46 Gilbert NL, Gyorkos TW, Beliveau C, Rahme E, Muecke C, Soto JC. Seroprevalence of parvovirus B19 infection in daycare educators. *Epidemiol Infect* 2005;133:299–304.

47 Anderson LJ, Gillespie SM, Torok TJ, Hurwitz ES, Tsou CJ, Gary GW. Risk of infection following exposures to human parvovirus B19. *Behring Inst Mitt* 1990;85:60–3.

48 Gillespie SM, Cartter ML, Asch S, Rokos JB, Gary GW, Tsou CJ, *et al.* Occupational risk of human parvovirus B19 infection for school and day-care personnel during an outbreak of erythema infectiosum. *J Am Med Assoc* 1990;263:2061–5.

49 Woolf AD, Campion GV, Chishick A, Wise S, Cohen BJ, Klouda PT, *et al.* Clinical manifestations of human parvovirus B19 in adults. *Arch Intern Med* 1989;149:1153–6.

50 Yaegashi N, Niinuma T, Chisaka H, Watanabe T, Uehara S, Okamura K, *et al.* The incidence of, and factors leading to, parvovirus B19-related hydrops fetalis following maternal infection; report of 10 cases and meta-analysis. *J Infect* 1998;37:28–35.

51 Tolfvenstam T, Broliden K. Parvovirus B19 infection. *Semin Fetal Neonatal Med* 2009;14:218–21.

52 Evans JP, Rossiter MA, Kumaran TO, Marsh GW, Mortimer PP. Human parvovirus aplasia: case due to cross infection in a ward. *Br Med J (Clin Res Ed)* 1984;288:681.

53 Brown T, Anand A, Ritchie LD, Clewley JP, Reid TM. Intrauterine parvovirus infection associated with hydrops fetalis. *Lancet* 1984;2: 1033–4.

54 Knott PD, Welply GA, Anderson MJ. Serologically proved intrauterine infection with parvovirus. *Br Med J (Clin Res Ed)* 1984;289: 1660.

55 White DG, Woolf AD, Mortimer PP, Cohen BJ, Blake DR, Bacon PA. Human parvovirus arthropathy. *Lancet* 1985;1:419–21.

56 Reid DM, Reid TM, Brown T, Rennie JA, Eastmond CJ. Human parvovirus-associated arthritis: a clinical and laboratory description. *Lancet* 1985;1:422–5.

57 Van Horn DK, Mortimer PP, Young N, Hanson GR. Human parvovirus-associated red cell aplasia in the absence of underlying hemolytic anemia. *Am J Pediatr Hematol Oncol* 1986;8:235–9.

58 Kurtzman GJ, Ozawa K, Cohen B, Hanson G, Oseas R, Young NS. Chronic bone marrow failure due to persistent B19 parvovirus infection. *N Engl J Med* 1987;317:287–94.

59 Coulombel L, Morinet F, Mielot F, Tchernia G, Knisely AS, Shlossman P, *et al.* Parvovirus infection, leukaemia, and immunodeficiency. *Lancet* 1989;333:101–2.

60 Isa A, Kasprowicz V, Norbeck O, Loughry A, Jeffery K, Broliden K, *et al.* Prolonged activation of virus-specific CD8+ T cells after acute B19 infection. *PLoS Med* 2005;2:e343.

61 Zerbini M, Musiani M, Venturoli S, Gallinella G, Gibellini D, Gentilomi G, *et al.* Different syndromes associated with B19 parvovirus viraemia in paediatric patients: report of four cases. *Eur J Pediatr* 1992;151:815–7.

62 Naides SJ. Rheumatic manifestations of parvovirus B19 infection. *Rheum Dis Clin North Am* 1998;24:375–401.

63 Saarinen UM, Chorba TL, Tattersall P, Young NS, Anderson LJ, Palmer E, *et al.* Human parvovirus B19-induced epidemic acute red cell aplasia in patients with hereditary hemolytic anemia. *Blood* 1986;67:1411–7.

64 Centers for Disease Control. Risks associated with human parvovirus B19 infection. *MMWR Morb Mortal Wkly Rep* 1989;38:81–7.

65 Ager EA, Chin TD, Poland JD. Epidemic erythema infectiosum. *N Engl J Med* 1966;275:1326–31.

66 Beigi RH, Wiesenfeld HC, Landers DV, Simhan HN. High rate of severe fetal outcomes associated with maternal parvovirus b19 infection in pregnancy. *Infect Dis Obstet Gynecol* 2008;2008: 524–601.

67 Young N. Hematologic and hematopoietic consequences of B19 parvovirus infection. *Semin Hematol* 1988;25:159–72.

68 Anderson MJ, Lewis E, Kidd IM, Hall SM, Cohen BJ. An outbreak of erythema infectiosum associated with human parvovirus infection. *J Hyg (Lond)* 1984;93:85–93.

69 Anderson MJ, Jones SE, Fisher-Hoch SP, Lewis E, Hall SM, Bartlett CLR, *et al.* Human parvovirus, the cause of erythema infectiosum (fifth disease)? *Lancet* 1983;321:1378.

70 Serjeant GR, Goldstein AR. B19 virus infection and the aplastic crisis. In: Pattison JR, editor. *Parvoviruses and Human Disease*. Boca Raton, FL: CRC Press, 2010. pp. 85–92.

71 Young NS, Brown KE. Parvovirus B19. *N Engl J Med* 2004;350: 586–97.

72 Broliden K, Tolfvenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. *J Intern Med* 2006;260:285–304.

73 Silver RM, Varner MW, Reddy U, Goldenberg R, Pinar H, Conway D, *et al.* Work-up of stillbirth: a review of the evidence. *Am J Obstet Gynecol* 2007;196:433–44.

74 Goldenberg RL, Thompson C. The infectious origins of stillbirth. *Am J Obstet Gynecol* 2003;189:861–73.

75 Smith MA, Shah NR, Lobel JS, Cera PJ, Gary GW, Anderson LJ. Severe anemia caused by human parvovirus in a leukemia patient on maintenance chemotherapy. *Clin Pediatr (Phila)* 1988;27:383–6.

76 Kurtzman GJ, Cohen B, Meyers P, Amunullah A, Young NS. Persistent B19 parvovirus infection as a cause of severe chronic anaemia in children with acute lymphocytic leukaemia. *Lancet* 1988;2: 1159–62.

77 Kerr JR, O'Neill HJ, Coyle PV, Thompson W. An outbreak of parvovirus B19 infection; a study of clinical manifestations and the incidence of fetal loss. *Ir J Med Sci* 1994;163:65–7.

78 Kinney JS, Anderson LJ, Farrar J, Strikas RA, Kumar ML, Kliegman RM, *et al.* Risk of adverse outcomes of pregnancy after human parvovirus B19 infection. *J Infect Dis* 1988;157:663–7.

79 Harger JH, Adler SP, Koch WC, Harger GF. Prospective evaluation of 618 pregnant women exposed to parvovirus B19: risks and symptoms. *Obstet Gynecol* 1998;91:413–20.

80 Jensen IP, Thorsen P, Jeune B, Moller BR, Vestergaard BF. An epidemic of parvovirus B19 in a population of 3,596 pregnant women: a study of sociodemographic and medical risk factors. *BJOG* 2000;107:637–43.

81 van Gessel PH, Gaytant MA, Vossen AC, Galama JM, Ursem NT, Steegers EA, *et al.* Incidence of parvovirus B19 infection among an unselected population of pregnant women in the Netherlands: a prospective study. *Eur J Obstet Gynecol Reprod Biol* 2006;128:46–9.

82 Yaegashi N, Niinuma T, Chisaka H, Uehara S, Okamura K, Shinkawa O, *et al.* Serologic study of human parvovirus B19 infection in pregnancy in Japan. *J Infect* 1999;38:30–5.

83 Koch WC, Adler SP. Human parvovirus B19 infections in women of childbearing age and within families. *Pediatr Infect Dis J* 1989;8: 83–7.

84 Chisaka H, Ito K, Niikura H, Sugawara J, Takano T, Murakami T, *et al.* Clinical manifestations and outcomes of parvovirus B19 infection during pregnancy in Japan. *Tohoku J Exp Med* 2006;209: 277–83.

85 Nunoue T, Kusuhara K, Hara T. Human fetal infection with parvovirus B19: maternal infection time in gestation, viral persistence and fetal prognosis. *Pediatr Infect Dis J* 2002;21:1133–6.

86 Nyman M, Skjoldebrand-Sparre L, Broliden K. Non-hydropic intrauterine fetal death more than 5 months after primary parvovirus B19 infection. *J Perinat Med* 2005;33:176–8.

87 Sheikh AU, Ernest JM, O'Shea M. Long-term outcome in fetal hydrops from parvovirus B19 infection. *Am J Obstet Gynecol* 1992; 167:337–41.

88 Brennand J, Cameron A. Fetal anaemia: diagnosis and management 1. *Best Pract Res Clin Obstet Gynaecol* 2008;22:15–29.

89 Miller E, Fairley CK, Cohen BJ, Seng C. Immediate and long term outcome of human parvovirus B19 infection in pregnancy. *Br J Obstet Gynaecol* 1998;105:174–8.

90 Prospective study of human parvovirus (B19) infection in pregnancy. Public Health Laboratory Service Working Party on Fifth Disease. *Br Med J* 1990;300:1166–70.

91 Anderson LJ, Hurwitz ES. Human parvovirus B19 and pregnancy. *Clin Perinatol* 1988;15:273–86.

92 Porter HJ, Khong TY, Evans MF, Chan VT, Fleming KA. Parvovirus as a cause of hydrops fetalis: detection by in situ DNA hybridisation. *J Clin Pathol* 1988;41:381–3.

93 Anderson MJ, Khousam MN, Maxwell DJ, Gould SJ, Happerfield LC, Smith WJ. Human parvovirus B19 and hydrops fetalis. *Lancet* 1988;1:535.

94 Franciosi RA, Tattersall P. Fetal infection with human parvovirus B19. *Hum Pathol* 1988;19:489–91.

95 Caul EO, Usher MJ, Burton PA. Intrauterine infection with human parvovirus B19: a light and electron microscopy study. *J Med Virol* 1988;24:55–66.

96 Porter HJ, Quantrill AM, Fleming KA. B19 parvovirus infection of myocardial cells. *Lancet* 1988;1:535–6.

97 Sarfraz AA, Samuelsen SO, Bruu AL, Jenum PA, Eskild A. Maternal human parvovirus B19 infection and the risk of fetal death and low birthweight: a case–control study within 35 940 pregnant women. *BJOG* 2009;116:1492–8.

98 Tolfvenstam T, Papadogiannakis N, Norbeck O, Petersson K, Broliden K. Frequency of human parvovirus B19 infection in intrauterine fetal death. *Lancet* 2001;357:1494–7.

99 Morey AL, Keeling JW, Porter HJ, Fleming KA. Clinical and histopathological features of parvovirus B19 infection in the human fetus. *Br J Obstet Gynaecol* 1992;99:566–74.

100 Komischke K, Searle K, Enders G. Maternal serum alpha-fetoprotein and human chorionic gonadotropin in pregnant women with acute parvovirus B19 infection with and without fetal complications. *Prenat Diagn* 1997;17:1039–46.

101 O'Malley A, Barry-Kinsella C, Hughes C, Kelehan P, Devaney D, Mooney E, *et al.* Parvovirus infects cardiac myocytes in hydrops fetalis. *Pediatr Dev Pathol* 2003;6:414–20.

102 Zerbini M, Musiani M, Gentilomi G, Venturoli S, Gallinella G, Gibellini D, *et al.* Symptomatic parvovirus B19 infection of one fetus in a twin pregnancy. *Clin Infect Dis* 1993;17:262–3.

103 Pustilnik TB, Cohen AW. Parvovirus B19 infection in a twin pregnancy. *Obstet Gynecol* 1994;83:834–6.

104 Foster RT Sr, Allen SR. Differential transmission of parvovirus B19 in a twin gestation: a case report. *Twin Res* 2004;7:412–4.

105 Dickinson JE, Keil AD, Charles AK. Discordant fetal infection for parvovirus B19 in a dichorionic twin pregnancy. *Twin Res Hum Genet* 2006;9:456–9.

106 Bekhit MT, Greenwood PA, Warren R, Aarons E, Jauniaux E. In utero treatment of severe fetal anaemia due to parvovirus B19 in one fetus in a twin pregnancy – a case report and literature review. *Fetal Diagn Ther* 2009;25:153–7.

107 Jordan JA. Identification of human parvovirus B19 infection in idiopathic nonimmune hydrops fetalis. *Am J Obstet Gynecol* 1996;174: 37–42.

108 Gratacos E, Torres PJ, Vidal J, Antolin E, Costa J, Jimenez de Anta MT, *et al.* The incidence of human parvovirus B19 infection during pregnancy and its impact on perinatal outcome. *J Infect Dis* 1995;171:1360–3.

109 Rodis JF, Quinn DL, Gary GW Jr, Anderson LJ, Rosengren S, Cartter ML, *et al.* Management and outcomes of pregnancies complicated

by human B19 parvovirus infection: a prospective study. *Am J Obstet Gynecol* 1990;163:1168–71.
110 Koch WC, Harger JH, Barnstein B, Adler SP. Serologic and virologic evidence for frequent intrauterine transmission of human parvovirus B19 with a primary maternal infection during pregnancy. *Pediatr Infect Dis J* 1998;17:489–94.
111 Enders M, Weidner A, Zoellner I, Searle K, Enders G. Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases. *Prenat Diagn* 2004;24:513–8.
112 Cubel RC, Garcia AG, Pegado CS, Ramos HI, Fonseca ME, Clewley JP, *et al.* Human parvovirus B19 infection and hydrops fetalis in Rio de Janeiro, Brazil. *Mem Inst Oswaldo Cruz* 1996;91:147–51.
113 Oliveira SA, Camacho LA, Pereira AC, Faillace TF, Setubal S, Nascimento JP. Clinical and epidemiological aspects of human parvovirus B19 infection in an urban area in Brazil (Niteroi city area, State of Rio de Janeiro, Brazil). *Mem Inst Oswaldo Cruz* 2002;97:965–70.
114 Torok TJ. Human parvovirus B19 infections in pregnancy. *Pediatr Infect Dis J* 1990;9:772–6.
115 Siegel G. Biology and pathogenicity of autonomous parvoviruses. In: Berns KI, editor. *The Parvoviruses*. New York: Plenum Press, 1984. pp. 297–362.
116 Weiland HT, Vermey-Keers C, Salimans MMM, Fleuren GJ, Verwey RA, Anderson MJ. Parvovirus B19 associated with fetal abnormality. *Lancet* 1987;329:682–3.
117 Rodis JF, Hovick TJ Jr, Quinn DL, Rosengren SS, Tattersall P. Human parvovirus infection in pregnancy. *Obstet Gynecol* 1988;72:733–8.
118 Hartwig NG, Vermeij-Keers C, Van Elsacker-Niele AM, Fleuren GJ. Embryonic malformations in a case of intrauterine parvovirus B19 infection. *Teratology* 1989;39:295–302.
119 Guidozzi F, Ballot D, Rothberg AD. Human B19 parvovirus infection in an obstetric population. A prospective study determining fetal outcome. *J Reprod Med* 1994;39:36–8.
120 Riipinen A, Vaisanen E, Nuutila M, Sallmen M, Karikoski R, Lindbohm ML, *et al.* Parvovirus B19 infection in fetal deaths. *Clin Infect Dis* 2008;47:1519–25.
121 Norbeck O, Papadogiannakis N, Petersson K, Hirbod T, Broliden K, Tolfvenstam T. Revised clinical presentation of parvovirus B19-associated intrauterine fetal death. *Clin Infect Dis* 2002;35:1032–8.
122 Skjoldebrand-Sparre L, Tolfvenstam T, Papadogiannakis N, Wahren B, Broliden K, Nyman M. Parvovirus B19 infection: association with third-trimester intrauterine fetal death. *BJOG* 2000;107:476–80.
123 Syridou G, Spanakis N, Konstantinidou A, Piperaki ET, Kafetzis D, Patsouris E, *et al.* Detection of cytomegalovirus, parvovirus B19 and herpes simplex viruses in cases of intrauterine fetal death: association with pathological findings. *J Med Virol* 2008;80:1776–82.
124 Hall SM, McCandlish AP. Human parvovirus (B19) infection. *Br J Gen Pract* 1991;41:86.
125 Nyman M, Tolfvenstam T, Petersson K, Krassny C, Skjoldebrand-Sparre L, Broliden K. Detection of human parvovirus B19 infection in first-trimester fetal loss. *Obstet Gynecol* 2002;99:795–8.
126 Bond PR, Caul EO, Usher J, Cohen BJ, Clewley JP, Field AM, *et al.* Intrauterine infection with human parvovirus. *Lancet* 1986;327:448–9.
127 Carrington D, Gilmore DH, Whittle MJ, Aitken D, Gibson AA, Patrick WJ, *et al.* Maternal serum alpha-fetoprotein – a marker of fetal aplastic crisis during intrauterine human parvovirus infection. *Lancet* 1987;1:433–5.
128 Woernle CH, Anderson LJ, Tattersall P, Davison JM. Human parvovirus B19 infection during pregnancy. *J Infect Dis* 1987;156:17–20.
129 Maeda H, Shimokawa H, Satoh S, Nakano H, Nunoue T. Nonimmunologic hydrops fetalis resulting from intrauterine human parvovirus B-19 infection: report of two cases. *Obstet Gynecol* 1988;72:482–5.
130 Young N, Harrison M, Moore J, Mortimer P, Humphries RK. Direct demonstration of the human parvovirus in erythroid progenitor cells infected in vitro. *J Clin Invest* 1984;74:2024–32.
131 Garcia AG, Pegado CS, Cubel RC, Fonseca ME, Sloboda I, Nascimento JP. Feto-placentary pathology in human parvovirus B19 infection. *Rev Inst Med Trop Sao Paulo* 1998;40:145–50.
132 Chisaka H, Morita E, Yaegashi N, Sugamura K. Parvovirus B19 and the pathogenesis of anaemia. *Rev Med Virol* 2003;13:347–59.
133 Corcoran A, Doyle S. Advances in the biology, diagnosis and host–pathogen interactions of parvovirus B19. *J Med Microbiol* 2004;53:459–75.
134 Bittencourt AL, Garcia AG. Pathogenesis and pathology of hematogenous infections of the fetus and newborn. *Pediatr Pathol Mol Med* 2002;21:353–99.
135 Jordan JA, DeLoia JA. Globoside expression within the human placenta. *Placenta* 1999;20:103–8.
136 Berry PJ, Gray ES, Porter HJ, Burton PA. Parvovirus infection of the human fetus and newborn. *Semin Diagn Pathol* 1992;9:4–12.
137 von Kaisenberg CS, Bender G, Scheewe J, Hirt SW, Lange M, Stieh J, *et al.* A case of fetal parvovirus B19 myocarditis, terminal cardiac heart failure, and perinatal heart transplantation. *Fetal Diagn Ther* 2001;16:427–32.
138 Bultmann BD, Klingel K, Nabauer M, Wallwiener D, Kandolf R. High prevalence of viral genomes and inflammation in peripartum cardiomyopathy. *Am J Obstet Gynecol* 2005;193:363–5.
139 Fett JD. Viral particles in endomyocardial biopsy tissue from peripartum cardiomyopathy patients 1. *Am J Obstet Gynecol* 2006;195:330–1.
140 Jordan JA, Huff D, DeLoia JA. Placental cellular immune response in women infected with human parvovirus B19 during pregnancy. *Clin Diagn Lab Immunol* 2001;8:288–92.
141 Jordan JA, Butchko AR. Apoptotic activity in villous trophoblast cells during B19 infection correlates with clinical outcome: assessment by the caspase-related M30 cytodeath antibody. *Placenta* 2002;23:547–53.
142 Morgan-Capner P, Crowcroft NS. Guidelines on the management of, and exposure to, rash illness in pregnancy (including consideration of relevant antibody screening programmes in pregnancy). *Commun Dis Public Health* 2002;5:59–71.
143 Davidkin I, Valle M, Peltola H, Hovi T, Paunio M, Roivainen M, *et al.* Etiology of measles- and rubella-like illnesses in measles, mumps, and rubella-vaccinated children. *J Infect Dis* 1998;178:1567–70.
144 Ramsay M, Reacher M, O'Flynn C, Buttery R, Hadden F, Cohen B, *et al.* Causes of morbilliform rash in a highly immunised english population. *Arch Dis Child* 2002;87:202–6.
145 Davidkin I, Jokinen S, Paananen A, Leinikki P, Peltola H. Etiology of mumps-like illnesses in children and adolescents vaccinated for measles, mumps, and rubella. *J Infect Dis* 2005;191:719–23.
146 Oliveira MI, Curti SP, Figueiredo CA, Afonso AM, Theobaldo M, Azevedo RS, *et al.* Rash after measles vaccination: laboratory analysis of cases reported in Sao Paulo, Brazil. *Rev Saude Publica* 2002;36:155–9.
147 Bruu AL, Nordbo SA. Evaluation of five commercial tests for detection of immunoglobulin M antibodies to human parvovirus B19. *J Clin Microbiol* 1995;33:1363–5.
148 Tolfvenstam T, Ruden U, Broliden K. Evaluation of serological assays for identification of parvovirus B19 immunoglobulin M. *Clin Diagn Lab Immunol* 1996;3:147–50.
149 Butchko AR, Jordan JA. Comparison of three commercially available serologic assays used to detect human parvovirus B19-specific immunoglobulin M (IgM) and IgG antibodies in sera of pregnant women. *J Clin Microbiol* 2004;42:3191–5.

150 Takahashi T, Ozawa K, Takahashi K, Okuno Y, Takahashi T, Muto Y, *et al.* DNA replication of parvovirus B19 in a human erythroid leukemia cell line (JK-1) in vitro. *Arch Virol* 1993;131:201–8.

151 Miyagawa E, Yoshida T, Takahashi H, Yamaguchi K, Nagano T, Kiriyama Y, *et al.* Infection of the erythroid cell line, KU812Ep6 with human parvovirus B19 and its application to titration of B19 infectivity. *J Virol Methods* 1999;83:45–54.

152 Shimomura S, Komatsu N, Frickhofen N, Anderson S, Kajigaya S, Young NS. First continuous propagation of B19 parvovirus in a cell line. *Blood* 1992;79:18–24.

153 Cohen BJ, Mortimer PP, Pereira MS. Diagnostic assays with monoclonal antibodies for the human serum parvovirus-like virus (SPLV). *J Hyg (Lond)* 1983;91:113–30.

154 Ferguson M, Heath A. Report of a collaborative study to calibrate the second international standard for parvovirus B19 antibody. *Biologicals* 2004;32:207–12.

155 Kurtzman GJ, Gascon P, Caras M, Cohen B, Young NS. B19 parvovirus replicates in circulating cells of acutely infected patients. *Blood* 1988;71:1448–54.

156 Landolsi H, Yacoubi MT, Bouslama L, Lahmar A, Trabelsi A, Hmissa S, *et al.* Detection of the human Parvovirus B19 in nonimmune hydrops fetalis using immunohistochemistry and nested-PCR in formalin-fixed and paraffin-embedded placenta and fetal tissues. *Pathol Biol (Paris)* 2009;57:e1–7.

157 Morey AL, Porter HJ, Keeling JW, Fleming KA. Non-isotopic in situ hybridisation and immunophenotyping of infected cells in the investigation of human fetal parvovirus infection. *J Clin Pathol* 1992;45:673–8.

158 Knoll A, Louwen F, Kochanowski B, Plentz A, Stussel J, Beckenlehner K, *et al.* Parvovirus B19 infection in pregnancy: quantitative viral DNA analysis using a kinetic fluorescence detection system (TaqMan PCR). *J Med Virol* 2002;67:259–66.

159 Zerbini M, Musiani M, Gentilomi G, Venturoli S, Gallinella G, Morandi R. Comparative evaluation of virological and serological methods in prenatal diagnosis of parvovirus B19 fetal hydrops. *J Clin Microbiol* 1996;34:603–8.

160 Wattre P, Dewilde A, Subtil D, Andreoletti L, Thirion V. A clinical and epidemiological study of human parvovirus B19 infection in fetal hydrops using PCR Southern blot hybridization and chemiluminescence detection. *J Med Virol* 1998;54:140–4.

161 Cassinotti P, Weitz M, Siegl G. Human parvovirus B19 infections: routine diagnosis by a new nested polymerase chain reaction assay. *J Med Virol* 1993;40:228–34.

162 Carriere C, Boulanger P, Delsert C. Rapid and sensitive method for the detection of B19 virus DNA using the polymerase chain reaction with nested primers. *J Virol Methods* 1993;44:221–34.

163 Bonvicini F, Manaresi E, Gallinella G, Gentilomi GA, Musiani M, Zerbini M. Diagnosis of fetal parvovirus B19 infection: value of virological assays in fetal specimens. *BJOG* 2009;116:813–7.

164 Knisely AS, O'Shea PA, McMillan P, Singer DB, Magid MS. Electron microscopic identification of parvovirus virions in erythroid-line cells in fatal hydrops fetalis. *Pediatr Pathol* 1988;8:163–70.

165 Cotmore SF, McKie VC, Anderson LJ, Astell CR, Tattersall P. Identification of the major structural and nonstructural proteins encoded by human parvovirus B19 and mapping of their genes by procaryotic expression of isolated genomic fragments. *J Virol* 1986;60:548–57.

166 Morey AL, O'Neill HJ, Coyle PV, Fleming KA. Immunohistological detection of human parvovirus B19 in formalin-fixed, paraffin-embedded tissues. *J Pathol* 1992;166:105–8.

167 Wright C, Hinchliffe SA, Taylor C. Fetal pathology in intrauterine death due to parvovirus B19 infection. *Br J Obstet Gynaecol* 1996;103:133–6.

168 Quemelo PR, Lima DM, da Fonseca BA, Peres LC. Detection of parvovirus B19 infection in formalin-fixed and paraffin-embedded placenta and fetal tissues. *Rev Inst Med Trop Sao Paulo* 2007;49:103–7.

169 Barton RB. Parvovirus B19: twenty-five years in perspective. *Pediatr Dev Pathol* 1999;2:296–315.

170 de Jong EP, de Haan TR, Kroes AC, Beersma MF, Oepkes D, Walther FJ. Parvovirus B19 infection in pregnancy. *J Clin Virol* 2006;36:1–7.

171 Enders M, Schalasta G, Baisch C, Weidner A, Pukkila L, Kaikkonen L, *et al.* Human parvovirus B19 infection during pregnancy – value of modern molecular and serological diagnostics. *J Clin Virol* 2006;35:400–6.

172 Dieck D, Schild RL, Hansmann M, Eis-Hubinger AM. Prenatal diagnosis of congenital parvovirus B19 infection: value of serological and PCR techniques in maternal and fetal serum. *Prenat Diagn* 1999;19:1119–23.

173 Skjoldebrand-Sparre L, Nyman M, Broliden K, Wahren B. All cases of intrauterine fetal death should be evaluated for parvovirus B19 viral deoxyribonucleic acid. *Am J Obstet Gynecol* 1999;180:1595–6.

174 Petersson K, Norbeck O, Westgren M, Broliden K. Detection of parvovirus B19, cytomegalovirus and enterovirus infections in cases of intrauterine fetal death. *J Perinat Med* 2004;32:516–21.

175 Wolff K, Broliden K, Marsk A, Tolfvenstam T, Papadogiannakis N, Westgren M. One stillborn and one severely hydropic twin due to parvovirus B19 infection; successful outcome of the surviving twin. *Acta Obstet Gynecol Scand* 1999;78:828–30.

176 Prowse C, Ludlam CA, Yap PL. Human parvovirus B19 and blood products. *Vox Sang* 1997;72:1–10.

177 Lefrere JJ, Servant-Delmas A, Candotti D, Mariotti M, Thomas I, Brossard Y, *et al.* Persistent B19 infection in immunocompetent individuals: implications for transfusion safety. *Blood* 2005;106:2890–5.

178 Lindblom A, Isa A, Norbeck O, Wolf S, Johansson B, Broliden K, *et al.* Slow clearance of human parvovirus B19 viremia following acute infection. *Clin Infect Dis* 2005;41:1201–3.

179 Ross DS, Rasmussen SA, Cannon MJ, Anderson B, Kilker K, Tumpey A, *et al.* Obstetrician/gynecologists' knowledge, attitudes, and practices regarding prevention of infections in pregnancy. *J Womens Health (Larchmt)* 2009;18:1187–93.

180 Bizjak G, Blondin D, Hammer R, Kozlowski P, Siegmann HJ, Stressig R. Acute infection with parvovirus B19 in early pregnancy. *Ultrasound Obstet Gynecol* 2009;34:234–5.

181 Delle CL, Buck G, Grab D, Terinde R. Prediction of fetal anemia with Doppler measurement of the middle cerebral artery peak systolic velocity in pregnancies complicated by maternal blood group alloimmunization or parvovirus B19 infection. *Ultrasound Obstet Gynecol* 2001;18:232–6.

182 Cosmi E, Mari G, Delle CL, Detti L, Akiyama M, Murphy J, *et al.* Noninvasive diagnosis by Doppler ultrasonography of fetal anemia resulting from parvovirus infection. *Am J Obstet Gynecol* 2002;187:1290–3.

183 Hernandez-Andrade E, Scheier M, Dezerega V, Carmo A, Nicolaides KH. Fetal middle cerebral artery peak systolic velocity in the investigation of non-immune hydrops. *Ultrasound Obstet Gynecol* 2004;23:442–5.

184 Borna S, Mirzaie F, Hanthoush-Zadeh S, Khazardoost S, Rahimi-Sharbaf F. Middle cerebral artery peak systolic velocity and ductus venosus velocity in the investigation of nonimmune hydrops. *J Clin Ultrasound* 2009;37:385–8.

185 Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, *et al.* Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative

Group for Doppler assessment of the blood velocity in anemic fetuses. *N Engl J Med* 2000;342:9–14.
186 Mari G. Middle cerebral artery peak systolic velocity for the diagnosis of fetal anemia: the untold story. *Ultrasound Obstet Gynecol* 2005;25:323–30.
187 Gray ES, Anand A, Brown T. Parvovirus infections in pregnancy. *Lancet* 1986;1:208.
188 Brennand JE, Cameron AD. Human parvovirus B19 in pregnancy. *Hosp Med* 2000;61:93–6.
189 Schild RL, Bald R, Plath H, Eis-Hubinger AM, Enders G, Hansmann M. Intrauterine management of fetal parvovirus B19 infection. *Ultrasound Obstet Gynecol* 1999;13:161–6.
190 Forestier F, Tissot JD, Vial Y, Daffos F, Hohlfeld P. Haematological parameters of parvovirus B19 infection in 13 fetuses with hydrops foetalis. *Br J Haematol* 1999;104:925–7.
191 Simms RA, Liebling RE, Patel RR, Denbow ML, Abdel-Fattah SA, Soothill PW, *et al.* Management and outcome of pregnancies with parvovirus B19 infection over seven years in a tertiary fetal medicine unit. *Fetal Diagn Ther* 2009;25:373–8.
192 Segata M, Chaoui R, Khalek N, Bahado-Singh R, Paidas MJ, Mari G. Fetal thrombocytopenia secondary to parvovirus infection. *Am J Obstet Gynecol* 2007;196:61–4.
193 Cohen BJ, Kumar S. Parvovirus B19 infection in pregnancy. *Fetal Matern Med Rev* 2005;16:123–50.
194 Smoleniec JS, Pillai M. Management of fetal hydrops associated with parvovirus B19 infection. *Br J Obstet Gynaecol* 1994;101: 1079–81.
195 von Kaisenberg CS, Jonat W. Fetal parvovirus B19 infection. *Ultrasound Obstet Gynecol* 2001;18:280–8.
196 Fairley CK, Smoleniec JS, Caul OE, Miller E. Observational study of effect of intrauterine transfusions on outcome of fetal hydrops after parvovirus B19 infection 1. *Lancet* 1995;346:1335–7.
197 Xu J, Raff TC, Muallem NS, Neubert AG. Hydrops fetalis secondary to parvovirus B19 infections. *J Am Board Fam Pract* 2003;16:63–8.
198 Rodis JF, Borgida AF, Wilson M, Egan JF, Leo MV, Odibo AO, *et al.* Management of parvovirus infection in pregnancy and outcomes of hydrops: a survey of members of the Society of Perinatal Obstetricians. *Am J Obstet Gynecol* 1998;179:985–8.
199 Nagel HT, de Haan TR, Vandenbussche FP, Oepkes D, Walther FJ. Long-term outcome after fetal transfusion for hydrops associated with parvovirus B19 infection. *Obstet Gynecol* 2007;109:42–7.
200 Palmer GA, Brogdon JL, Constant SL, Tattersall P. A nonproliferating parvovirus vaccine vector elicits sustained, protective humoral immunity following a single intravenous or intranasal inoculation 1. *J Virol* 2004;78:1101–8.
201 Ballou WR, Reed JL, Noble W, Young NS, Koenig S. Safety and immunogenicity of a recombinant parvovirus B19 vaccine formulated with MF59C. 1. *J Infect Dis* 2003;187:675–8.
202 Selbing A, Josefsson A, Dahle LO, Lindgren R. Parvovirus B19 infection during pregnancy treated with high-dose intravenous gammaglobulin. *Lancet* 1995;345:660–1.
203 Matsuda H, Sakaguchi K, Shibasaki T, Takahashi H, Kawakami Y, Furuya K. Intrauterine therapy for parvovirus B19 infected symptomatic fetus using B19 IgG-rich high titer gammaglobulin. *J Perinat Med* 2005;33:561–3.
204 Gigler A, Dorsch S, Hemauer A, Williams C, Kim S, Young NS, *et al.* Generation of neutralizing human monoclonal antibodies against parvovirus B19 proteins. *J Virol* 1999;73:1974–9.
205 Alger LS. Toxoplasmosis and parvovirus B19. *Infect Dis Clin North Am* 1997;11:55–75.
206 Enders M, Weidner A, Rosenthal T, Baisch C, Hedman L, Soderlund-Venermo M, *et al.* Improved diagnosis of gestational parvovirus B19 infection at the time of nonimmune fetal hydrops. *J Infect Dis* 2008;197:58–62.

