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Parvovirus B19 Infection in Human Pregnancy

Ronald F. Lamont, BSc, MB, ChB, MD, FRCOG^{1,2}, Jack Sobel, MD³, Edi Vaisbuch, MD^{1,2}, Juan Pedro Kusanovic, MD^{1,2}, Shali Mazaki-Tovi, MD^{1,2}, Sun Kwon Kim, MD, PhD¹, Niels Uldbjerg, MD, DMSc¹, and Roberto Romero, MD^{1,2,4}

¹Perinatology Research Branch, NICHD/NIH/DHHS, Bethesda, Maryland and Detroit, Michigan, USA

²Wayne State University School of Medicine, Department of Obstetrics and Gynecology, Detroit, Michigan, USA

³Wayne State University School of Medicine, Department of Infectious Diseases, Detroit, Michigan, USA

⁴Center for Molecular Medicine and Genetics, Wayne State University, Detroit, Michigan, USA

Abstract

Human parvovirus B19 infection is widespread. Approximately 30-50% of pregnant women are non-immune 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 infections sequelae. B19 infection should be considered in any case of non-immune hydrops. Diagnosis is mainly through serology and PCR. Surveillance requires sequential ultrasound and Doppler screening for signs of fetal anemia, heart failure, and hydrops. Immunoglobulins antiviral and vaccination are not yet available but intrauterine transfusion in selected cases can be lifesaving.

Introduction

Human parvovirus (hPV) B19 infection is the most common viral agent associated with rashes in school-age children.¹ Approximately 65% of pregnant women in North America have evidence of past infection and while the incidence of acute hPV B19 infection in pregnancy is ~ 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 hematological conditions, or infected fetuses where there is widespread tissue inflammation and red-cell destruction, mortality and serious morbidity may occur.

History and Nomenclature

Human parvovirus B19 infection may be manifest as Erythema Infectiosum (EI), or “fifth disease” or “slapped face syndrome”. The term “slapped face syndrome” exists across

Address correspondence to: Ronald F. Lamont, BSc, MB, ChB, MD, FRCOG and Roberto Romero, M.D., Perinatology Research Branch, NICHD, NIH, DHHS, Wayne State University/Hutzel Women's Hospital, 3990 John R, Box 4, Detroit, MI 48201, USA, Telephone (313) 993-2700, Fax: (313) 993-2694, rlamont@med.wayne.edu and prbchiefstaff@med.wayne.edu.

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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, while 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

Taxonomy and Description

Parvovirus B19 is a single-stranded DNA, non-enveloped 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 to other viruses, hPV B19 is physically and genetically quite stable with only few mutations,⁷ and causes pathology through blocking erythropoiesis and by inducing inflammation.⁸ Other genotypes have been described, but their identification, virulence, transmission, and ability to cause disease remains poorly elucidated.⁹⁻¹² The morphology, genetics, capsid proteins, culture and viral life cycle have been reviewed elsewhere.¹³

Epidemiology

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 laboratories²³⁻²⁷ though this may not be of relevance to hPV B19 infection in pregnancy in the 21st century.

Human parvovirus B19 infection occurs worldwide,^{28;29} but seroprevalence rates vary according to age and geography.³⁰⁻³⁶ Approximately 15% of pre-school 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, viremia or detection of viral DNA in serum is rare in healthy individuals. Human parvovirus 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

*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 with 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”.

susceptible children and 25% in susceptible teachers.^{34;47-50} Nosocomial transmission in adult, pediatric 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 ~20% of children and adults exposed to the virus.^{14;15} Human parvovirus B19 infection has been associated with fetal loss, acute arthritis and arthralgias as well as chronic anemia in immunodeficient individuals.^{24;53-62} The incubation period before the onset of mild illness with prodromal symptoms ranges from 4-14 days after exposure but may be as long as three weeks.²⁶ Serum specimens are usually negative by seven 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 hematological conditions such as sickle-cell disease, are more likely to develop transient aplastic crisis.^{24;66-74} In addition, severe chronic anemia 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

While 30-50% of pregnant women are susceptible to hPV B19, only a small percentage of them will be infected with this virus.^{41;66;77-82} The hPV B19 specific IgG seroconversion incidence in susceptible pregnant women may rise 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 due to cardiorespiratory congenital defects. Fetal anemia and hydrops may be due to immune conditions such red-cell or Kell alloimmunization or non-immune hydrops due to hPV B19. The diagnosis and management of fetal anemia and hydrops in general has 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, it may result in severe fetal anemia, generalized edema, congestive heart failure, myocarditis, and hydropic or non-hydropic 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 Human parvovirus B19 infection is thought to account for 8-20% of non-immune 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 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 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 due to hPV B19 infection,¹²⁵ though this may differ between epidemic and non-epidemic periods. According to gestational age, maternal infection in the first trimester, 13-20 weeks and after 20 weeks is associated with a risk of fetal death of 19%, 15% and 6%, respectively.⁶⁴ Spontaneous fetal resolution appears to occur since healthy neonates have been born with specific hPV B19 IgM in umbilical cord blood.⁷⁸ Human parvovirus 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 non-immune hydrops.^{21;25;53;92-94;117;126-129}

Pathophysiology of fetal complications due to hPV B19 infection

The pathophysiology of fetal adverse effects is mainly due to anemia caused by the destruction of red blood cell precursors,¹³⁰ but may also be due to hypoalbuminemia, hepatitis, myocarditis, and placentitis. These may culminate in cardiac failure and subsequent hydrops fetalis or fetal death.^{131;132} Erythropoiesis is inhibited due to the ability of the virus to produce cytotoxic apoptosis and lysis of erythroid precursors.¹³³ The presence of the virus in the 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 due to 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 non-existent in the third trimester.¹³⁵ In the second trimester, hemopoiesis occurs in the fetal liver and due to the increased demand from the growing fetus, there is a 34-fold increase in red blood cell mass, concomitantly 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 anemia, hPV B19 viremia 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 the third trimester infection may stem from the fact that the need for a high number of red blood cells is decreased and the life span of these cells increase.

Cardiac failure may be due to severe anemia but may also be associated to myocarditis which can cause arrhythmias or even cardiac arrest without evidence of anemia, cardiac failure or hydrops.^{131;137} Direct damage to fetal myocardial cells by hPV B19 has been reported⁹⁶ 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 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 specificity¹⁴⁷⁻¹⁴⁹ that 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 detection of IgM antibodies to hPV B19. The specificities of 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 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 used but have little use in routine practice.^{8;96;156;165-168} Human parvovirus 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 immunosuppressed, 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 Since most pregnancies infected with hPV B19 have a favorable outcome, it would appear that invasive prenatal diagnostic testing should only be used if there are definitive signs of fetal anemia or hydrops fetalis.¹³

Management

Unlike VZV infection in pregnancy, no specific antiviral therapy or vaccine is available for hPV B19 infection. Accordingly, it is important that practicing 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 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 anemia.¹⁸⁰ After confirmation of maternal hPV B19 infection in the first 20 weeks of gestation, fetal surveillance should be initiated no later than four 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 center. If no fetal abnormality is detected, the ultrasound should be repeated at intervals of one to two weeks. If there is no fetal abnormality at or later than 30 weeks 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 anemia.¹⁷⁹⁻¹⁸⁶ The early ultrasound signs of cardiac failure are cardiomegaly and ascites^{53;126;187} which may be a manifestation of hepatitis and hypoalbuminemia as much as cardiac failure from anemia.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 B19¹⁸⁹⁻¹⁹² such that many fetomaternal 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 Since most fetal adverse effects occur remote from term, a lifesaving 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 those hydropic pregnancies managed expectantly compared to those with active intervention with intrauterine red blood cell transfusion.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 to only 6% of those who were transfused.¹⁹⁸ While 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 to other causes of fetal anemia and hydrops, fetal complications due to hPV B19 have the potential to resolve as the fetus mounts its own immune response. Surveillance might identify those babies which, though anemic 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 differs in such women from their western counterparts but the proportion who in pregnancy would be susceptible to infection 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 immunoglobulins 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 sero-negative women of childbearing age. Although no hPV B19 vaccine is currently available, a phase I study has showed that a recombinant vaccine against hPV B19 was safe and demonstrated immunogenicity in 24 subjects.²⁰¹

Unlike varicella zoster immunoglobulin administration for VZV infection, maternal IgG administration, fetal hPV B19 IgG rich high titre gamma-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 gammaglobulin was used in placental exchange transfusion,²⁰² and IgG monoclonal antibodies with potent neutralizing 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 using 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 non-immune hydrops. In a study to evaluate the diagnostic value of supplementary molecular or serologic assays following maternal hPV B19 infection at the time of hPV B9 induced fetal hydrops, B19 DNA in maternal blood had the best diagnostic sensitivity for identifying hPV B19 infection. However, supplementary measure of IgG avidity improved the precision of diagnosis and management of pregnant women infected by hPV B19.²⁰⁶ This needs further evaluation. Strict protocols for invasive testing should also be tested against standardized 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 standardized. Such interventions may need to be centralized to specific tertiary referral centers to carry out research which will address the particular problems of fetal anemia and hydrops directly attributable to hPV B19 infection, rather than having these lumped together with other causes. Following such interventions, research follow-up should be long term to detect any neurodevelopmental disability.

Conclusion

Human parvovirus B19 infection during pregnancy is common. Approximately 30-50% of pregnant women are non-immune 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 though most neonates are born healthy. While 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 anemia, cardiac failure, fetal hydrops and fetal death. Accordingly, hPV B19 should be considered in any case of non-immune hydrops. Fetal surveillance using ultrasound and Doppler to detect signs of fetal anemia 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 anemia 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, development of an effective vaccine as well as treatment options such antiviral therapy and immunoglobulins are necessary.

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Figure 1.
Investigation for parvovirus B19 of pregnant women exposed to rash illness
From the 2000 Public Health Laboratory Service Working Party on "Rash Diagnosis in
"Pregnancy and Rubella Screening" subsequently reported¹⁴²

Figure 2.
Management of confirmed parvovirus B19 infection in pregnancy
From the 2000 Public Health Laboratory Service Working Party on “Rash Diagnosis in
“Pregnancy and Rubella Screening” subsequently reported¹⁴²