Abstract

Objectives: This guideline reviews the evidence relating to the effects of parvovirus B19 on the pregnant woman and fetus, and discusses the management of women who are exposed to, who are at risk of developing, or who develop parvovirus B19 infection in pregnancy.

Outcomes: The outcomes evaluated were maternal outcomes including erythema infectiosum, arthropathy, anemia, and myocarditis, and fetal outcomes including spontaneous abortion, congenital anomalies, hydrops fetalis, stillbirth, and long-term effects.

Evidence: Published literature was retrieved through searches of PubMed and The Cochrane Library on July 8, 2013, using appropriate controlled vocabulary (MeSH terms “parvovirus” and “pregnancy”) and key words (parvovirus, infection, pregnancy, hydrops). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date restrictions but results were limited to English or French language materials. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, and national and international medical specialty.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Recommendations

1. Investigation for parvovirus B19 infection is recommended as part of the standard workup for fetal hydrops or intrauterine fetal death. (II-2A)

2. Routine screening for parvovirus immunity in low-risk pregnancies is not recommended. (II-2E)

3. Pregnant women who are exposed to, or who develop symptoms of, parvovirus B19 infection should be assessed to determine whether they are susceptible to infection (non-immune) or have a current infection by determining their parvovirus B19 immunoglobulin G and immunoglobulin M status. (II-2A)

4. If parvovirus B19 immunoglobulin G is present and immunoglobulin M is negative, the woman is immune and should be reassured that she will not develop infection and that the virus will not adversely affect her pregnancy. (II-2A)
**INTRODUCTION**

Parvovirus B19 is a single-stranded DNA virus that is responsible for erythema infectiosum, a common childhood illness. The virus was identified in 1975 during routine blood screening for hepatitis B surface antigen, and was identified as the cause of erythema infectiosum in 1983.

It was subsequently linked to cases of non-immune hydrops and fetal death. The B19 parvovirus strain infects only humans and animal strains infect only animals, not humans.

Parvovirus B19 is most commonly spread by respiratory secretions or from hand to mouth contact. Other modes of transmission include blood product infusion and transplacental transfer. As the main mode of transmission is respiratory, epidemics of parvovirus B19 infection can occur. Outbreaks usually happen in spring (but can occur any time of the year), and mainly affect children aged 4 to 11. Outbreaks usually occur yearly, with larger epidemics every four to five years, and may last up to six months. Most cases in pregnant women seem to occur in late spring and summer. Viremia occurs 4 to 14 days after exposure and may last up to 20 days. Fever and prodromal symptoms may develop in the last few days of the incubation period, but many people remain asymptomatic. A rash and arthralgia may begin around day 15, by which time the person is usually no longer infectious. Current data suggest that infection with parvovirus B19 usually confers lifelong immunity. Because outbreaks can be frequent and many infected people are asymptomatic, encounters that risk exposure to parvovirus infection are often unrecognized.

Approximately 50% to 75% of women of reproductive age have developed immunity to parvovirus B19. Without known exposure, about 1% to 3% of susceptible pregnant women will develop serologic evidence of infection in pregnancy, rising to over 10% in epidemic periods. Where there is extensive opportunity for exposure to parvovirus...
B19, such as in a daycare centre or school, it is estimated that 20% to 30% of susceptible women\textsuperscript{19,20} will develop infection, while 50% of susceptible women exposed through household contacts will become infected.\textsuperscript{19,21} Nursery school teachers have a 3-fold higher risk of acute infection than other pregnant women, and other school teachers have a 1.6-fold increased risk.\textsuperscript{16} The population-attributable risk of infection in susceptible pregnant women is about 55% from their own children and 6% for occupational exposure.\textsuperscript{16} Women at increased risk include mothers of preschool and school-age children, workers at daycare centres, and school teachers. Assessment of parvovirus B19 immunity at the beginning of the pregnancy can be considered in this population.

Since the publication of the 2002 guideline, there have been publications of the natural history, outcomes, diagnosis, and management of parvovirus in pregnancy. This updated guideline provides a review of this literature. The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

**CLINICAL PRESENTATION**

The multiple ways parvovirus B19 may present are described below and summarized in Table 2.

1. *Asymptomatic*: Up to 50% of non-pregnant women who develop parvovirus B19 infection, and up to 70% of infected pregnant women, will be asymptomatic.\textsuperscript{9,18–23}

2. *Erythema infectiosum (fifth disease)*: Children with parvovirus B19 infection most commonly develop erythema infectiosum, initially presenting with flu-like symptoms, fever, and headache, followed 1 to 4 days later by a “slapped cheek” rash that becomes lacy in appearance, and after about 1 week may spread to the trunk and limbs.\textsuperscript{13} Adults with parvovirus B19 infection usually do not have an extensive rash. The onset of the rash usually coincides with the appearance of parvovirus B19 antibodies (IgM), suggesting that this symptom is immune-mediated.\textsuperscript{14} Other dermatologic syndromes associated with parvovirus infection in adults include papular-purpuric “gloves and socks” syndrome.

3. *Arthropathy*: For those adults with symptoms, the most common symptom is arthropathy. It affects up to 50% of pregnant women with parvovirus infection,\textsuperscript{12} and may last several weeks to months. The arthropathy usually presents as symmetric polyarthritis, affecting the hands, wrists, ankles, and knees.\textsuperscript{12,19,24,25} The onset of the arthritis is coincident with the increase in parvovirus B19 antibodies (IgM), suggesting that, similar to erythema infectiosum, it is immune-mediated.

4. *Anemia and transient aplastic crisis*: Parvovirus B19 has an affinity for hematopoietic system cells, including erythroid progenitor cells, and to a lesser degree, leukocyte and megakaryocyte cell lines, notably through the P antigen.\textsuperscript{1,9,14,26,27} The virus attacks cells of the red blood cell lines in the bone marrow, causing hemolysis and red blood cell aplasia.\textsuperscript{1,27} The decline in hemoglobin level is usually minimal in healthy children and adults because the red cell aplasia lasts only 7 to 10 days and red blood cells have a long half-life of 2 to 3 months.\textsuperscript{10} The anemia, however, may be significant in those with underlying hematologic disorders including sickle cell disease, hereditary spherocytosis, pyruvate kinase deficiency, thalassemia, and autoimmune hemolytic anemia, who have low hemoglobin levels prior to infection.\textsuperscript{9,27–31} Presentation of transient nonspecific prodromal symptoms followed by aplastic crisis includes pallor and fatigue and is usually not associated with rash.

5. *Immunocompromised patients*: Chronic bone marrow suppression after parvovirus B19 infection leading to chronic severe anemia has been described in immunodeficient patients including those with HIV, acute lymphocytic leukemia on chemotherapy, and congenital immunodeficiency.\textsuperscript{9,31–35}

6. *Myocarditis*: Case reports have suggested a rare association between parvovirus B19 infection and acute myocarditis leading to heart failure.\textsuperscript{36,37}

**PARVOVIRUS B19 INFECTION IN PREGNANCY**

Pregnancy does not appear to affect the course of the infection, but infection may affect the pregnancy.\textsuperscript{27} The transmission rate of maternal parvovirus B19 infection to the fetus is 17% to 33%.\textsuperscript{12,38,39} Most fetuses infected with parvovirus B19 have spontaneous resolution with no adverse outcomes.\textsuperscript{1,14} (Table 3)
### Table 3. Risk of hydrops and fetal death with parvovirus B19 maternal infection

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases (N)</th>
<th>Fetal loss</th>
<th>Hydrops</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public Health Laboratory Service Working Party on Fifth Disease[^38]</td>
<td>186</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Rodis et al.[^45]</td>
<td>39</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Gratacós et al.[^39]</td>
<td>60</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Harger et al.[^12]</td>
<td>52</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Miller et al.[^42]</td>
<td>427</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td>Guidozzi et al.[^44]</td>
<td>64</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rodis et al.[^47]</td>
<td>113 (115 fetuses)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Koch et al.[^46]</td>
<td>43</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enders et al.[^55]</td>
<td>1018</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Schwarz et al.[^26]</td>
<td>39</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Simms et al.[^48]</td>
<td>47</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2090 fetuses</td>
<td>179 (8.6%)</td>
<td>68 (2.9%)</td>
</tr>
</tbody>
</table>

| *Does not include data of Gratacós et al.[^39], Harger et al.[^12], Guidozzi et al.[^44], Koch et al.[^46], or Schwarz et al.[^26] because gestational age was not indicated for all cases of infection. |
Fetal Effects of Parvovirus B19 Infection

Parvovirus infection can lead to spontaneous miscarriage and stillbirth. The spontaneous loss rate of fetuses affected with parvovirus B19 before 20 weeks’ gestation is 13.0% and after 20 weeks’ gestation is 0.5%. The reason for this difference is uncertain, but the largest study suggests it may be related to multisystem organ damage, which is possible even without anemia or hydrops.

Currently, there does not appear to be any evidence that parvovirus B19 infection increases the risk of congenital anomalies in humans, though there have been case reports of central nervous system, craniofacial, musculoskeletal, and eye anomalies. In other species with other strains of parvovirus infection, congenital anomalies have been reported.

Parvovirus B19 has been associated with hydrops fetalis. The overall incidence in fetuses whose mothers have been infected by parvovirus during pregnancy is 2.9% (Table 3). The risk of fetal hydrops appears to be greater when infection occurs earlier in pregnancy. Enders et al. noted the rate of hydrops to be 4.7% if maternal infection occurred before 25 weeks’ gestation compared with 2.3% after this gestation. Possible mechanisms for hydrops include fetal anemia due to the virus crossing the placenta, combined with the shorter half-life of fetal red blood cells (especially during the hepatic stage of hematopoiesis), leading to the severe anemia, hypoxia, and high output cardiac failure that are associated with fetal hydrops. Other possible causes include fetal viral myocarditis leading to cardiac failure, and impaired hepatic function caused by direct damage to hepatocytes and indirect damage due to hemosiderin deposits.

If a fetus develops hydrops, ultrasound signs include ascites, skin edema, pleural and pericardial effusions, and placental edema. It is estimated that parvovirus B19 infection accounts for 8% to 10% of non-immune hydrops, although some studies found molecular evidence of parvovirus B19 in 18% to 27% of cases of non-immune hydrops.

Thrombocytopenia has been reported among up to 97% of hydropic transfused fetuses, with an incidence of severe thrombocytopenia (< 50 x 10^9 platelets/L) up to 46%. This must be taken into account when the decision is made to perform a cordocentesis or intrauterine transfusion.

Long-term Neonatal Outcome

Studies of the long-term effects on children of maternal parvovirus B19 infection suggest most infants do not have long-term adverse sequelae, but further research is needed. Case reports of neonatal complications of maternal parvovirus B19 infection have been reported, including hepatic insufficiency, myocarditis, transfusion dependent anemia, and central nervous system abnormalities. However, a case series of 108 children born to women with parvovirus B19 infection during pregnancy and 99 women who had immunological evidence of past infection reported no difference between the groups in the incidence of congenital anomalies, overall learning disabilities, or neurological handicaps. Through a questionnaire survey, Miller et al. found no increased risk of adverse outcome in children of mothers with parvovirus infection in pregnancy at one year (182 children) and 7 to 10 years (129 children) of age. On the other hand, Nagel et al. found an abnormal neurodevelopmental status in 5 of 16 infants who had intrauterine blood transfusions for parvovirus B19 infection.

Parvovirus B19 itself, in the absence of hydrops or significant fetal anemia, does not seem to cause long-term neurological morbidity, but severe anemia and fetal hydrops may be an independent risk factor for long-term neurological sequelae. Consideration could be made for cerebral imaging studies in neonates who had severe hydrops or anemia. Moreover, parvovirus B19 myocarditis can lead to severe dilated cardiomyopathy and may even require heart transplantation.

**Recommendation**

1. Investigation for parvovirus B19 infection is recommended as part of the standard workup for fetal hydrops or intrauterine fetal death. (II-2A)

**MANAGEMENT OF PARVOVIRUS B19**

**Exposure/Infection in Pregnancy**

Systematic screening for parvovirus immunity in low-risk pregnancies is not currently recommended. If a pregnant woman is exposed to, or develops signs or symptoms of parvovirus B19 infection, it should be determined whether she is immune through testing for both parvovirus B19-specific IgG and IgM. (Figure) It is recommended to use enzyme-linked immunosorbent IgM and IgG assays based on recombinant conformational epitopes of polyomavirus capsid proteins 1 and 2 or polyomavirus capsid protein 2 alone. B19 IgM usually appears within 2 to 3 days of acute infection (10 to 12 days after inoculation) and may persist up to 6 months. Parvovirus B19 IgG appears a few days after IgM appears and usually remains present for life. The presence of IgG and the absence of IgM with recent exposure suggest immunity. If the woman is
immune, she can be reassured that she will not develop the infection during pregnancy, and that exposure will not result in adverse consequences in the pregnancy. However, absence of IgM 8 to 12 weeks after maternal acute infection should be interpreted with caution because of the possibility that rapid clearance of IgM could lead to false-negative results.\(^\text{10}\)

The presence of parvovirus B19 IgM antibodies with no evidence of parvovirus B19 IgG antibodies suggests either a very recent infection or a false-positive result.\(^\text{9,69}\) In this situation, it is recommended that testing for parvovirus B19 IgG and IgM be repeated in 1 to 2 weeks. If recent infection has occurred, then the IgG should also be positive at that time.\(^\text{9–11,18}\) (Figure)

If both parvovirus B19 IgG and IgM are negative, the woman is not immune and is therefore susceptible to infection.\(^\text{9,69}\) If she has had a recent exposure to the virus, and may be incubating the infection, it is suggested that the IgG and IgM tests be repeated 2 to 4 weeks later. If exposure is ongoing, serology may be repeated every 2 to 4 weeks. Occasionally maternal IgM levels in acute infection may be below detection. In these cases PCR can be used in maternal serum for the diagnosis of acute infection.\(^\text{10,11}\) However, the interpretation of this result is complicated by the possible persistence of low parvovirus B19 DNA levels in the blood for several months after acute infection.

If testing reveals both parvovirus B19 IgG and IgM to be present, this may suggest recent infection.\(^\text{9,69}\) If stored blood is available from the woman, testing may confirm seroconversion. If stored blood is not available, repeat blood work should reveal an increasing parvovirus B19 IgG titre if recent infection has occurred (Figure). If the titre does not increase, this may indicate an older infection
Women who do not have immunity need to be assessed for their exposure risk. Hand washing has been suggested as a measure to decrease infection, but not yet evaluated. During an outbreak, parents of preschool and school-aged children, as well as preschool and school employees, should be informed of the risk of infection and its management, and should be advised to minimize the risk of exposure at work or at home. Each woman should be counselled about her individual risk, based on her risk of infection, gestational age, and other obstetrical considerations. The decision to leave work to try to minimize the risk of infection during an outbreak of parvovirus B19 infection should be made by the woman after discussion with her physician, family members, public health officials, and employers, taking into account her specific risk. There is no evidence that susceptible women will reduce their risk of infection by leaving work. It has been noted that the risk of acquiring infection in the workplace (such as school) is less than through household contacts, and some studies have found that working in child daycare was not associated with an occupational risk for parvovirus infection. Therefore it is not recommended to routinely remove women susceptible to infection from high risk occupations.

If the woman has developed a recent infection, the virus may be transmitted to the fetus and may cause non-immune hydrops. Therefore, it is recommended that these women be referred to an obstetrician or maternal–fetal medicine specialist and that they have serial ultrasounds to detect evidence of hydrops for 8 to 12 weeks after infection, because the development of hydrops may be delayed. There are no randomized trials of the frequency of ultrasounds required; however, most maternal–fetal medicine specialists perform ultrasonographic assessment weekly or every 2 weeks. Ultrasound assessment of the fetus should include Doppler measurement of the MCA peak systolic velocity to assess for fetal anemia. According to the limited published data, this measurement has a sensitivity of 83% to 100%, and a specificity of 93% to 100% for diagnosis of anemia in parvovirus B19 infected fetuses. Other ultrasound signs of parvovirus B19 infection include increased placenta thickness, echogenic bowel/meconium peritonitis, first trimester increased nuchal translucency, and amniotic fluid abnormalities. As fetuses with hydrops tend to move less, women should also be instructed to monitor fetal movement daily. If there is a delay in establishing the woman’s immunity status, serial ultrasounds for the detection of hydrops and anemia may be obtained until information regarding immunity is available.

**Recommendations**

2. Routine screening for parvovirus immunity in low-risk pregnancies is not recommended. (II-2E)

3. Pregnant women exposed to, or who develop symptoms of, parvovirus B19 infection should be assessed to determine whether they are susceptible to infection (non-immune) or have a current infection by determining their parvovirus B19 immunoglobulin G and immunoglobulin M status. (II-2A)

4. If parvovirus B19 immunoglobulin G is present and immunoglobulin M is negative, the woman is immune and should be reassured that she will not develop infection and that the virus will not adversely affect her pregnancy. (II-2A)

5. If both parvovirus B19 immunoglobulin G and immunoglobulin M are negative (and the incubation period has passed), the woman is not immune and has not developed the infection. She should be advised to minimize exposure at work and at home. Absence from work should be considered on a case-by-case basis. (II-2C) Further studies are recommended to address ways to lessen exposure including the risk of occupational exposure. (III-A)

**DIAGNOSIS OF FETAL INFECTION**

Parvovirus B19 cannot usually be cultured in regular culture media. It can be identified histologically by characteristic intranuclear inclusions or by the presence of viral particles by electron microscopy. Fetal infection can be detected with amniotic fluid or fetal serum using the most sensitive molecular methods available (nested PCR or reverse transcription PCR). Although there is the possibility of diagnosing parvovirus B19 infection with amniotic fluid obtained by amniocentesis, invasive diagnosis of this condition is not required for all suspected or confirmed maternal infections. If amniocentesis is performed for a fetal indication, a PCR for parvovirus B19 should be requested as part of the workup. The presence of viral particles, however, can only be seen during the viremic stage. The presence of parvovirus B19 IgM in fetal blood cannot be depended upon to make the diagnosis of fetal infection, because the fetus does not begin to make its own IgM until 22 weeks’ gestation. There have been false-negative results even when the fetus is beyond 22 weeks.
Elevated MSAFP levels have been associated with fetal parvovirus B19 infection in several case reports\(^8,\)\(^9\),\(^10\) but in one study that found an association between MSAFP and fetal infection,\(^8\) the authors judged it to be weak, and thus it cannot be used as a reliable marker of fetal parvovirus B19 infection.\(^14\)

**MANAGEMENT OF FETAL HYDROPS AND ANEMIA**

Every pregnancy identified with fetal anemia or hydrops should be referred to a tertiary care centre with a maternal–fetal medicine specialist. The current management of fetuses with hydrops or anemia due to parvovirus B19 infection is to consider cordocentesis, to assess fetal hemoglobin and reticulocyte count, and intrauterine transfusion, if necessary.\(^14\) If the fetus is at or near term, delivery should be considered.\(^14\) If delivery of a hydropic or anemic infant is planned this should occur in a tertiary care centre with staff and resources to manage these neonates.

The use of corticosteroids to accelerate lung maturity is not contraindicated. For fetuses at younger gestational ages, the options of expectant management or intravascular transfusion have been proposed.\(^9\),\(^14\) No randomized trials to date have evaluated the best management for fetal hydrops or anemia caused by parvovirus B19 infection.

A summary of 14 studies involving a total of 1436 cases of fetal parvovirus infection found a survival rate of 82% with transfusion compared with 55% in those who were not transfused.\(^80\) The upper limit of gestational age for transfusion is case- and centre-dependent. Two to three transfusions may be required before resolution of the fetal hydrops or anemia, which usually occurs 3 to 6 weeks after the first transfusion.\(^8\) The degree of hydrops may not correlate with fetal hemoglobin because of myocarditis. The role of fetal echocardiography should be explored.

The role of Doppler measurement of the MCA peak systolic flow in the management of hydropic fetuses needs further research, but cohort studies suggest it helps to determine the likelihood of anemia as the cause of the hydrops and to measure its severity.\(^75\)–\(^77,\)\(^79\)

Expectant management may be chosen if the hydrops or anemia appears to be mild or improving (based on ultrasound, MCA Doppler, and/or cordocentesis).\(^1\) Fairley et al. compared outcomes of expectant management with intravascular transfusion, controlling for severity of hydrops and gestational age, and found a greater than 7-fold reduction in fetal death with intravascular transfusion.\(^86\) In a survey of maternal–fetal medicine specialists involving 539 cases of parvovirus B19-induced hydrops, death occurred after intravascular transfusion in 6% of cases, and in 30% of cases without intravascular transfusion.\(^14\)

### Recommendation

6. If a recent parvovirus B19 infection has been diagnosed in the woman, referral to an obstetrician or a maternal–fetal medicine specialist should be considered. (III-B) The woman should be counselled regarding risks of fetal transmission, fetal loss, and hydrops and serial ultrasounds should be performed every 1 to 2 weeks, up to 12 weeks after infection, to detect the development of anemia (using Doppler measurement of the middle cerebral artery peak systolic velocity) and hydrops. (III-B) If hydrops or evidence of fetal anemia develops, referral should be made to a specialist capable of fetal blood sampling and intravascular transfusion. (II-2B)

### REFERENCES


