

PARVOVIRUS B19 INFECTION IN PREGNANCY

This document has been reviewed by the Maternal Fetal Medicine and Infectious Diseases Committees and approved by Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objectives: (1) To review the effects of parvovirus B19 on the pregnant woman and fetus, and (2) to discuss the management of women who are exposed to, who are at risk of developing, or who develop parvovirus B19 infection in pregnancy.

Outcomes: Maternal outcomes of parvovirus B19 including erythema infectiosum, arthropathy, anemia, and myocarditis. Fetal outcomes including spontaneous abortion, congenital anomalies, hydrops fetalis, stillbirth, and long-term effects.

Evidence: MEDLINE search from 1966 to January 2002 for articles relating to parvovirus B19 infection, using key words "parvovirus" and "pregnancy," and guidelines of professional organizations including the American College of Obstetricians and Gynecologists.

Values: The evidence obtained was reviewed and evaluated by both the Maternal Fetal Medicine and Infectious Diseases Committees of the Society of Obstetricians and Gynaecolo-

gists of Canada (SOGC) and recommendations were made according to guidelines developed by the Canadian Task Force on the Periodic Health Examination.

Recommendations:

1. Pregnant women exposed to, or who develop symptoms of, parvovirus B19 infection should be assessed to determine if they are susceptible to infection (nonimmune) or if they have a current infection, by determining their parvovirus B19 IgG and IgM status. (II-2A)
2. If parvovirus B19 IgG is present and IgM is negative, the woman is immune and can be reassured that she will not develop infection and that the virus will not adversely affect her pregnancy. (II-2A)
3. If both parvovirus B19 IgG and IgM are negative (and the incubation period has passed), the woman is not immune and has not developed the infection. Although she may wish to minimize further exposure, leave from the workplace is controversial and is not routinely recommended. Further studies are needed in this area. (III-B)
4. If a recent parvovirus B19 infection has been diagnosed in the woman, then referral to an obstetrician or a maternal-fetal

Key Words

Parvovirus, infection, pregnancy, hydrops

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medicine specialist should be considered (III-B). The woman should be counselled regarding risks of fetal transmission, fetal loss, and hydrops. Serial ultrasounds should be performed up to 8 to 12 weeks after infection to detect the development of hydrops (III-B). If hydrops develops, referral to a maternal-fetal medicine specialist should be made and consideration should be given to fetal blood sampling and intravascular transfusion (II-2B).

Validation: These guidelines have been reviewed and approved by the Maternal Fetal Medicine and Infectious Diseases Committees of the SOGC, and the Council of the SOGC.

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

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INTRODUCTION

Parvovirus B19 is a single-stranded DNA virus that is responsible for erythema infectiosum,¹ a common childhood illness.¹ The virus was identified in 1975 during routine blood screening for hepatitis B surface antigen,² and was identified as the cause of erythema infectiosum in 1983.³ Subsequently, it was linked to cases of nonimmune hydrops and fetal death.⁴⁻⁷ The B19 parvovirus strain only infects humans. Animal strains do not infect humans.¹ The virus attaches to the P antigen on red blood cell precursors before invading them.⁸

Parvovirus B19 is most commonly spread by respiratory secretions or from hand to mouth contact.⁹ 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). Outbreaks usually occur every four to five years and may last up to six months.¹⁰ Viremia occurs 4 to 14 days after exposure (may last up to 20 days).¹¹ Fever and prodromal symptoms may develop in the last few days of the incubation period,¹² 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 confers lifelong immunity.¹²

Approximately 50% to 65% of women of reproductive age have developed immunity to parvovirus B19.^{13,14} Without known exposure, about 1% to 3% of susceptible pregnant women will develop serologic evidence of infection in pregnancy.^{14,15} Where there is high opportunity for exposure to parvovirus B19, such as in a day care centre or school, it is estimated that 20% to 30% of susceptible women^{15,16} will develop infection, while 50% of susceptible women exposed through household contacts will become infected.^{15,17} Compared with other pregnant women, nursery school teachers have a 3-fold increased risk of acute infection and other school teachers have a 1.6-fold increased risk.¹⁴ The population-attributable risk of infection in susceptible pregnant women is about 55% for own children and 6% for occupational exposure.¹⁴ Women at increased risk include mothers of preschool and school-age children, workers at day care centres, and school teachers.

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 the Periodic Health Exam (Table 1).¹⁸

TABLE 1 QUALITY OF EVIDENCE ASSESSMENT ¹⁸	CLASSIFICATION OF RECOMMENDATIONS
<p>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 the Periodic Health Exam.</p> <p>I: Evidence obtained from at least one properly randomized controlled trial.</p> <p>II-1: Evidence from well-designed controlled trials without randomization.</p> <p>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.</p> <p>II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.</p> <p>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</p>	<p>Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.</p> <p>A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.</p> <p>D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.</p> <p>E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.</p>

CLINICAL PRESENTATION

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

1. *Asymptomatic*: 20% to 25% of adults who develop parvovirus B19 infection will be asymptomatic.^{10,15,17,19}
2. *Erythema infectiosum (fifth disease)*: Children with parvovirus B19 infection most commonly develop erythema infectiosum (or fifth disease), 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 one week may spread to the trunk and limbs.¹¹ 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.¹²
3. *Arthropathy*: The most common symptom in adults is arthropathy. This affects up to 80% of adults infected with parvovirus B19 and may last several weeks to months. The arthropathy usually presents as symmetric polyarthralgia, affecting the hands, wrists, ankles, and knees.^{15,20,21} 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.^{1,10,12,22,23} The virus attacks cells of the red blood cell lines in the bone marrow, causing hemolysis and red blood cell aplasia.^{1,22} The effects are usually minimal in healthy children and adults as the duration of red cell aplasia is only 7 to 10 days and red blood cells have a long half life of 2 to 3 months.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.^{10,22-26} 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.^{15,26-30}
6. *Myocarditis*: Case reports have suggested a rare association between parvovirus B19 infection and acute myocarditis leading to heart failure.^{31,32}

PARVOVIRUS B19 INFECTION IN PREGNANCY

Pregnancy does not appear to affect the course of the infection, but infection may affect the pregnancy.²² The transmission rate of maternal parvovirus B19 infection to the fetus is 17% to 33%.³³⁻³⁵ Most fetuses infected with parvovirus B19 have spontaneous resolution with no adverse outcomes.^{1,12}

FETAL EFFECTS OF PARVOVIRUS B19 INFECTION

1. SPONTANEOUS ABORTION

As indicated in Table 3, the overall spontaneous abortion rate for women infected with parvovirus B19 is similar to the background rate of first-trimester loss.³⁶ The spontaneous loss rate of fetuses affected with parvovirus B19 before 20 weeks' gestation is 14.8% and after 20 weeks' gestation is 2.3%.^{33,37-39} The reason is uncertain but may be related to multisystem organ damage.¹

2. CONGENITAL ANOMALIES

Currently, there does not appear to be any evidence that parvovirus B19 infection increases the risk of congenital anomalies in humans,^{1,12} though there have been case reports of central nervous system,^{1,12} craniofacial,^{1,12} and eye anomalies.^{1,12} In other species with other strains of parvovirus infection, congenital anomalies have been reported.^{1,12}

3. HYDROPS

Parvovirus B19 has been associated with hydrops fetalis.^{15,33-35,37,38,40,41} Possible mechanisms for this include fetal anemia due to the virus crossing the placenta, combined with the shorter half life of fetal red blood cells, 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 of hepatocytes and indirect damage due to hemosiderin deposits.^{15,33-35,37,38,40}

Table 3 summarizes published studies of the rate of fetal loss and hydrops with parvovirus B19 infection.^{15,33-35,37,38,40-42} Several studies found a higher fetal loss rate when the infection was acquired before 19 to 20 weeks' gestation (14.8%)^{33,37,38,41}

TABLE 2

PRESENTATION OF PARVOVIRUS B19 INFECTION

Maternal:

- Asymptomatic
- Erythema infectiosum/rash
- Arthropathy
- Anemia
- Myocarditis

Fetal:

- Fetal loss
- Hydrops

compared to that after 20 weeks (2.3%).^{33,37,38,41} If a fetus develops hydrops, ultrasound signs include ascites, skin edema, pleural and pericardial effusions, as well as placental edema.¹ It is estimated that parvovirus B19 infection accounts for 8% to 10% of nonimmune hydrops,¹ although some studies found molecular evidence of parvovirus B19 in 18% to 27% of cases of non-immune hydrops.¹²

4. LONG-TERM NEONATAL OUTCOME

There have been few studies of the long-term effects on children of maternal parvovirus B19 infection.^{9,10,31,37,39,41-46} Case reports of neonatal complications of maternal parvovirus B19 infection have been reported, including hepatic insufficiency,^{39,43,44} myocarditis,^{9,31,45} transfusion dependent anemia,^{1,12} and central

nervous system abnormalities.^{9,39,44} 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 neurologic handicaps.⁴¹ Through a questionnaire survey, Miller *et al.*³⁷ 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. Most children born to mothers who develop parvovirus B19 infection in pregnancy do not appear to suffer long-term sequelae, but further studies are needed.¹⁰ Parvovirus B19 itself does not seem to cause long-term neurologic morbidity, but severe anemia may be an independent risk factor for long-term neurologic sequelae.⁴⁶

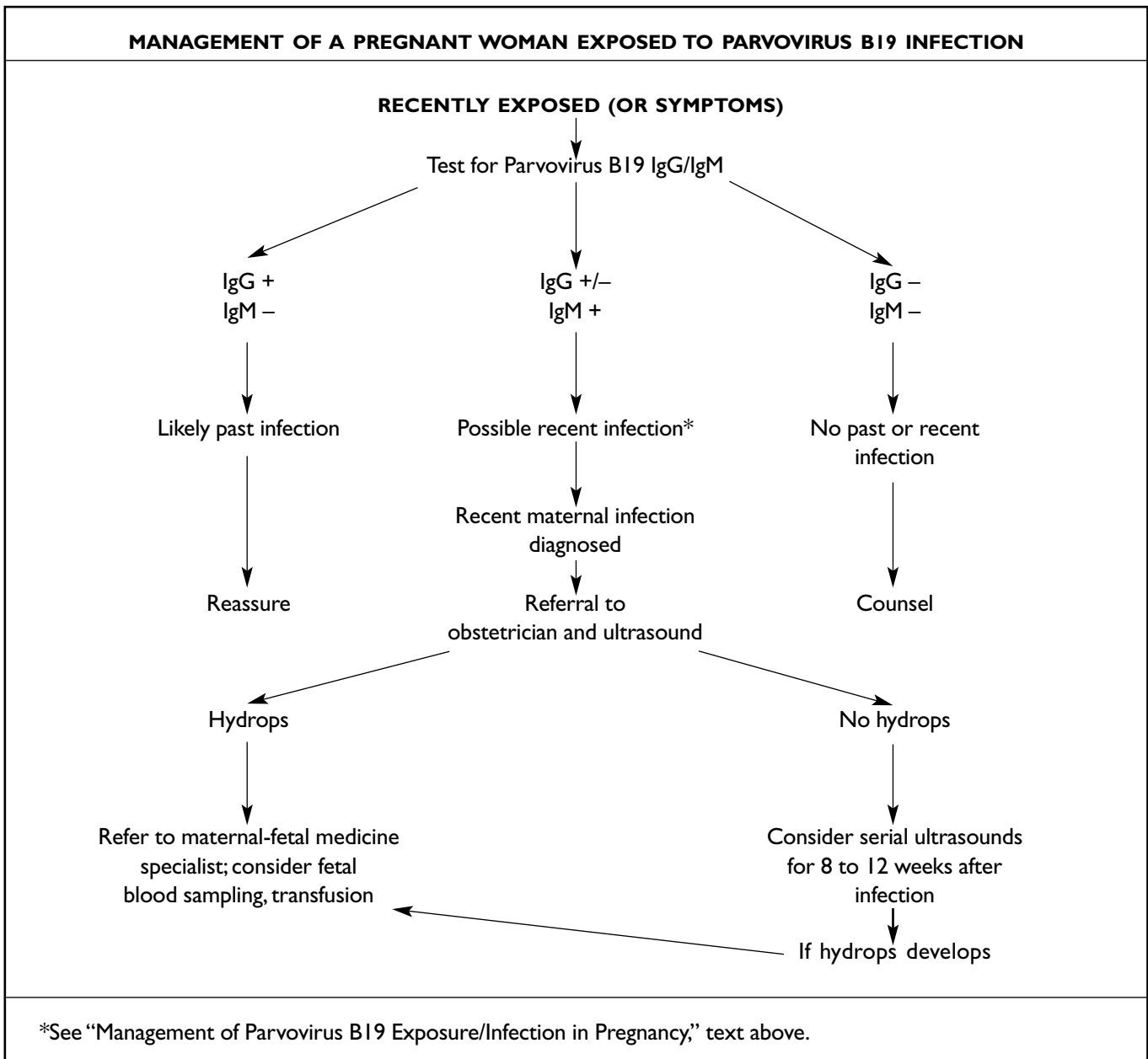
Author	Cases (N)	Fetal Loss	Hydrops
Centers for Disease Control ¹⁵	49	2	1
Public Health Laboratory Service ³³	186	30 <div style="display: flex; justify-content: space-around; font-size: small;"> ≤20 weeks 28/166 >20 weeks 1/17 </div>	1
Rodis ³⁸	39	2 <div style="display: flex; justify-content: space-around; font-size: small;"> <19 weeks 2/23 ≥19 weeks 0/16 </div>	0
Gratacos ³⁵	60	5	0
Harger ³⁴	52	0	0
Miller ³⁷	427	58 <div style="display: flex; justify-content: space-around; font-size: small;"> ≤20 weeks 57/373 >20 weeks 1/54 </div>	7
Guidozzi ⁴⁰	64	1	0
Rodis ⁴¹	113	6 <div style="display: flex; justify-content: space-around; font-size: small;"> <20 weeks 5/60 ≥20 weeks 1/45 </div>	2
Koch ⁴²	19	0	0
TOTAL	1089	104 (10.3%) <div style="display: flex; justify-content: space-around; font-size: small;"> <19-20 wks 97/722 (14.8%) >20 wks 3/132 (2.3%) </div>	11 (1.1%)

MANAGEMENT OF PARVOVIRUS B19 EXPOSURE/INFECTION IN PREGNANCY

If a pregnant woman is exposed to or develops signs or symptoms of parvovirus B19 infection, one should determine if she is immune (see figure)^{10,47} through testing for both parvovirus B19-specific IgG and IgM. Parvovirus B19 IgM usually appears within 2 to 3 days of acute infection and may persist up to 6 months. Parvovirus B19 IgG appears a few days after IgM appears and usually remains present for life.¹⁰

1. The presence of IgG and the absence of IgM with recent exposure suggests immunity.¹⁰ 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.

2. 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.¹⁰ In this situation, it is recommended that 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 (see * in figure).¹⁰
3. If both parvovirus B19 IgG and IgM are negative, the woman is not immune and therefore susceptible to infection.¹⁰ 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, one may wish to repeat serology every 2 to 4 weeks.
4. If testing reveals both parvovirus B19 IgG and IgM to be present, this may suggest recent infection.¹⁰ 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 (see * in figure). If the titre is not increasing, this may represent an older infection (up to 6 months prior). Serologic diagnosis with parvovirus B19 IgM alone for recent infection may be difficult due to lab sensitivity for IgM being positive up to 6 months after acute infection.

Women who do not have immunity need to be assessed with regard to their exposure risk. Hand washing has been suggested as a measure to decrease infection¹⁵ but not yet evaluated. During an outbreak, parents of preschool and school children as well as employees should be informed of the risk of infection and its management. 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. As there is no evidence that susceptible women reduce their risk of infection by leaving work, and one study demonstrated no difference in infection rates between susceptible pregnant school teachers who left the workplace and those who stayed,¹⁶ it is not recommended that policies be pursued to routinely send home women susceptible to infection.¹⁵

If the woman has developed a recent infection, the virus may be transmitted to the fetus and may cause nonimmune hydrops. Therefore, it is recommended that these women be referred to an obstetrician or maternal-fetal medicine specialist and that these women have serial ultrasounds to detect evidence of hydrops for 8 to 12 weeks after infection, as the development of hydrops may be delayed.^{10,12,37,48,49} 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.⁴⁹ These follow-up ultrasounds could be limited to assessment of amniotic fluid volume and evidence of hydrops (level II ultrasound with documentation). As fetuses with hydrops tend to move less, women should also be instructed to monitor fetal movement daily.¹⁰ If there is a delay in establishing the woman's immunity status, one may wish to obtain serial ultrasounds for the detection of hydrops, until this information regarding immunity is available.⁵⁰

DIAGNOSIS OF FETAL INFECTIONS

Parvovirus B19 cannot usually be cultured in regular culture media.¹ It can be identified histologically by characteristic intranuclear inclusions or by the presence of viral particles by electron microscopy.¹ Viral DNA may also be identified by polymerase chain reaction (PCR) of amniotic fluid or fetal blood by cordocentesis. The most reliable way to diagnose acute

fetal infection is to detect in amniotic fluid or fetal serum viral DNA by PCR or viral particles by electron microscopy. Clinical use of these tests remains to be evaluated. Although there is the possibility of diagnosing parvovirus B19 infection through PCR on 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 can 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,⁷ as 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.⁵¹

Elevated maternal serum alpha fetoprotein (MSAFP) levels have been associated with fetal parvovirus B19 infection in several case reports;^{52,53} but the one study⁵⁴ found the association between MSAFP and fetal infection to be weak and thus it cannot be used as a reliable marker of fetal parvovirus B19 infection.¹²

MANAGEMENT OF FETAL HYDROPS

Every pregnancy identified with fetal hydrops should be referred to a tertiary care centre with a maternal-fetal medicine specialist. The current management of hydropic fetuses due to parvovirus B19 infection is somewhat controversial, but the primary management tool is cordocentesis to assess fetal hemoglobin and reticulocyte count, and intrauterine transfusion, if necessary.¹² If the fetus is term or near term, delivery should be considered.¹² If delivery is not imminently required, amniocentesis for lung maturity may be considered. The use of corticosteroids to accelerate lung maturity is not contraindicated. For fetuses at younger gestational ages or with pulmonary immaturity, the management options of expectant management or intravascular transfusion^{10,12} have been proposed. There are no randomized trials to evaluate the best management for fetal hydrops caused by parvovirus B19 infection. The upper limit of gestational age for transfusion is case and centre dependent. Due to myocarditis, the degree of hydrops may not correlate with fetal hemoglobin. Preliminary information has suggested a possible role for Doppler assessment of umbilical venous and middle cerebral artery flow velocities in the assessment of fetal anemia.⁵⁵⁻⁵⁸ Further research is needed in this area.

A summary of case reports of intravascular transfusion for fetal hydrops due to parvovirus B19 infection revealed a fetal mortality rate of 11%.¹ In all 18 cases, the fetal hemoglobin was less than 8 g/dL, and most had severe hydrops. Twenty cases were treated expectantly, with serial ultrasounds noting a fetal mortality of 26%. In those cases managed expectantly, this management was chosen based on the fact that the hydrops appeared to be mild or improving (based on ultrasound and/or

cordocentesis).¹ Failey *et al.*⁵⁹ 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.⁵⁹ 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.⁴⁹

RECOMMENDATIONS

1. **Pregnant women exposed to, or who develop symptoms of, parvovirus B19 infection should be assessed to determine if they are susceptible to infection (nonimmune) or if they have a current infection, by determining their parvovirus B19 IgG and IgM status. (II-2A)**
2. **If parvovirus B19 IgG is present and IgM is negative, the woman is immune and can be reassured that she will not develop infection and that the virus will not adversely affect her pregnancy. (II-2A)**
3. **If both parvovirus B19 IgG and IgM are negative (and the incubation period has passed), the woman is not immune and has not developed the infection. Although she may wish to minimize further exposure, leave from the workplace is controversial and is not routinely recommended. Further studies are needed in this area. (III-B)**
4. **If a recent parvovirus B19 infection has been diagnosed in the woman, then 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. Serial ultrasounds should be performed up to 8 to 12 weeks after infection to detect the development of hydrops (III-B). If hydrops develops, referral to a maternal-fetal medicine specialist should be made and consideration should be given to fetal blood sampling and intravascular transfusion (II-2B).**

REFERENCES

1. Levy R, Weissman A, Blomberg G, Hagay ZJ. Infection by parvovirus B19 during pregnancy: a review. *Obstet Gynecol Survey* 1997;52:254-9.
2. Cossart VE, Field AM, Cant B, Widdows D. Parvovirus-like particles in human sera. *Lancet* 1975;1:72-3.
3. Anderson MJ, Jones SE, Fisher-Hosh SP, Lewis E, Hall SM, Bartlett CL, et al. Human parvovirus, the cause of erythema infectiosum (fifth disease)? *Lancet* 1983;1:1378.
4. Brown T, Anand A, Ritchie LD, Clewley JP, Reid TMS. Intrauterine parvovirus infection associated with hydrops fetalis. *Lancet* 1984;2:1033-4.
5. Knott PD, Welby GAC, Anderson MJ. Serologically proven intrauterine infection with parvovirus. *Br Med J* 1984;289:1660.
6. 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(4):663-7.
7. Rodis JF, Hovick TJ Jr, Quinn DL, Rosengren SS, Tattersall P. Human parvovirus infection in pregnancy. *Obstet Gynecol* 1988;72:733-8.
8. Brown KE, Anderson SM, Young NS. Erythrocyte P antigen: cellular receptor for B19 parvovirus. *Science* 1993;262:114-7.
9. Torok T. Human parvovirus B19. In: Remington JS, Klein JO, editors. *Infectious disease of the fetus and newborn infant*. 4th ed. Philadelphia: Saunders; 1995. p. 668-702.
10. Rodis JF. Parvovirus infection. *Clin Obstet Gynecol* 1999;42:107-20.
11. Anderson LJ. Role of parvovirus B19 in human disease. *Pediatr Infect Dis J* 1987;6:711-8.
12. Markenson GR, Yancey MK. Parvovirus B19 infection in pregnancy. *Seminars Perinatol* 1998;22:309-17.
13. Cohen BJ, Buckley MM. The prevalence of antibody to human parvovirus B19 in England and Wales. *J Med Microbiol* 1988;25:151-3.
14. 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.
15. Centers for Disease Control. Risks associated with human parvovirus B19 infection. *MMWR Morb Mortal Wkly Rep* 1989;38:81-97.
16. 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.
17. 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.
18. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on the Periodic Health Exam. Ottawa: Canada Communication Group; 1994. p. xxxvii.
19. 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.
20. White DG, Woolf AD, Mortimer PP, Cohen BJ, Blake DR, Bacon PA. Human parvovirus arthropathy. *Lancet* 1985;1:419-21.
21. Reid DM, Reid TMS, Brown T, Rennie JAN, Eastmond CJ. Human parvovirus-associated arthritis: a clinical and laboratory description. *Lancet* 1985;1:422-5.
22. Alger LS. Tosoplasmosis and parvovirus B19. *Infect Disease Clin North Am* 1997;11:55-75.
23. Kelleher JF, Luban NLC, Cohen BJ, Mortimer PP. Human serum parvovirus as the cause of aplastic crisis in sickle cell disease. *Am J Dis Child* 1984;138:401-3.
24. Blacklock HA, Mortimer PP. Aplastic crisis and other effects of the human parvovirus infection. *Clin Haematol* 1984;13:679-91.
25. Serjeant GR, Topley JM, Mason K, Serjeant BE. Outbreak of aplastic crises in sickle cell anaemia associated with parvovirus-like agent. *Lancet* 1981;2:595-7.
26. Young N. Hematologic and hematopoietic consequences of B19 parvovirus infection. *Semin Hematol* 1988;25:159-72.
27. 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.
28. 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.
29. Coulombel L, Morinet F, Mielot F, Tchernia G. Parvovirus infection, leukemia, and immunodeficiency [letter]. *Lancet* 1989;1:101-2.
30. Koch WC, Massey G, Russell CE, Adler SP. Manifestations and treatment of human parvovirus B19 infection in immunocompromised patients. *J Pediatr* 1990;116:355-9.
31. Saint-Martin J, Choulot JJ, Bonnaud E, Morinet F. Myocarditis caused by parvovirus. *J Pediatr* 1990;116:1007-8.
32. Malm C, Fridell E, Jansson K. Heart failure after parvovirus B19 infection. *Lancet* 1993;341:1408-9.
33. Public Health Laboratory Service Working Party on Fifth Disease. Prospective study of human parvovirus infection in pregnancy. *Br Med J* 1990;300:1166-70.
34. Harger JH, Alder SP, Koch WC, Harger GF. Prospective evaluation of 618 pregnant women exposed to parvovirus B19: risks and symptoms. *Obstet Gynecol* 1998;91:413-20.

35. 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.
36. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. *N Engl J Med* 1988;319:189–94.
37. 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.
38. Rodis JF, Quinn DL, Gary GW Jr, Anderson LJ, Rosengren S, Cartter M, et al. Management and outcomes of pregnancies complicated by human B19 parvovirus infection: a prospective study. *Am J Obstet Gynecol* 1990;163:1168–71.
39. Cohen B. Parvovirus B19: an expanding spectrum of disease. *Br Med J* 1995;311:1549–52.
40. Guidozi F, Ballot D, Rothberg A. Human B19 parvovirus infection in an obstetric population – a prospective study determining fetal outcome. *J Reprod Med* 1994;39:36–8.
41. Rodis JF, Rodner C, Hansen AA, Borgida AF, Deoliveira I, Rosengren SS. Long-term outcome of children following maternal human parvovirus B19 infection. *Obstet Gynecol* 1998;91:125–8.
42. Koch WC, Adler SP, Harger J. Intrauterine parvovirus B19 infection may cause an asymptomatic or recurrent postnatal infection. *Ped Infect Dis J* 1993;12:747–50.
43. Metzman R, Anand A, DeGiulio A, Knisely AS. Hepatic disease associated with intrauterine parvovirus B19 infection in a newborn premature infant. *J Pediatr Gastroenterol Nutr* 1989;9:112–4.
44. Yoto Y, Kudoh T, Asanuma H, Numazaki K, Tsutsumi Y, Nakata S, et al. Transient disturbance of consciousness and hepatic dysfunction with human parvovirus B19 infection. *Lancet* 1994;344:624–5.
45. Porter HJ, Quantrill AM, Fleming KA. B19 parvovirus infection of myocardial cells. *Lancet* 1988;1:535–6.
46. Ryan G, Kelly EN, Inwood S, et al. Longterm pediatric follow up in non-immune hydrops secondary to parvovirus infection. *Am J Obstet Gynecol* 1997;176(Part 2):S86.
47. Crane JMG. Prenatal exposure to viral infections. *Can J CME* 1998;10:61–74.
48. Katz VL, Cheschier NC, Bethea M. Hydrops fetalis from B19 parvovirus infection. *J Perinatol* 1990;10:366–8.
49. Rodis JF, Borgida AF, Wilson M, Egan JF, Leo MV, Oibo 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.
50. Barrett J, Ryan G, Morrow R, Farine D, Kelly E, Mahony J. Human parvovirus B19 during pregnancy. *J Soc Obstet Gynaecol Can* 1994;16:1253–8.
51. Pryde PG, Nugent CE, Pridjian G, Barr M, Faix RG. Spontaneous resolution of nonimmune hydrops fetalis secondary to human parvovirus B19 infection. *Obstet Gynecol* 1992;79:859–61.
52. Carrington D, Gilmore DH, Whittle MJ, Aitken D, Gibson AA, Patrick WJ, et al. Maternal serum α -fetoprotein – a marker of fetal aplastic crisis during intrauterine human parvovirus infection. *Lancet* 1987;1:433–5.
53. Bernstein IM, Capeless EL. Elevated maternal serum alpha-fetoprotein and hydrops fetalis in association with fetal parvovirus B19 infection. *Obstet Gynecol* 1989;74:456–7.
54. Johnson DR, Fisher RA, Helwick JJ, Murray DL, Patterson MJ, Downes FP. Screening maternal serum alpha-fetoprotein levels and human parvovirus antibodies. *Prenat Diagn* 1994;14:455–8.
55. Mari G, for the Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. *N Engl J Med* 2000;342:9–14.
56. Roberts AB, Mitchell JM, Lake Y, Pattison NS. Ultrasonographic surveillance in red blood cell alloimmunization. *Am J Obstet Gynecol* 2001;184:1251–5.
57. Divakaran TG, Waugh J, Clark TJ, Khan KS, Whittle MJ, Kilby MD. Non-invasive techniques to detect fetal anemia due to red blood cell alloimmunization: a systematic review. *Obstet Gynecol* 2001;98:509–17.
58. Oepkes D. Invasive versus non-invasive testing in red-cell alloimmunized pregnancies. *Eur J Obstet Gynecol Reprod* 2000;92:83–9.
59. Fairley CK, Smoleniec JS, Caul OE, Miller E. Observational study of effect of intrauterine transfusion on outcome of fetal hydrops after parvovirus B19 infection. *Lancet* 1995;346:1335–7.