

Parvovirus B19 Infection in Pregnancy

This Clinical Practice Guideline has been prepared by the Maternal Fetal Medicine committee, reviewed by Infectious Disease and Family Physician Advisory Committees, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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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 Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice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)

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Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
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	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.⁸⁷

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.⁸⁷

- 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)
- 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)

INTRODUCTION

Parvovirus B19 is a single-stranded DNA virus that is responsible for erythema infectiosum, 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

ABBREVIATIONS

IgG	immunoglobulin G
IgM	immunoglobulin M
MCA	middle cerebral artery
MSAFP	maternal serum alpha fetoprotein
PCR	polymerase chain reaction

It was subsequently linked to cases of non-immune hydrops and fetal death.⁴⁻⁷ The B19 parvovirus strain infects only humans and animal strains infect only animals, not humans.¹

Parvovirus B19 is most commonly spread by respiratory secretions or from hand to mouth contact.⁸ 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.⁹⁻¹¹ Most cases in pregnant women seem to occur in late spring and summer.¹² Viremia occurs 4 to 14 days after exposure and may last up to 20 days.¹³ Fever and prodromal symptoms may develop in the last few days of the incubation period,¹⁴ 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.¹⁴ Because outbreaks can be frequent and many infectious 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.^{11,15-18} Without known exposure, about 1% to 3% of susceptible pregnant women will develop serologic evidence of infection in pregnancy,^{16,19} rising to over 10% in epidemic periods.¹⁰ 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^{19,20} will develop infection, while 50% of susceptible women exposed through household contacts will become infected.^{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.¹⁶ The population-attributable risk of infection in susceptible pregnant women is about 55% from their own children and 6% for occupational exposure.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.^{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.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.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,¹² and may last several weeks to months. The arthropathy usually presents as symmetric polyarthralgia, affecting the hands, wrists, ankles, and knees.^{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.

Table 2. Presentation of parvovirus B19 infection

Maternal:	
• Asymptomatic	
• Erythema infectiosum/rash	
• Arthropathy	
• Anemia	
• Myocarditis	
Fetal:	
• Fetal loss	
• Anemia	→ Hydrops
• Myocarditis	

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.^{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.^{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.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.^{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.^{9,31–35}
6. *Myocarditis*: Case reports have suggested a rare association between parvovirus B19 infection and acute myocarditis leading to heart failure.^{36,37}

PARVOVIRUS B19 INFECTION IN PREGNANCY

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

Table 3. Risk of hydrops and fetal death with parvovirus B19 maternal infection

Author	Cases (N)	Fetal loss	Hydrops
Public Health Laboratory Service Working Party on Fifth Disease ³⁸	186	30 <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> ≤ 20 weeks 28/166 </div> <div style="text-align: center;"> > 20 weeks 1/17 </div> </div>	1
Rodis et al. ⁴³	39	2 <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> < 19 weeks 2/23 </div> <div style="text-align: center;"> ≥ 19 weeks 0/16 </div> </div>	0
Gratacós et al. ³⁹	60	5	0
Harger et al. ¹²	52	2	0
Miller et al. ⁴²	427	58 <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> ≤ 20 weeks 57/373 </div> <div style="text-align: center;"> > 20 weeks 1/54 </div> </div>	7
Guidozzi et al. ⁴⁴	64	1	0
Rodis et al. ⁴⁷	113 (115 fetuses)	6 <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> < 20 weeks 5/60 </div> <div style="text-align: center;"> ≥ 20 weeks 1/45 </div> </div>	2
Koch et al. ⁴⁶	43	0	0
Enders et al. ⁵⁵	1018	64 <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> ≤ 20 weeks 64/579 </div> <div style="text-align: center;"> > 20 weeks 0/439 </div> </div>	40
Schwarz et al. ²⁶	39	7	10
Simms et al. ⁴⁸	47	4 <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> ≤ 20 weeks 2 </div> <div style="text-align: center;"> > 20 weeks 2 </div> </div>	8
Total*	2090 fetuses	179 (8.6%) <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> $< 19-20$ weeks 156/1201 (13.0%)* </div> <div style="text-align: center;"> > 20 weeks 3/571 (0.5%)* </div> </div>	68 (2.9%)

*Does not include data of Gratacós et al.,³⁹ Harger et al.,¹² Giudozzi 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.^{40,41} 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%.^{12,26,38,42–49} (Table 3). 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.¹⁰

Currently, there does not appear to be any evidence that parvovirus B19 infection increases the risk of congenital anomalies in humans,^{1,14} though there have been case reports of central nervous system, craniofacial, musculoskeletal, and eye anomalies.^{31,14,50–53} In other species with other strains of parvovirus infection, congenital anomalies have been reported.^{1,14}

Parvovirus B19 has been associated with hydrops fetalis.^{12,19,26,38,39,42–44,46,49,54–56} 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.⁵⁵ 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.^{12,19,38,39,42–44}

If a fetus develops hydrops, ultrasound signs include ascites, skin edema, pleural and pericardial effusions, and placental edema.¹ It is estimated that parvovirus B19 infection accounts for 8% to 10% of non-immune hydrops,^{1,14} although some studies found molecular evidence of parvovirus B19 in 18% to 27% of cases of non-immune hydrops.¹⁴

Thrombocytopenia has been reported among up to 97% of hydropic transfused fetuses, with an incidence of severe thrombocytopenia ($< 50 \times 10^9$ platelets/L) up to 46%.^{10,48,57} 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.^{8–11,18,36,42,46,47,58–63} Case reports of neonatal complications of maternal parvovirus B19 infection have been reported, including hepatic insufficiency,^{59–61} myocarditis,^{8,36,62} transfusion dependent anemia,^{1,14} and central nervous system abnormalities.^{8,59,61} 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.⁴⁷ 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.⁴² 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.⁶⁴

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.^{10,11,63,64} 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.^{8,59,62} and may even require heart transplantation.⁶⁵

Recommendation

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

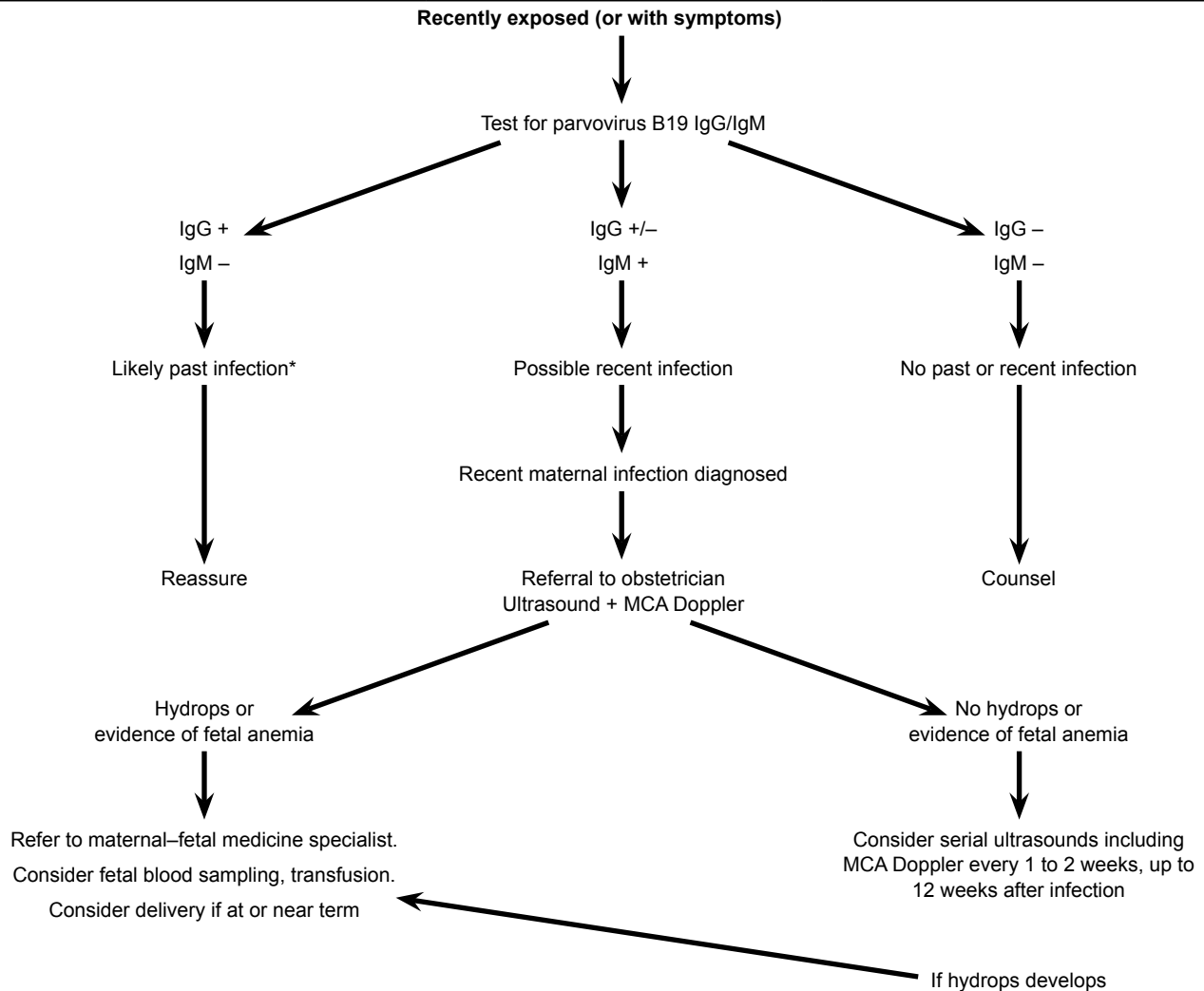
MANAGEMENT OF PARVOVIRUS B19

Exposure/Infection in Pregnancy

Systematic screening for parvovirus immunity in low-risk pregnancies is not currently recommended.⁶⁶ 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.^{9,67–69} (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.⁴⁹ 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.⁹

The presence of IgG and the absence of IgM with recent exposure suggest immunity.^{9–11,15} If the woman is

Management of a pregnant woman exposed to parvovirus B19 infection



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.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.^{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.^{9-11,18} (Figure)

If both parvovirus B19 IgG and IgM are negative, the woman is not immune and is therefore susceptible to infection.^{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.^{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.^{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

(up to 6 months prior). Serologic diagnosis with parvovirus B19 IgM alone for recent infection may be difficult because lab sensitivity for IgM is positive up to 6 months after acute 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,¹⁹ 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.^{70,71} 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.^{55,71} 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,^{19–21,55,71} and some studies have found that working in child daycare was not associated with an occupational risk for parvovirus infection.^{72,73} Therefore it is not recommended to routinely remove women susceptible to infection from high risk occupations.^{55,71}

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.^{9,14,42,54,69,74} 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.⁵⁴ Ultrasound assessment of the fetus should include Doppler measurement of the MCA peak systolic velocity to assess for fetal anemia.^{10,11,75–78} 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.^{76,77,79} Other ultrasound signs of parvovirus B19 infection include increased placenta thickness, echogenic bowel/meconium peritonitis, first trimester increased nuchal translucency, and amniotic fluid abnormalities.^{10,80} As fetuses with hydrops tend to move less, women should

also be instructed to monitor fetal movement daily.⁹ 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.⁸¹

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.¹ It can be identified histologically by characteristic intranuclear inclusions or by the presence of viral particles by electron microscopy.¹ Fetal infection can be detected with amniotic fluid or fetal serum using the most sensitive molecular methods available (nested PCR or reverse transcription PCR).⁴⁹ 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,⁷ 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.⁸²

Elevated MSAFP levels have been associated with fetal parvovirus B19 infection in several case reports^{83,84}; but in one study that found an association between MSAFP and fetal infection,⁸⁵ 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.⁵⁴

Recommendation

- 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

- Levy R, Weissman A, Blomberg G, Hagay ZJ. Infection by parvovirus B19 during pregnancy: a review. *Obstet Gynecol Surv* 1997;52:254–9.
- Cossart YE, Field AM, Cant B, Widdows D. Parvovirus-like particles in human sera. *Lancet* 1975;1:72–3.
- Anderson MJ, Jones SE, Fisher-Hoch SP, Lewis E, Hall SM, Bartlett CL, et al. Human parvovirus, the cause of erythema infectiosum (fifth disease)? *Lancet* 1983;1:1378.
- Brown T, Anand A, Ritchie LD, Clewley JP, Reid TM. Intrauterine parvovirus infection associated with hydrops fetalis. *Lancet* 1984;2:1033–4.
- Knott PD, Welply GA, Anderson MJ. Serologically proved intrauterine infection with parvovirus. *Br Med J (Clin Res Ed)* 1984;289:1660.
- 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.
- Rodis JF, Hovick TJ Jr, Quinn DL, Rosengren SS, Tattersall P. Human parvovirus infection in pregnancy. *Obstet Gynecol* 1988;72:733–8.
- Adler S, Koch WC. Human parvovirus B19. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn infant*. 7th ed. Philadelphia: Saunders; 2010:845–5.
- Rodis JF. Parvovirus infection. *Clin Obstet Gynecol* 1999;42:107–20; quiz 174–5.
- de Jong EP, Walther FJ, Kroes AC, Oepkes D. Parvovirus B19 infection in pregnancy: new insights and management. *Prenat Diagn* 2011;31:419–25. doi: 10.1002/pd.2714.
- Dijkmans AC, de Jong EP, Dijkmans BA, Lopriore E, Vossen A, Walther FJ, et al. Parvovirus B19 in pregnancy: prenatal diagnosis and management of fetal complications. *Curr Opin Obstet Gynecol* 2012;24:95–101. doi: 10.1097/GCO.0b013e3283505a9d.
- 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.
- Anderson LJ. Role of parvovirus B19 in human disease. *Pediatr Infect Dis J* 1987;6:711–8.
- Markenson GR, Yancey MK. Parvovirus B19 infections in pregnancy. *Semin Perinatol* 1998;22:309–17.
- Cohen BJ, Courouce AM, Schwarz TF, Okochi K, Kurtzman GJ. Laboratory infection with parvovirus B19. *J Clin Pathol* 1988;41:1027–8.

16. Valeur-Jensen AK, Pedersen CB, Westergaard T, Jensen IP, Lebech M, Andersen PK, et al. Risk factors for parvovirus B19 infection in pregnancy. *JAMA* 1999;281:1099–105.
17. Röhrer C1, Gärtner B, Sauerbrei A, Böhm S, Hottenträger B, Raab U, et al. Seroprevalence of parvovirus B19 in the German population. *Epidemiol Infect* 2008;136:1564–75. doi: 10.1017/S0950268807009958.
18. Lamont RF, Sobel JD, Vaisbuch E, Kusanovic JP, Mazaki-Tovi S, Kim SK, et al. Parvovirus B19 infection in human pregnancy. *BJOG* 2011;118:175–186. doi: 10.1111/j.1471-0528.2010.02749.x.
19. Centers for Disease Control (CDC). Risks associated with human parvovirus B19 infection. *MMWR Morb Mortal Wkly Rep* 1989;38:81–8, 93–7.
20. 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. *JAMA* 1990;263:2061–5.
21. 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;154:383–3.
22. 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. doi: 10.1056/NEJM198507113130203.
23. 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.
24. White DG, Woolf AD, Mortimer PP, Cohen BJ, Blake DR, Bacon PA. Human parvovirus arthropathy. *Lancet* 1985;1:419–21.
25. Reid DM, Reid TM, Brown T, Rennie JA, Eastmond CJ. Human parvovirus-associated arthritis: a clinical and laboratory description. *Lancet* 1985;1:422–5.
26. Schwarz TF, Roggendorf M, Hottenträger B, Deinhardt F, Enders G, Gloning KP, et al. Human parvovirus B19 infection in pregnancy. *Lancet* 1988;2:566–7.
27. Alger LS. Toxoplasmosis and parvovirus B19. *Infect Dis Clin North Am* 1997;11:55–75.
28. Kelleher JF Jr, Luban NL, 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.
29. Blacklock HA, Mortimer PP. Aplastic crisis and other effects of the human parvovirus infection. *Clin Haematol* 1984;13:679–91.
30. Serjeant GR, Topley JM, Mason K, Serjeant BE, Pattison JR, Jones SE, et al. Outbreak of aplastic crises in sickle cell anaemia associated with parvovirus-like agent. *Lancet* 1981;2:595–7.
31. Young N. Hematologic and hematopoietic consequences of B19 parvovirus infection. *Semin Hematol* 1988;25:159–72.
32. 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. doi: 10.1056/NEJM198707303170506.
33. 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.
34. Coulombel L, Morinet F, Mielot F, Tchernia G. Parvovirus infection, leukemia, and immunodeficiency. *Lancet* 1989;101. [letter]
35. 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.
36. Saint-Martin J, Choulot JJ, Bonnaud E, Morinet F. Myocarditis caused by parvovirus. *J Pediatr* 1990;116:1007–8.
37. Malm C, Fridell E, Jansson K. Heart failure after parvovirus B19 infection. *Lancet*. 1993;341:1408–9.
38. Public Health Laboratory Service Working Party on Fifth Disease. Prospective study of human parvovirus (B19) infection in pregnancy. *BMJ* 1990;300:1166–70.
39. Gratacós E, Torres PJ, Vidal J, Antolín E, Costa J, Jiménez 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.
40. Leduc L; SOGC Maternal-Fetal Medicine Committee. Stillbirth and bereavement: guidelines for stillbirth investigation. SOGC Clinical Practice Guidelines, No. 178, June 2006. *J Obstet Gynaecol Can* 2006;28:540–52.
41. Watt AP, Brown M, Pathiraja M, Anbazhagan A, Coyle PV. The lack of routine surveillance of parvovirus B19 infection in pregnancy prevents an accurate understanding of this regular cause of fetal loss and the risks posed by occupational exposure. *J Med Microbiol* 2013;62(Pt 1):86–92. doi: 10.1099/jmm.0.046714-0; 10.1099/jmm.0.046714-0.
42. 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.
43. 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(4 Pt 1):1168–71.
44. 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.
45. Koch WC, Adler SP, Harger J. Intrauterine parvovirus B19 infection may cause an asymptomatic or recurrent postnatal infection. *Pediatr Infect Dis J* 1993;12:747–50.
46. 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.
47. Rodis JF, Rodner C, Hansen AA, Borgida AF, Deoliveira I, Shulman Rosengren S. Long-term outcome of children following maternal human parvovirus B19 infection. *Obstet Gynecol* 1998;91:125–8.
48. 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. doi: 10.1159/000236149.
49. 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. doi: 10.1016/j.jcv.2005.11.002.
50. Weiland HT, Vermeij-Keers C, Salimans MM, Fleuren GJ, Verwey RA, Anderson MJ. Parvovirus B19 associated with fetal abnormality. *Lancet* 1987;1:682–3.
51. Katz VL, McCoy MC, Kuller JA, Hansen WF. An association between fetal parvovirus B19 infection and fetal anomalies: a report of two cases. *Am J Perinatol*. 1996;13:43–5. doi: 10.1055/s-2007-994201.
52. Barton LL, Lax D, Shehab ZM, Keith JC. Congenital cardiomyopathy associated with human parvovirus B19 infection. *Am Heart J* 1997;133:131–3.
53. Tiessen RG, van Elsacker-Niele AM, Vermeij-Keers C, Oepkes D, van Roosmalen J, Gorsira MC. A fetus with a parvovirus B19 infection and congenital anomalies. *Prenat Diagn*. 1994;14:173–6.
54. 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;179:985–88.

55. 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. doi: 10.1002/pd.940.
56. Desilets V, Audibert F; SOGC Genetics Committee. Investigation and management of non-immune fetal hydrops. SOGC Clinical Practice Guidelines, No. 297, October 2013. *J Obstet Gynaecol Can* 2013;35:923–38.
57. de Haan TR, van den Akker ES, Porcelijn L, Oepkes D, Kroes AC, Walther FJ. Thrombocytopenia in hydropic fetuses with parvovirus B19 infection: incidence, treatment and correlation with fetal B19 viral load. *BJOG* 2008;115:76–81. doi: 10.1111/j.1471-0528.2007.01555.x.
58. Dembinski J, Haverkamp F, Maara H, Hansmann M, Eis-Hubinger AM, Bartmann P. Neurodevelopmental outcome after intrauterine red cell transfusion for parvovirus B19-induced fetal hydrops. *BJOG* 2002;109:1232–4.
59. Cohen B. Parvovirus B19: an expanding spectrum of disease. *BMJ* 1995;311:1549–52.
60. Metzman R, Anand A, DeGiulio PA, Knisely AS. Hepatic disease associated with intrauterine parvovirus B19 infection in a newborn premature infant. *J Pediatr Gastroenterol Nutr* 1989;9:112–4.
61. Yoto Y, Kudoh T, Asanuma H, Numazaki K, Tsutsumi Y, Nakata S, et al. Transient disturbance of consciousness and hepatic dysfunction associated with human parvovirus B19 infection. *Lancet* 1994;344:624–5.
62. Porter HJ, Quantrill AM, Fleming KA. B19 parvovirus infection of myocardial cells. *Lancet* 1988;1:535–6.
63. Ryan G, Kelly EN, Inwood S, Altman D, Seaward PGR, McParland P, et al. Long-term pediatric follow-up in non-immune hydrops secondary to parvovirus infection. *Am J Obstet Gynecol* 1997;176(1 Part 2):S86.
64. 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. doi: 10.1097/01.AOG.0000249611.67873.94.
65. 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.
66. Wong SF, Chan FY, Cincotta RB, Tilse M. Human parvovirus B19 infection in pregnancy: should screening be offered to the low-risk population? *Aust N Z J Obstet Gynaecol*. 2002;42:347–51.
67. Crane JM. Prenatal exposure to viral infections. *Canadian J CME* 1998;10:61–74.
68. American College of Obstetrics and Gynecologists. ACOG practice bulletin. Perinatal viral and parasitic infections. No 20, Sept 2000. *Int J Gynaecol Obstet* 2002;76:95–107.
69. Health Protection Agency Rash Guidance Working Group. Guidance on viral rash in pregnancy – investigation, diagnosis and management of viral rash illness, or exposure to viral rash illness, in pregnancy. London: Health Protection Agency; 2011.
70. Cartter ML, Farley TA, Rosengren S, Quinn DL, Gillespie SM, Gary GW, et al. Occupational risk factors for infection with parvovirus B19 among pregnant women. *J Infect Dis* 1991;163:282–5.
71. Crowcroft NS, Roth CE, Cohen BJ, Miller E. Guidance for control of parvovirus B19 infection in healthcare settings and the community. *J Public Health Med*. 1999;21:439–46.
72. de Villemeur AB, Gratacap-Cavallier B, Casey R, Baccard-Longère M, Goirand L, Seigneurin JM, et al. Occupational risk for cytomegalovirus, but not for parvovirus B19 in child-care personnel in France. *J Infect* 2011;63:457–67. doi: 10.1016/j.jinf.2011.06.012.
73. 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. doi: 10.1007/s10096-008-0635-y.
74. Katz VL, Chescheir NC, Bethea M. Hydrops fetalis from B19 parvovirus infection. *J Perinatol* 1990;10:366–8.
75. Borna S, Mirzaie F, Hanthoush-Zadeh S, Khazardoost S, Rahimi-Sharbat F. Middle cerebral artery peak systolic velocity and ductus venosus velocity in the investigation of nonimmune hydrops. *J Clin Ultrasound* 2009;37:385–8. doi: 10.1002/jcu.20613.
76. Cosmi E, Mari G, Delle Chiaie L, 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.
77. Delle Chiaie L, 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. doi: 10.1046/j.0960-7692.2001.00540.x.
78. 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. doi: 10.1056/NEJM20001063420102.
79. Chauvet A, Dewilde A, Thomas D, Joriot S, Vaast P, Houfflin-Debarge V, et al. Ultrasound diagnosis, management and prognosis in a consecutive series of 27 cases of fetal hydrops following maternal parvovirus B19 infection. *Fetal Diagn Ther* 2011;30:41–7. doi: 10.1159/000323821; 10.1159/000323821.
80. von Kaisenberg CS, Jonat W. Fetal parvovirus B19 infection. *Ultrasound Obstet Gynecol*. 2001;18:280–8. doi: 10.1046/j.1469-0705.2001.00471.x.
81. 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.
82. Pryde PG, Nugent CE, Pridjian G, Barr M Jr, Faix RG. Spontaneous resolution of nonimmune hydrops fetalis secondary to human parvovirus B19 infection. *Obstet Gynecol*. 1992;79(5 Pt 2):859–61.
83. 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.
84. Bernstein IM, Capeless EL. Elevated maternal serum alpha-fetoprotein and hydrops fetalis in association with fetal parvovirus B-19 infection. *Obstet Gynecol* 1989;74(3 Pt 2):456–7.
85. 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.
86. Fairley CK, Smoleniec JS, Caul OE, Miller E. Observational study of effect of intrauterine transfusions on outcome of fetal hydrops after parvovirus B19 infection. *Lancet* 1995;346:1335–7.
87. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. *CMAJ* 2003;169:207–8.