CLINICAL PRACTICE GUIDELINE

TITLE:

**Parvovirus B19 Exposure /
Infection during Pregnancy**

Institute of Obstetricians and Gynaecologists

Royal College of Physicians of Ireland

and

Clinical Strategy and Programmes Division,

Health Service Executive

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Contents

1. Revision History

Version No.	Date	Modified By	Description
1.0	September 2014	Dr Mairead Kennelly	Version 1.0 Draft for review

2. Key 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 (non-immune) or if they have a current infection, by determining their parvovirus B19 IgG and IgM status. Women should be counselled that 50-65% of the pregnant population are immune, that even in cases of confirmed maternal infection, placental passage rates are 17-33% (Broliden, Tolfvenstam and Norbeck, 2006), and placental passage only results in an adverse fetal outcome in 10% of cases (although this proportion is dependent on gestational age) .

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 (Levy et al., 1997; SOGC, 2002; Broliden, Tolfvenstam and Norbeck, 2006; de Jong et al., 2006; Ergaz and Ornoy, 2006; Health Protection Agency, 2008, 2009; Tolfvenstam and Broliden, 2009; Public Health England, 2014).

3. If an acute/recent B19V infection has been diagnosed, then the woman should be tested for the presence of B19V DNA in blood (IgM, IgG). If recent B19V infection is confirmed (IgM +ve, IgG –ve/+ve), the woman should be referred to an obstetrician or a maternal-foetal medicine specialist. 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 anaemia or hydrops. If anaemia / hydrops develops, referral to a maternal-fetal medicine specialist should be made and consideration should be given to fetal blood sampling and intravascular transfusion (SOGC, 2002; de Jong et al., 2006; Ergaz and Ornoy, 2006; Health Protection Agency, 2008, 2009; Tolfvenstam and Broliden, 2009; Public Health England, 2014).

4. 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. Frequent handwashing may be recommended as a simple measure to reduce the risk of acquiring the infection.

5. During an outbreak, parents of preschool and school children as well as employees should be informed by public health of the risk of infection and its management. Each woman should be counselled by her obstetrician about her individual risk, based on her risk of infection, gestational age, and other obstetrical considerations. 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 (Gillespie et al., 1990). It is not recommended that policies be pursued to routinely send home women susceptible to infection.

3. Purpose and Scope

The purpose of this guideline is to outline investigation and management of pregnant women exposed to / experiencing symptoms of Parvovirus B19. This document summarizes the relevant evidence and provides practice recommendations related to the investigation and management of serology positive cases of Parvovirus B19. Consultation with the multidisciplinary team including obstetrician, fetomaternal specialist and neonatologist is recommended. These guidelines are designed to guide clinical judgement but not replace it. In individual cases a healthcare professional may, after careful consideration, decide not to follow a guideline if it is deemed to be in the best interests of the woman and her baby.

4. Background and Introduction

4.1 Definition

Human parvovirus B19 is a single-stranded DNA virus which is droplet spread with a predilection for infecting rapidly dividing cell lines, such as bone marrow erythroid progenitor cells (cells that form red blood cells), which are found in bone marrow, fetal liver, umbilical cord, and peripheral blood (de Jong et al., 2006).

It is responsible for 'erythema infectiosum', 'fifth disease' or 'slapped cheek syndrome', a common mild self-limiting childhood illness. 11However, parvovirus B19 infection can cause serious complications, especially in people who have haematological disorders or who are immunocompromised, and in women who are pregnant. It is a cause of nonimmune hydrops and fetal death.

Parvovirus B19 is most commonly spread by respiratory secretions or from hand to mouth contact (Torok, 1995). 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 occur every three to five years and may last up to six months (Rodis, Borgida, et al., 1998a). The incubation period is 4 to 20 days until the rash appears (Anderson et al., 1985). 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 confers lifelong immunity (Markenson and Yancey, 1998). Approximately 50% to 65% of women of reproductive age have immunity to parvovirus B19 (Cohen and Buckley, 1988; Valeur-Jensen et al., 1999). In the setting of an Irish maternity unit, 60.7% of pregnant women were immune to parvovirus. 18 Without known exposure, about 1% to 3% of susceptible pregnant women will develop serologic evidence of infection in pregnancy (Valeur-Jensen et al., 1999). Women at increased risk of infection include mothers of preschool and school-age children, workers at day care centres, and school teachers.

4.2   Prevalence

Infection with parvovirus B19 is common in developed countries. Studies have indicated that about 15% of preschool children, 50% of adults, and 85% of elderly people have serological evidence of past infection. Seasonal outbreaks of parvovirus B19 infection occur every 3–5 years. During school outbreaks, 10–60% of exposed children develop symptoms consistent with parvovirus B19 infection (Centers for Disease Control (CDC), 1989).

4.3   Clinical Presentation

The multiple ways parvovirus B19 may present are described below.

Asymptomatic: 20% to 25% of adults who develop parvovirus B19 infection will be asymptomatic (Rodis, Borgida, et al., 1998a).

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 after about one week may spread to the trunk and limbs. 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 (Markenson and Yancey, 1998).

Arthropathy: The most common symptom in adults affecting up to 80% of adult women 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 (White et al., 1985). 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.

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 (Reid et al., 1985; Alger, 1997). The virus attacks cells of the red blood cell lines in the bone marrow, causing hemolysis and red blood cell aplasia (Alger, 1997). 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. The anaemia, 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 (Young, 1988; Alger, 1997; Rodis, Borgida, et al., 1998a).

Myocarditis: Case reports have suggested a rare association between parvovirus B19 infection and acute myocarditis leading to heart failure (Saint-Martin et al., 1990; Malm, Fridell and Jansson, 1993).

5. Methodology

Medline, EMBASE and Cochrane Database of Systematic Reviews were searched using terms relating to Parvovirus B19, pregnancy, non-immune hydrops and management. Searches were limited to humans and restricted to the titles of English language articles published between 1980 to date. Relevant meta-analyses, systematic reviews, intervention and observational studies were reviewed. Guidelines / recommendations reviewed included Royal College of Obstetricians and Gynaecologists, Society of Obstetricians and Gynaecologists of Canada and NICE recommendations.

The principal guideline developer was Dr Mairead M Kennelly, Consultant Obstetrician and subspecialist in Fetal and Maternal Medicine. The guideline was peer-reviewed by: Dr Noirin Russell, Dr Susan Knowles, Dr Jeff Connell, Dr Elizabeth Dunn, Dr Paul Hughes.

6. Parvovirus B19 Infection in Pregnancy

Pregnancy does not appear to affect the course of the infection, but infection may affect the pregnancy (Alger, 1997). Gestational parvovirus B19 infection is usually a minor illness for the mother with a transplacental transmission rate of 17% to 33% to the fetus with a mean of about 6 weeks between maternal infection and fetal symptoms (Gratacós et al., 1995; Harger et al., 1998). The fetus is most vulnerable when it is infected in the second trimester, with the peak risk occurring at 17–24 weeks' gestation. Most fetuses infected with parvovirus B19 have spontaneous resolution with no adverse outcomes (Markenson and Yancey, 1998).

In endemic periods it is women who have contact with children at home who have the highest risk of a new infection in pregnancy. Pregnant women who are occupationally exposed to children under 6 have a slightly increased infection risk, especially in the first years of their career (Valeur-Jensen et al., 1999; Knowles et al., 2004). During epidemic periods the extremely stable parvoviruses are ubiquitous, leaving susceptible individuals with a similar exposure risk to affected individuals or contaminated objects. Current evidence does not support a general prohibition on working for seronegative pregnant women who have occupational contact with children (Modrow and Gärtner, 2006).

Individual risk assessment should consider

- Is the outbreak laboratory confirmed and ongoing
- Is there close contact with children under 6 years of age (in Ireland classes under 2nd class) but no close contact with children outside the work setting
- In the rare situations when exclusion from work is considered , this would not usually extend beyond the peak period of risk ie 24 weeks gestation

6.1   Fetal Effects of Parvovirus B19 Infection

1. Spontaneous Abortion

First and second trimester parvovirus infections carry an excess loss risk 10% above baseline (5%) but a low risk of long term sequalae during childhood (Wilcox et al., 1988) . The spontaneous loss rate of foetuses affected with parvovirus B19 before 20 weeks' gestation is 14.8% and after 20 weeks' gestation is 2.3% (Wilcox et al., 1988; Harger et al., 1998). The reason is uncertain but may be related to multisystem organ damage.

2. Congenital Anomalies

Currently, there does not appear to be any evidence that parvovirus B19 infection increases the risk of congenital anomalies in humans (Levy et al., 1997; Markenson and Yancey, 1998).

3. Hydrops

Parvovirus B19 has been associated with hydrops fetalis (Wilcox et al., 1988; Rodis et al., 1990; Cohen, 1995; Gratacós et al., 1995; Harger et al., 1998; Miller et al., 1998). 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 (Wilcox et al., 1988; Malm, Fridell and Jansson, 1993; Harger et al., 1998; Miller et al., 1998). Another mechanism is the rapidly expanding erythrocyte volume which increases 34-fold during the second trimester. This along with the shorter fetal red cell half life causes increased fetal sensitivity to transient red cell aplasia. There are a number of published studies of the rate of fetal loss and hydrops with parvovirus B19 infection (Rodis et al., 1990; Koch, Adler and Harger, 1993; Gratacós et al., 1995; Harger et al., 1998; Markenson and Yancey, 1998; Miller et al., 1998). Several studies found a higher fetal loss rate when the infection was acquired before 19 to 20 weeks' gestation (14.8%) [28,29,32] compared to that after 20 weeks (2.3%) (Public Health Laboratory Service Working Party on Fifth Disease, 1990; Rodis et al., 1990; Miller et al., 1998; Rodis, Rodner, et al., 1998). If a fetus develops

hydrops, ultrasound signs include ascites, skin edema, pleural and pericardial effusions, as well as placental edema (Levy et al., 1997). It is estimated that parvovirus B19 infection accounts for 8% to 10% of non-immune hydrops (Levy et al., 1997), although some studies found molecular evidence of parvovirus B19 in 18% to 27% of cases of non immune hydrops (Torok, 1995).

6.2   Long-term Neonatal Outcome

There have been few studies of the long-term effects on children of maternal parvovirus B19 infection (Porter, Quantrill and Fleming, 1988; Yoto et al., 1994; Torok, 1995; Ryan, Kelly and Inwood, 1997; Rodis, 1999). Case reports of neonatal complications of maternal parvovirus B19 infection have been reported, including hepatic insufficiency (Metzman et al., 1989), myocarditis, transfusion dependent anemia (Levy et al., 1997; Markenson and Yancey, 1998), and central nervous system abnormalities (Torok, 1995). 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 morbidity (Rodis, Rodner, et al., 1998). 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 (Rodis, 1999). Parvovirus B19 itself does not seem to cause long-term neurologic morbidity, but severe anaemia may be an independent risk factor for long-term neurologic sequelae (Ryan, Kelly and Inwood, 1997).

6.3   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 1) (Rodis, 1999) 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 (Public Health Laboratory Service Working Party on Fifth Disease, 1990).

1.   The presence of IgG and the absence of IgM with recent exposure suggests immunity (Rodis, 1999). 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 (Public Health Laboratory Service Working Party on Fifth Disease, 1990). 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 (Public Health Laboratory Service Working Party on Fifth Disease, 1990).

3. If both parvovirus B19 IgG and IgM are negative, the woman is not immune and therefore susceptible to infection (Public Health Laboratory Service Working Party on Fifth Disease, 1990). 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 4 weeks. Current evidence does not support a general prohibition on working for seronegative pregnant women who have occupational contact with children. For factors influencing an individual risk assessment see bullet points on page 8.

4. If testing reveals both parvovirus B19 IgG and IgM to be present, this may suggest recent infection (Rodis, 1999). Stored booking bloods are available from all women for a year. Testing booking bloods contemporaneously with bloods at the gestation of infection 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. 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.   In cases of uncertainty where seroconversion has not been demonstrated the woman should be tested for the presence of B19V DNA in blood"

5. If the woman has developed a recent infection, the virus may be transmitted to the fetus (17 to 33%) and may cause nonimmune hydrops. The occurrence of hydrops is most prevalent in the second trimester and rare near term. 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 (Wilcox et al., 1988; Markenson and Yancey, 1998; Rodis, Borgida, et al., 1998b; Rodis, 1999). 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 for a period of 10 weeks (Rodis, 1999). 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 (Public Health Laboratory Service Working Party on Fifth Disease, 1990). 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 (Barrett et al., 1994).
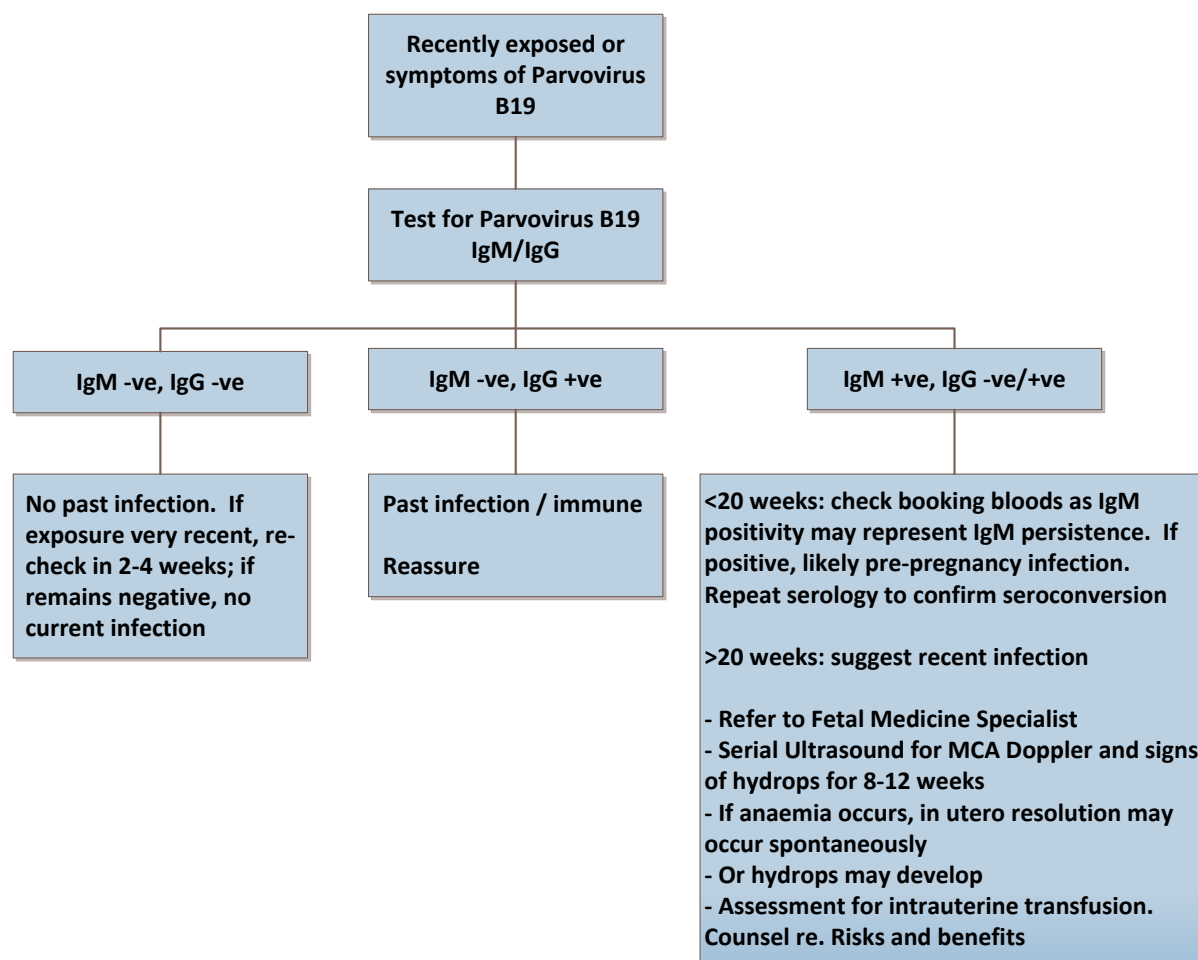
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┌─────────────────────────┐
│   Recently exposed or   │
│ symptoms of Parvovirus  │
│           B19           │
└─────────────────────────┘
             │
┌─────────────────────────┐
│   Test for Parvovirus   │
│         B19 IgM/IgG      │
└─────────────────────────┘
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IgM -ve, IgG -ve	IgM -ve, IgG +ve	IgM +ve, IgG -ve/+ve
No past infection. If exposure very recent, re-check in 2-4 weeks; if remains negative, no current infection	Past infection / immune Reassure	**<20 weeks:** check booking bloods as IgM positivity may represent IgM persistence. If positive, likely pre-pregnancy infection. Repeat serology to confirm seroconversion **>20 weeks:** suggest recent infection - Refer to Fetal Medicine Specialist - Serial Ultrasound for MCA Doppler and signs of hydrops for 8-12 weeks - If anaemia occurs, in utero resolution may occur spontaneously - Or hydrops may develop - Assessment for intrauterine transfusion. Counsel re. Risks and benefits

Figure 1. Management of a pregnant woman exposed to Parvovirus B19 infection recently exposed (or symptoms)

6.4   Diagnosis of Fetal Infections

Parvovirus B19 cannot usually be cultured in regular culture media (Levy et al., 1997). It can be identified histologically by characteristic intranuclear inclusions or by the presence of viral particles by electron microscopy (Levy et al., 1997). 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 (Rodis et al., 1988), 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 (Pryde et al., 1992).

6.5   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 haemoglobin and reticulocyte count, and intrauterine transfusion, if necessary (Torok, 1995). If the fetus is term or near term, delivery should be considered (Torok, 1995). 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 (Torok, 1995; Rodis, 1999) 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. Doppler assessment of the middle cerebral artery flow velocities is the mainstay of current assessment of fetal anemia (Mari et al., 2000; Oepkes, 2000; Divakaran et al., 2001). A summary of case reports of intravascular transfusion for fetal hydrops due to parvovirus B19 infection revealed a fetal mortality rate of 11% (Levy et al., 1997). In all 18 cases, the fetal haemoglobin was less than 8 g/dL, and most had severe hydrops. Failey et al.46 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 (Fairley et al., 1995). 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 (Rodis, Borgida, et al., 1998b).

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8. Implementation Strategy

- Distribution of guideline to all members of the Institute and to all maternity units.
- Implementation through HSE Obstetrics and Gynaecology programme local implementation boards.
- Distribution to the Director of Acute Hospital Services for dissemination through line management in all acute hospitals
- Distribution to other interested parties and professional bodies.

9. Qualifying Statement

These guidelines have been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. Clinical material offered in this guideline does not replace or remove clinical judgement or the professional care and duty necessary for each pregnant woman. Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible for:

- Discussing care with women in an environment that is appropriate and which enables respectful confidential discussion.

- Advising women of their choices and ensure informed consent is obtained.
- Meeting all legislative requirements and maintaining standards of professional conduct.
- Applying standard precautions and additional precautions, as necessary, when delivering care.
- Documenting all care in accordance with local and mandatory requirements.