



**UK National  
Screening Committee**

# **Parvovirus B19 Infection in Pregnancy**

## **A Brief Review of Literature**

External review against programme appraisal criteria  
for the UK National Screening Committee (UK NSC)

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at <http://www.screening.nhs.uk/policies> and the policy review process is described in detail at <http://www.screening.nhs.uk/policyreview>

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### ***Purpose***

The purpose of this brief paper is to review the literature on parvovirus B19 infection in pregnancy and to make a recommendation on whether a full review of the evidence on screening is required at this point.

### ***Introduction***

Human Parvovirus B19 is a small single stranded DNA virus that requires rapidly dividing cells for replication. It is the only parvovirus pathogenic to humans. The virus was first discovered in 1975 in sera from healthy blood donors<sup>(1)</sup> and was shown subsequently to be associated with aplastic crisis in children with sickle cell anaemia.<sup>(2, 3)</sup> In 1983, parvovirus B19 was shown to be the causative agent of erythema infectiosum, also known as fifth disease.<sup>(4)</sup> In 1984 following case reports describing hydrops fetalis associated with confirmed congenital infection parvovirus was identified as a fetal pathogen.<sup>(5)</sup>

Erythema infectiosum, or fifth disease, is a mild, acute exanthematous disease mainly of children. Parvovirus is an airborne virus and the main route of transmission is through respiratory droplets. In temperate climates epidemics typically occur in three to five year cycles with outbreaks occurring mainly in late winter and early spring.

Most women who are infected with parvovirus B19 in pregnancy have a satisfactory outcome. Maternal infection early in pregnancy may result in fetal loss or non-immune hydrops fetalis, which results from, infection of fetal erythroid progenitor cells leading to profound anaemia and cardiac failure.

### ***Clinical manifestations***

Parvovirus B19 infection is a common infection, especially in school age children. It usually manifests as a non-specific flu-like illness and is characterised by a diffuse erythema of the cheeks, often referred to as “slapped- cheek syndrome”, followed by the spread of a maculopapular rash on the trunk, back and extremities. The infection is usually self-limiting within a few weeks. Viraemia precedes the rash and once the rash is present the subject is no longer infectious. The incubation period is 13-18 days. In adults, particularly women, arthralgia is a common complication and the rash may be absent. The clinical presentation is similar to that of rubella and current guidelines emphasise the importance of considering all infections causing maculopapular rash in the diagnostic pathway.

In both adults and children about 20-30% of cases of infection are not associated with symptoms.

### ***Population seroprevalence***

Infection occurs worldwide but seroprevalence rates vary with age, point in the epidemic cycle and geography. Infection is most common in school age children with the peak age of infection

of 6-7 years. Seroprevalence increases with age in temperate climates such as the UK where about 60-70% of women of childbearing age have serological evidence of past exposure to parvovirus and are not at risk of infection in pregnancy.<sup>(6, 7)</sup> The remaining 30-40% of women are susceptible to acute infection in pregnancy.<sup>(8, 9)</sup> Infection appears to confer lifelong immunity in immunocompetent hosts. Risk of infection is increased in susceptible women with nursery or school aged children in the family and those working with children<sup>(7, 10)</sup> and this places limitations on the potential of avoidance of exposure as a strategy in seronegative women of childbearing age.

Seroconversion among susceptible pregnant women in a non-epidemic situation is estimated to be around 1% and in an epidemic this increases to around 13%.<sup>(6, 7)</sup> In this situation there is likely to be awareness of local outbreaks. A review by Lamont et al suggest that more needs to be known about role of ethnicity in the variation of seroprevalence within Western populations.<sup>(9)</sup>

### ***Mother-to-child transmission and pregnancy outcome***

The mother-to-child transmission rate is about 30%.<sup>(11, 12)</sup> Most women with confirmed parvovirus infection in pregnancy have healthy babies. However prospective studies suggest that in a small number, particularly those exposed in the first 20 weeks of pregnancy, there is a risk of fetal loss or non-immune hydrops fetalis. This is due to infection of the fetal erythroid progenitor cells in the bone marrow and liver which may result in profound anaemia and the infection has been associated with compromised cardiac function.

### ***Fetal hydrops***

Fewer than 10% of all cases of non-immune hydrops fetalis are caused by infections including parvovirus B19.<sup>(13)</sup>

Prospective cohort studies of women with parvovirus B19 infection provide information on risk of adverse outcomes.<sup>(10, 14)</sup> The observed risk of fetal hydrops in women with parvovirus B19 infection ranges from 0-6% (8, 10, 14-16) and the critical time of risk is infection occurring between 9-20 weeks gestation. Reported rates of adverse effects in different studies are likely to reflect, the different distribution of gestational age at infection and study population. For example retrospective case series studies have reported higher rates of non immune hydrops but have also highlighted the possibility of this resulting from selection bias.<sup>(24, 25)</sup>

Based on a single centre in France, covering a catchment area of 58,000 births, approximately 3 per 100,000 births were complicated by parvovirus B19 fetal hydrops.<sup>(17)</sup> This is close to the estimate of Miller et al of 2 per 100,000 pregnancies.<sup>(14)</sup>

A proportion of cases of fetal hydrops caused by parvovirus have been reported to be detected during the routine mid trimester anomaly scan.<sup>(17)</sup>

### *Fetal loss*

The overall fetal loss rate after infection has been estimated as 5-10% but reported rates vary according to gestation age at infection, most deaths occurring in the second trimester of pregnancy<sup>(7, 10, 14, 18)</sup> following exposure between 9 – 20 weeks. The risk of fetal loss after acute parvovirus infection in the first trimester of pregnancy was estimated in Denmark taking advantage of national registries and parvovirus B19 testing in serum from 40,000 samples from an antenatal syphilis population screening programme. Although primary infection during the first trimester was associated with a 71% increased relative risk of fetal loss. The absolute risk is much lower and the Danish population-based setting only 0.1% of 2,918 fetal losses were attributable to parvovirus infection. It was estimated that this proportion could increase to 1% during epidemic periods.<sup>(19)</sup>

### *Birth outcome and follow-up*

There is no evidence from observational prospective studies of women with infection and their infants that infection in pregnancy results in birth defects or developmental problems appearing later in childhood.<sup>(14, 20, 21)</sup>

### ***Treatment, management and prevention***

There is no vaccine currently available to prevent acquisition of infection by seronegative women. However one paper reported the results of a phase I human vaccine study.<sup>(9)</sup> It is unclear whether this has progressed to a phase II study.

Measures to prevent infection are problematic as parvovirus ceases to be infectious once the rash develops. Furthermore, avoidance of exposure may be limited as a prevention strategy in the pregnant population given that the source of parvovirus infection is frequently found in children.

There are no interventions which can alter the course of infection prior to the development of hydrops and fetal losses due to anaemia or cardiac failure could not be prevented. The development of immunoglobulins and antiviral therapies as treatment options was identified as a requirement in one recent review.<sup>(9)</sup>

However, if infection is detected in pregnancy current guidelines recommend that the fetus should be monitored with regular ultrasound examinations to detect fetal anaemia and hydrops. If significant anaemia or hydrops develops, an intrauterine blood transfusion is often required and the procedure may be complicated; as pre-existing thrombocytopenia is often present leading to higher pregnancy loss rates. Current maternal testing options cannot predict which fetuses will develop severe anaemia and which cases of anaemia will progress to hydrops requiring treatment. The inability to identify a group requiring treatment prior to the onset of hydrops has been identified as an area requiring further research.<sup>(9)</sup>

Despite progress in intrauterine transfusion there is evidence to suggest that neurodevelopmental and psychomotor impairment is increased in children who survived intrauterine transfusion for parvovirus infection compared with the general population but further studies are required to determine potential risk factors. <sup>(17, 22)</sup>

### ***Screening tests and confirmation of infection***

Within current guidance, all pregnant women presenting with a non-vesicular rash compatible with a systemic virus infection should be investigated for parvovirus, measles and rubella infection, irrespective of a prior history of rubella vaccination or previous positive rubella antibody test. As infection may be asymptomatic pregnant women with significant contact (defined as being in the same room for over 15 minutes or face-to-face contact) with a non-vesicular illness should be investigated for parvovirus B19, measles and rubella infection, irrespective of whether they develop a rash or not. The laboratory test are well described and detect antibodies that reflect past infection and those that confirm acute infection. <sup>(23)</sup>

Diagnosis of parvovirus B19 infection includes measurement of B19 IgG and IgM antibodies in blood and B19 DNA in blood or tissue samples by PCR. These tests are well established but do not appear to have been tested in population screening programmes and variations in sensitivities and specificities between different assays have been reported. Lamont et al <sup>(9)</sup> suggest that this may result in misdiagnosis as measles or rubella and are concerned to point out uncertainties in the diagnostic pathway.

### **Conclusion**

The UK NSC criteria require evidence on the condition, the test, the intervention and the screening programme. No papers exploring the effectiveness of screening were identified in the literature search.

In addition, the review by Lamont et al identified a broad range of research needs relating to seroprevalence, the testing process and prevention and treatment options. The need for research on such fundamental issues suggests that it is unlikely that a full review of the literature would find sufficient evidence to justify a screening programme. The recommendation of this paper is not to commission a more comprehensive review.

If screening was recommended all women would need to be screened in early pregnancy for the presence of B19 antibodies. About 30-40% of women would be expected to be seronegative and susceptible to infection. Susceptible women would then need to be tested regularly from the first trimester onwards to detect seroconversion and those with confirmed infection would require regular fetal monitoring with ultrasound. The optimum time for initial screening, further testing and its frequency have not been considered in the publications identified by the literature search.

No vaccine is available to prevent acquisition of infection. Avoidance of exposure on such a large scale has not been evaluated but is likely to be limited in effectiveness. There are no interventions to prevent transmission to the fetus if the mother is infected or to alter the course of the infection if transmitted to the fetus. The only exception to this is to monitor women with proven infection to detect hydrops fetalis at a stage when treatment is more effective. However there are reports of treatment related harm to the fetus. Furthermore, a proportion of cases of fetal hydrop are already detected during the mid trimester fetal anomaly scan.

Infection is associated with increased fetal loss and fetal hydrops but the overall burden of losses is small, even in epidemics, and for most women the outcome of pregnancy is satisfactory. Up to 90% of the small number of miscarriages and intrauterine deaths are without evidence of fetal hydrops and would not benefit from ultrasound monitoring. As such the majority of fetal losses associated with parvovirus could not be prevented.

The components of a screening programme are not currently in place. However the clinical features of parvovirus infection are similar to those of rubella and current guidance recommends that any pregnant women presenting with, or in contact with, a rash associated illness should be referred to a health professional for immediate assessment and investigation so that a definitive diagnosis can be made (23). This approach is supported by recommendations from the RCOG, HPA and NICE Clinical Knowledge summaries. There may be opportunities for the NHS IDPS Programme to increase awareness of the strategy with health professionals. Similarly there may also be opportunities to ensure that parvovirus B19 is considered in cases of non immune fetal hydrops detected during pregnancy.

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