Slovenian recommendations for parvovirus B19 infection in pregnancy

Nina Osvald Avguštin,[1] Barbara Šajina Stritar,[1] Faris Mujezinović,[2] Tanja Premru-Sršen[1]

[1] Department of Perinatology, Division of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia

[2] Department of Perinatology, Division of Gynecology and Perinatology, University Medical Centre Maribor, Maribor, Slovenia

Correspondence: Tanja Premru Sršen, e: tanja.premru@gmail.com

Key words: erythema infectiosum; fetal anemia; fetal death; non-immune hydrops fetalis (NIFH); intrauterine transfusion (IUT)

Received: 12. 5. 2017
Accepted: 25. 10. 2017

Abstract

Parvovirus B19 (B19V) causes a mild disease called erythema infectiosum, also known as the fifth disease that affects mostly children and young adults. The virus can be transferred to the fetus during pregnancy in 31 to 51 % of the cases and can cause severe anaemia, non-immune hydrops fetalis or fetal death due to inhibition of erythropoiesis. It also affects the heart muscle, central nervous system, bones, and most likely can cause a subsequent arrest in children's neurological development. It is estimated that 25–45 % of pregnant women are seronegative with a high risk of infection during pregnancy. A B19V infection in pregnant women is determined by detecting specific IgM and IgG antibodies, and in case of doubt, by using PCR method to detect viral DNA. Fetal infection with B19V is confirmed by detecting viral DNA in the amniotic fluid. In the case of either a suspected or confirmed fetal infection we monitor the fetus by ultrasound screening in a tertiary centre. We treat the fetus with an intrauterine transfusion at the first signs of anaemia or hydrops. To prevent fresh infections with B19V during pregnancy we should raise awareness amongst women and healthcare workers about the risks it poses for the fetus. The recommendations for management of women who are exposed to, are at risk of developing, or have developed B19V infection in pregnancy are published in this article.

Citirajte kot/Cite as: Osvald Avguštin N, Šajina Stritar B, Mujezinović F, Premru Sršen T. [Slovenian recommendations for parvovirus B19 infection in pregnancy]. Zdrav Vestn. 2018;87(1–2):91–101.

DOI: 10.6016/ZdravVestn.2618

Priporočila je sprejelo Združenje za perinatalno medicino SZD dne 2. 2. 2017 in GSS SZD dne 14. 3. 2017.

1. Purpose

Recommendations are intended to present the foetal risk in primary maternal infection with parvovirus B19 and the management of suspected or confirmed infection in pregnancy.

2. Background

Human parvovirus B19V was discovered in 1975 by Cossart and colleagues and reported on in The Lancet (1). A whole decade passed before B19V was associated with a mostly mild illness erythema infectiosum, known as fifth disease, which most commonly afflicts children and young adults (2). A patient has a typical rash on the face, which resembles the redness appearing after a slapped cheek. Arthropathy is an accompanying symptom in 10 % of children and 80 % of adult women, from whom the particles of the virus from the syno-

vial fluid have been isolated (3,4). Both symptoms coincide with the appearance of IgM antibodies, indicating the immune mechanism during the appearance of both (56). B19V is a potent inhibitor of erythropoiesis, which may cause additional complications. In individuals with a previous disorder of erythropoiesis it may cause a severe aplastic crisis (5). In pregnant women, the infection can be transmitted to the foetus. Moreover, the infection may also have permanent consequences for the foetus (6).

2.1. Pathogenesis

Cellular B19V receptors are found on erythroid progenitor cells, such as erythroblasts and megakaryocytes, making the virus a potent inhibitor of haematopoiesis. The receptors are also found on erythrocytes, synovium, placenta, foetal myocardium, and endothelial cells (7,8). Viral reproduction is limited to erythroid progenitor cells, causing toxic cell damage and triggering apoptosis (9-11). After viremia occurs in the blood of a pregnant woman, it reaches its peak in about a week. The symptoms such as erythema, mild fever, arthropathy, and headache occur approximately 10–14 days after infection in approximately 50 % of infected pregnant women. A vertical transfer of the infection from the mother to the foetus occurs within one to three weeks after the maternal infection. The risk of foetal infection is the greatest when IgM antibodies appear in the maternal serum, presumably during the time of maximal viremia, i.e. about day 7 after the infection (12). Foetal infection is in most cases resolved spontaneously without consequences, but it may lead to serious complications such as non-immune hydrops foetalis (NIHF) and foetal death. Foetal complications are the consequence of infection and lysis of erythroid progenitor cells by inhibition of erythropoiesis, and the infection of the placenta and myocardium (13,14).

2.2. Clinical presentation of foetal infection

Parvovirus B19 infection may be manifested by foetal death, NIHF due to severe anaemia, thrombocytopoenia, hyperechogenic bowel, myocarditis, and central nervous system abnormalities. It may also lead to bone changes (29). In 60 % of cases the infection can occur without clinical signs (27,30). In pregnant women showing no signs of infection the interval between the time of infection and the appearance of signs of foetal infection ranges between 3 and 15 weeks. The signs of foetal infection can be diagnosed ultrasonically between the 17th and 33rd week of gestation, regardless of gestational age at the time of maternal infection (27).

2.2.1. Foetal death

Intrauterine foetal death most commonly occurs between the 20th and 24th week of gestation, however, foetal deaths as early as at 10 weeks of gestation and as late as at 41 weeks have also been described (22). The foetus may also die without the signs of NIHF and erythropoiesis (31). The risk of foetal death is 1.7 times higher if IgM antibodies to B19V in maternal serum are positive (32).

2.2.2. Non-immune hydrops foetalis

The observed risk for NIHF due to B19V infection is 3.9–11.9 % (22,27). The cause of NIHF is severe anaemia leading to cardiac failure. Anaemia most commonly occurs during haematopoiesis in the liver between 8 and 20 weeks of gestation (33), since during this period the erythrocyte life span is shorter than at

the time of haematopoiesis in the bone marrow and spleen (7). The time interval between B19V infection and the occurrence of NIHF is usually 2–6 weeks (33), it can also be 10–12 weeks (34), and exceptionally 20 weeks (35). The highest incidence of NIHF due to B19V is between 17 and 24 weeks of gestation (23). Ultrasound examination shows signs of hydrops with ascites, cardiomegaly, and pericardial effusion. The advanced stage is represented by the development of a generalized oedema and large placental oedema. The latter most likely causes the development of a preeclampsia-like condition in the mother with oedema, hypertension, and proteinuria due to perfusion disorders. The condition is called *mirror syndrome* because the symptoms in the mother are a reflection of those in the foetus (21,36).

2.2.3. Thrombocytopenia

Moderate to severe thrombocytopenia may also develop in the foetus with anaemia and NIHF due to B19V infection. Haan et al. have described thrombocytopenia with less than 50×10^9/L of platelets just before intrauterine transfusion in 14 of the 30 foetuses (46 %) infected with B19V (37). In none of the foetuses haemorrhage was observed.

2.2.4. Neurological effects

B19V can cause neurological complications such as encephalopathy, impaired neural migration, abnormal gyration, and neonatal encephalitis (38-40) in the foetus and newborn. Less is known about the long-term neurological consequences. Only two smaller studies have been published. One study reported good predictors of neurodevelopmental outcome in all 20 surviving children after an intrauterine transfusion due to NIHF after B19V infection; however, 35 % of the children were lost to follow-up (41). In the other study neurodevelopmental disorders were found in three of the 28 (11 %) children aged 1.5–13 years who received an intrauterine transfusion due to foetal anaemia after B19V infection (42,43). One developed cerebral palsy; two others developed severe neurodevelopmental delay. Developmental abnormalities of the central nervous system can be due to hypoxic and ischemic brain damage as a result of severe anaemia and NIHF.

2.2.5. Morbidity in children

A Danish study on 1,095 children with mean age 9.2 years who were born to mothers with primary B19V infection in pregnancy, has not found an increased risk for 19 of the 20 observed diseases (44). However, they observed a 6-fold increase in the risk of central nervous system cancer, although the number of children was low.

2.3. Epidemiology

B19V infection is common and widespread throughout the world. The virus is transmitted mainly by droplets, but also with blood and blood products, and also vertically from the mother to the foetus (6). Vertical transmission of the infection from the mother to the foetus does not occur if the mother has acquired resistance when exposed to the virus, therefore, she has IgG anti-B19V antibodies in the serum, which is intended to provide life-time protection against a primary infection. B19V epidemics occur every 4 years, reaching its peak in late spring (15). The seroprevalence of IgG B19V antibodies in the population is from 2–15 % in children aged one to five years, 15–60 % in children aged 16–19 years, 30–60 % in adults, and over 85 % in the elderly (16). Seroprevalence in women of reproductive age is esti-

mated to be 66 % and greater in women (73–89 %) working with children, and women with children (81 %) (17,18). It is estimated that 25–45 % of pregnant women is seronegative, which means that there is a risk of primary infection in pregnancy in a considerable proportion of pregnant women (17). The estimated incidence of primary B19V infection in pregnancy is 1–2 % in the endemic period, which increases to more than 10 % during an epidemic (19-21). The infection is transferred from the mother to the foetus in 32–51 % (17–33 %) of cases, and the risk of complications in the foetus is about 10 % (7.22–24.56). The risk of complications in the foetus is higher if the infection occurs before the 22nd week of gestation (25-27) and drops with gestational age, probably because of the passive transfer of the mother's antibodies after the 25th week of gestation, which later protect the foetus (6,28).

A Slovenian retrospective study included 34 pregnant women with parvovirus B19 infection confirmed by serology and/or PCR on viral DNA in the years 2011 and 2012 (45). The infection most commonly occurred in the first trimester. Most had a favourable outcome of pregnancy with the delivery of a healthy baby (28/34). An unfavourable outcome occurred in 3 cases: one case of foetal hydrops and poor maternal condition, one intrauterine foetal death at 18 weeks of gestation, and a cystic formation in the abdomen that resulted in termination of pregnancy in one case. One case presented with foetal anaemia requiring an intrauterine transfusion. In one case, the MCA flow was increased without an IUT. One case presented with a cardiac malformation (patent ductus arteriosus and foramen ovale), and one with IUGR and oligohydramnios. Despite largely satisfactory outcomes of pregnancy, there is, nevertheless, a significant risk of foetal loss and non-immune hydrops foetalis in the second trimester (45).

3. Identification and assessment of evidence

These recommendations are based on the Clinical practice guideline Parvovirus B19 Infection in Pregnancy prepared by the Society of Obstetricians and Gynecologists of Canada (SOGC), Cytomegalovirus, parvovirus B19, varicella zoster and toxoplasmosis in pregnancy published by the American College of Obstetricians and Gynecologists (ACOG) in Practice bulletin no. 151, and a review article with the recommendations of the Dutch Leiden University Medical Centre (36).

3.1. Recommendations

3.1.1. Prevention of B19V infection in pregnant women

In order to avoid foetal morbidity and mortality due to B19V infection, it is advisable to prevent primary infection in the mother. B19V vaccine has not yet been developed and is not available for clinical use (54). Therefore, other preventive measures are needed, such as raising the awareness among women of reproductive age and healthcare professionals about the risks of primary infection in pregnancy. Research has shown that the lack of knowledge about the risks of an infection in pregnancy is present not only in women, but also in physicians (55,56).

Recommendation	C 2^{+}
Routine screening of pregnant women for the presence of IgM is not necessary.	

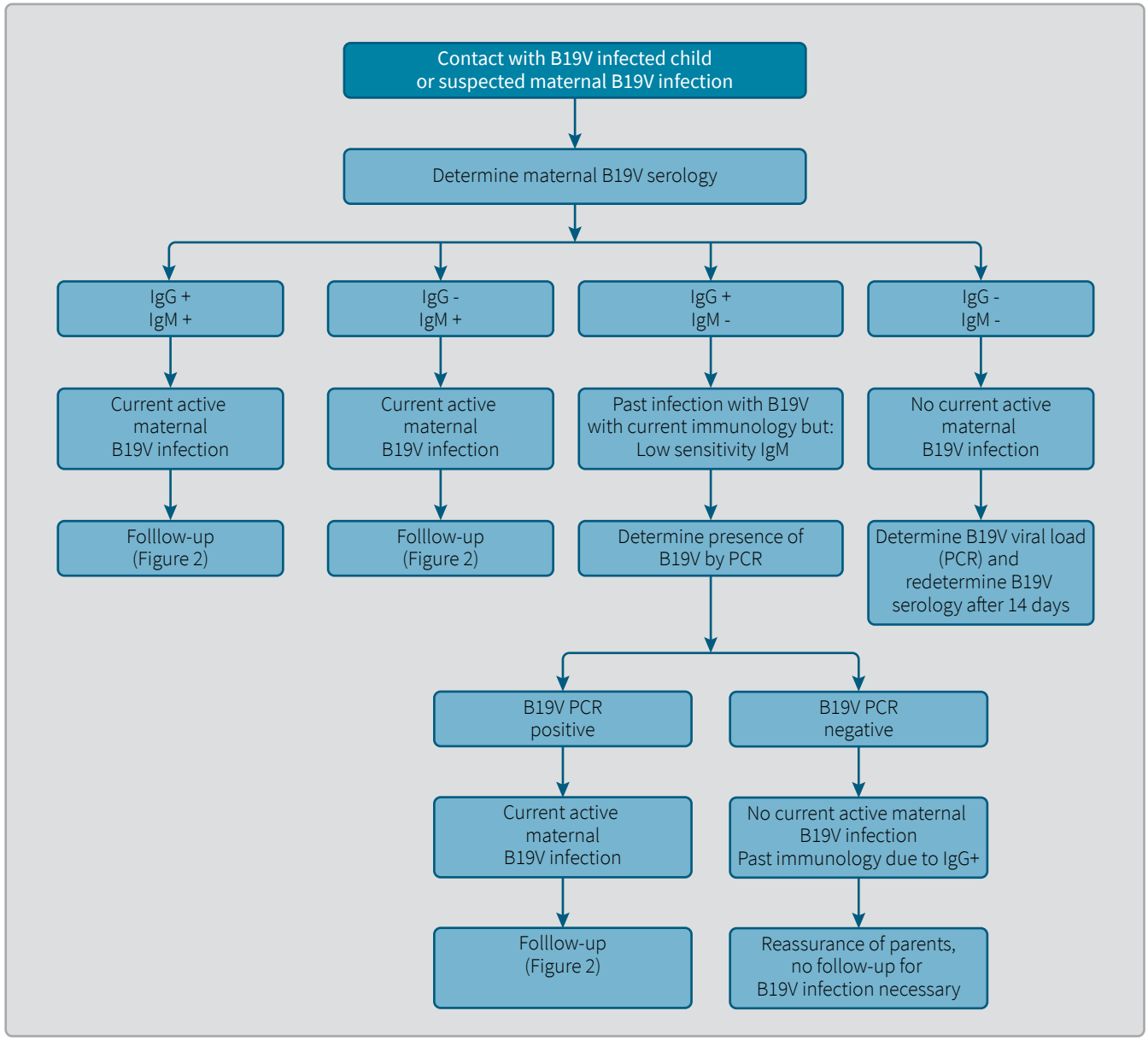

Figure 1: Detection of B19V infection in pregnant woman (36).

The opinion of the *UK National Screening Committee* (UK NSC) was that further research on the prevalence and testing methods was necessary in order to screen pregnant women for susceptibility to infection with B19V. Although screening would identify a large number of infectious women, there are currently no agreed treatment or prevention methods for foetal protection (60).

Recommendation D 4

Pregnant women are advised to avoid possible exposure to infection. Decision to recommend absence from work should be individual according to occupational exposure.

Diagnosis of B19V infection in pregnancy

Primary B19V infection in pregnancy can be suspected after contact with a diseased person, the onset of clinical signs of the disease, or the onset of foetal symptoms, such as reduced foetal movement or hydrops.

Recommendation **C 2+**

Investigation for parvovirus B19 infection is recommended as part of the standard diagnostic workup in the case of foetal hydrops or intrauterine death.

3.1.2. Diagnosis of maternal infection

B19V infection may be subclinical; therefore, we cannot rely solely on clinical signs specific to the disease.

B19V infection is diagnosed by determining specific IgM and IgG antibodies in the maternal serum (Figure 1). IgM antibodies can be detected between the 7^{th} and 10^{th} day after the infection. They peak between the 10^{th} and 14^{th} day and then decrease in the next two to three months (46). IgG antibodies gradually increase from day 14 and reach a plateau at four weeks after the infection (46). IgG antibodies are said to be present in the serum for an extended period of time and are intended to provide lifelong protection against re-infection. In the absence of specific antibodies in the serum, the serologic window period after the infection is about 7 days, which must be taken into account in the diagnosis of an infection (47).

The sensitivity of IgM antibodies determination in a pregnant woman between 8 and 12 weeks after the infection ranges between 63 and 94 % (48,49), while the DNA test can correctly detect an infection in 96 % of cases (27). When in doubt, a PCR analysis can importantly contribute to the accuracy of the infection diagnosis in the pregnant woman (50), however, we must be aware that low levels of B19V DNA can be maintained long after the acute phase of infection.

Recommendation **C 2+**

Pregnant women who have been in contact with an infected person or have developed signs of infection should be tested for the presence of antibodies in order to determine whether they are susceptible to infection or to confirm primary infection. PCR is used to detect B19 DNA when in doubt.

Recommendation **C 2+**

When IgG antibodies are present, and IgM and PCR B19V DNA are negative, the pregnant woman should be assured that she cannot become infected and that there is no risk to the foetus.

Recommendation **C 2+**

If no IgG and IgM antibodies are present, PCR B19V DNA is negative, and the incubation period has passed, the pregnant woman is not immune and has not been infected.

3.1.3. Diagnosis of foetal infection

Foetal infection cannot be reliably diagnosed by B19V antibodies determination in maternal or foetal serum (47,50).

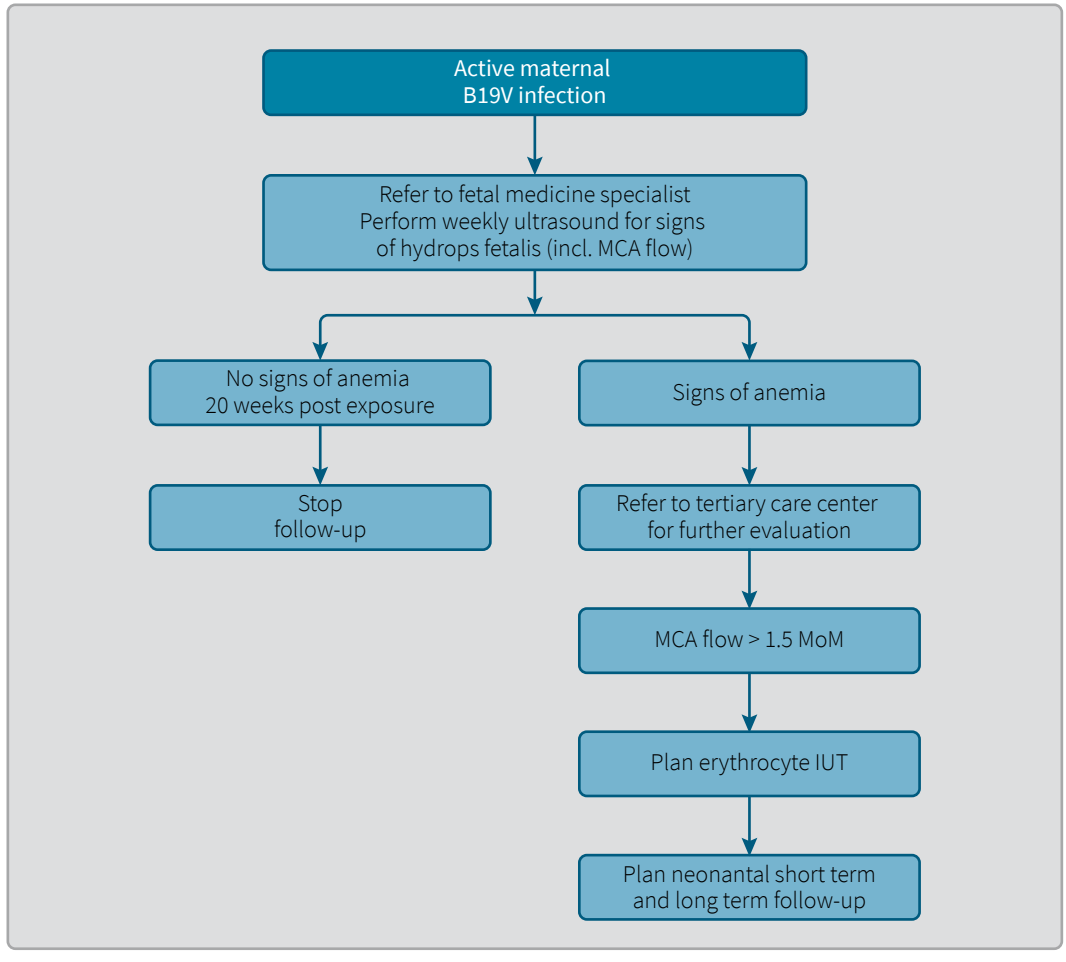

Figure 2: Management of primary B19 infection in pregnant woman (36).

It can be effectively detected by determination of viral DNA with PCR method in the foetal blood or amniotic fluid (50,51). The concentration of viral DNA in the foetus can be high and is maintained throughout the foetal infection period. Amniocentesis can quite reliably confirm foetal infection, however, the procedure is indicated only in cases in which foetal infection is very likely, and maternal tests and ultrasound examinations have been inconclusive (50-52).

3.1.4. Identification of foetal complications

Confirmed or suspected maternal infection requires serial ultrasound monitoring of the foetus. The main goal of ultrasound examinations is to determine foetal anaemia and NIHF. Foetal anaemia can be quite reliably detected with non-invasive Doppler measurements of the middle cerebral artery peak systolic velocity (53).

Hydrops, resulting from anaemia, begins with ascites and enlarged heart with thickened cardiac walls. Untreated hydrops progresses and leads to skin oedema, pericardial effusion, and placental thickening. Pleural effusion develops late and is usually not large in volume in the anaemic foetus. The volume of amniotic fluid is usually normal or low, polyhydramnios seldom occurs (26).

3.1.5. Recommended guidelines in pregnancy with a confirmed maternal parvovirus B19 infection

Recommendation	D 4
Pregnant woman with primary infection is to be referred to a tertiary centre.	

Recommendation	D 4
We inform the pregnant woman about the risks of transmission of the infection to the foetus, the development of foetal hydrops or intrauterine death. The foetus is monitored ultrasonically every 1–2 weeks for 12 weeks for the signs of hydrops or anaemia (MCA flow).	

In confirmed maternal B19V infection the foetus is monitored weekly using ultrasonography at a tertiary centre with Doppler measurements of the middle cerebral artery peak systolic velocity. Additionally, the early signs of hydrops are being looked for (Figure 2). The foetus is monitored for 12 to 20 weeks after maternal infection.

Recommendation	C 2^{+}
Intrauterine transfusion is indicated in the case of hydrops or anaemia.	

When the first signs of anaemia or hydrops appear, the foetus is treated with an intrauterine transfusion (IUT). Foetal death can be prevented by a timely IUT. A single IUT is usually sufficient to improve the condition of the foetus. After an IUT it may take several weeks before the signs of hydrops gradually disappear.

The significance of thrombocytopenia in the foetus is not fully understood. Although intrauterine platelet transfusions can be performed safely, care must be taken not to burden the anaemic foetus with a possibly damaged heart with an excessive amount of transfused blood products and further aggravate the condition due to heart failure.

Recommendation	D 4
If a pregnancy is close to term, the childbirth is planned to take place in a facility with a neonatal intensive care unit in case of hydrops or anaemia. The use of corticosteroids to promote foetal lung maturation is not contraindicated.	

4. Conclusion

A pregnant woman who may have acquired a B19V infection or has signs of an infection should be referred to serological testing. If the findings confirm a primary infection, she is referred to a tertiary centre where the foetus is monitored ultrasonically every 1–2 weeks for up to 12 weeks after the infection. When the signs of anaemia or hydrops occur in the foetus, the foetus is treated with an intrauterine transfusion. If past infection has been detected, the pregnant woman should be reassured that there is no need for follow-up. In the case of a negative serology the tests must be repeated for serologic window period. If the second serologic tests are negative, the pregnant woman should be informed about preventive measures to avoid infection.

Evaluation of recommendations and evaluation of the level of evidence is shown in Table 1 (61).

Table 1: Evaluation of recommendations (61).

Level of evidence / Grade of recommendation	
A	Recommendation is based on at least one meta-analysis or on a set of evidence from experimental studies (controlled randomised studies) or systemic reviews of experimental studies with *very little* bias, on consistent results and on direct applicability for the target population.
B	Recommendation is based on quality systemic reviews of case control studies and cohort studies or on case control and cohort studies themselves with *very low* risk of bias.
C	Recommendation is based on quality case control studies and cohort studies with *low risk* of bias.
D	Recommendation is based on evidence from cases or case series or on expert opinions.

Level of evidence	
1^{++}	High-quality meta-analyses, systemic reviews of randomized controlled trials (RCT) or RCT themselves with very low risk of bias.
1^{+}	Well-performed meta analyses, systemic reviews of RCT or RCT themselves with low risk of bias.
1^{-}	Meta-analyses, systemic reviews of RCT or RCT themselves with high risk of bias.
2^{++}	High quality systemic reviews of case control studies or cohort studies or case control studies or cohort studies themselves with very low risk of bias.
2^{+}	High quality case control studies or cohort studies with low risk of bias.
2^{-}	Case control studies or cohort studies with high risk of bias.
3	Non-analytic studies (studies of cases or case series)
4	Expert opinions

References

1. Cossart YE, Cant B, Field AM, Widdows D. PARVOVIRUS-LIKE PARTICLES IN HUMAN SERA. The Lancet. 1975;305(7898):72–3.
2. Anderson MJ, Lewis E, Kidd IM, Hall SM, Cohen BJ. An outbreak of erythema infectiosum associated with human parvovirus infection. Journal of Hygiene. 1984;93(01):85–93.
3. Dijkmans BA, Breedveld FC, Weiland HT. [Acute joint symptoms in a parvovirus infection]. Nederlands tijdschrift voor geneeskunde. 1986;130(38):1702-5.
4. Dijkmans BAC, Van Elsacker-Niele AMW, Salimans MMM, Van Albada-Kuipers GA, De Vries E, Weiland HT. Human parvovirus b19 dna in synovial fluid. Arthritis & Rheumatism. 1988;31(2):279–81.
5. Rao KRP. Infection with Parvovirus-like Virus and Aplastic Crisis in Chronic Hemolytic Anemia. Annals of Internal Medicine. 1983;98(6):930.
6. 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. Prenatal Diagnosis. 2004;24(7):513–8.
7. Chisaka H, Morita E, Yaegashi N, Sugamura K. Parvovirus B19 and the pathogenesis of anaemia. Reviews in Medical Virology. 2003;13(6):347–59.
8. Young NS, Brown KE. Parvovirus B19. New England Journal of Medicine. 2004;350(6):586–97.
9. Yaegashi N, Niinuma T, Chisaka H, Uehara S, Moffatt S, Tada K, et al. Parvovirus B19 infection induces apoptosis of erythroid cells *in vitro* and in vivo. Journal of Infection. 1999;39(1):68–76.
10. Weigel-Kelley KA. 5 1 integrin as a cellular coreceptor for human parvovirus B19: requirement of functional activation of 1 integrin for viral entry. Blood. 2003;102(12):3927–33.
11. Munakata Y. Ku80 autoantigen as a cellular coreceptor for human parvovirus B19 infection. Blood. 2005;106(10):3449–56.
12. de Haan T, Oepkes D, Beersma M, Walther F. Aetiology, Diagnosis and Treatment of Hydrops Foetalis. Current Pediatric Reviews. 2005;1(1):63–72.
13. Broliden K, Tolfvenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. Journal of Internal Medicine. 2006;260(4):285–304.

14. Pasquinelli G, Bonvicini F, Foroni L, Salfi N, Gallinella G. Placental endothelial cells can be productively infected by Parvovirus B19. Journal of Clinical Virology. 2009;44(1):33–8.
15. Kooistra K, Mesman HJ, de Waal M, Koppelman MHGM, Zaaijer HL. Epidemiology of high-level parvovirus B19 viraemia among Dutch blood donors, 2003–2009. Vox Sanguinis. 2010;100(3):261–6.
16. Heegaard ED, Brown KE. Human Parvovirus B19. Clinical Microbiology Reviews. 2002;15(3):485–505.
17. RÖHrer C, GÄRtner B, Sauerbrei A, BÖHm S, HottentrÄGer B, Raab U, et al. Seroprevalence of parvovirus B19 in the German population. Epidemiology and Infection. 2008;136(11):1564.
18. van Rijckevorsel GGC, Bovée LPMJ, Damen M, Sonder GJB, Schim van der Loeff MF, van den Hoek A. Increased seroprevalence of IgG-class antibodies against cytomegalovirus, parvovirus B19, and varicella-zoster virus in women working in child day care. BMC Public Health. 2012;12(1).
19. Valeur-Jensen AK. Risk Factors for Parvovirus B19 Infection in Pregnancy. JAMA. 1999;281(12):1099.
20. Dembinski J. Long term follow up of serostatus after maternofetal parvovirus B19 infection. Archives of Disease in Childhood. 2003;88(3):219–21.
21. de Jong EP, de Haan TR, Kroes ACM, Beersma MFC, Oepkes D, Walther FJ. Erratum to "Parvovirus B19 infection in pregnancy" [J. Clin. Virol. 36 (2006) 1–7]. Journal of Clinical Virology. 2007;38(2):188.
22. Norbeck O, Papadogiannakis N, Petersson K, Hirbod T, Broliden K, Tolfvenstam T. Revised Clinical Presentation of Parvovirus B19–Associated Intrauterine Fetal Death. Clinical Infectious Diseases. 2002;35(9):1032–8.
23. Enders M, Klingel K, Weidner A, Baisch C, Kandolf R, Schalasta G, et al. Risk of fetal hydrops and non-hydropic late intrauterine fetal death after gestational parvovirus B19 infection. Journal of Clinical Virology. 2010;49(3):163–8.
24. Puccetti C, Contoli M, Bonvicini F, Cervi F, Simonazzi G, Gallinella G, et al. Parvovirus B19 in pregnancy: possible consequences of vertical transmission. Prenatal Diagnosis. 2012:1–6.
25. Brkic S, Bogavac MA, Simin N, Hrnjakovic-Cvetkovic I, Milosevic V, Maric D. Unusual high rate of asymptomatic maternal parvovirus B19 infection associated with severe fetal outcome. The Journal of Maternal-Fetal & Neonatal Medicine. 2010;24(4):647–9.
26. van Kamp IL, Klumper FJCM, Bakkum RSLA, Oepkes D, Meerman RH, Scherjon SA, et al. The severity of immune fetal hydrops is predictive of fetal outcome after intrauterine treatment. American Journal of Obstetrics and Gynecology. 2001;185(3):668–73.
27. Bonvicini F, Puccetti C, Salfi NCM, Guerra B, Gallinella G, Rizzo N, et al. Gestational and Fetal Outcomes in B19 Maternal Infection: a Problem of Diagnosis. Journal of Clinical Microbiology. 2011;49(10):3514–8.
28. Weiffenbach J, Bald R, Gloning K-P, Minderer S, Gärtner BC, Weidner A, et al. Serological and Virological Analysis of Maternal and Fetal Blood Samples in Prenatal Human Parvovirus B19 Infection. The Journal of Infectious Diseases. 2012;205(5):782–8.
29. Cantey JB, Pritchard MA, Sanchez PJ. Bone Lesions in an Infant With Congenital Parvovirus B19 Infection. PEDIATRICS. 2013;131(5):e1659-e63.
30. 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. The Pediatric Infectious Disease Journal. 1998;17(6):489–94.
31. Nyman M, Skjöldebrand-Sparre L, Broliden K. Non-hydropic intrauterine fetal death more than 5 months after primary parvovirus B19 infection. Journal of Perinatal Medicine. 2005;33(2).
32. Lassen J, Jensen AKV, Bager P, Pedersen CB, Panum I, Norgaard-Pedersen B, et al. Parvovirus B19 Infection in the First Trimester of Pregnancy and Risk of Fetal Loss: A Population-based Case-Control Study. American Journal of Epidemiology. 2012;176(9):803–7.
33. Yageashi N, Niinuma T, Chisaka H, Watanabe T, Uehara S, Okamura K, et al. The incidence of, and factors leading to, parvovirus B19-related hydrops fetalis following maternal infection; report of 10 cases and meta-analysis. Journal of Infection. 1998;37(1):28–35.
34. 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 diagnosis and therapy. 2009;25(4):373–8.
35. Nunoue T, Kusuhara K, Hara T. Human fetal infection with parvovirus B19: maternal infection time in gestation, viral persistence and fetal prognosis. The Pediatric Infectious Disease Journal. 2002;21(12):1133–6.
36. Dijkmans AC, de Jong EP, Dijkmans BAC, Lopriore E, Vossen A, Walther FJ, et al. Parvovirus B19 in pregnancy. Current Opinion in Obstetrics and Gynecology. 2012;24(2):95–101.
37. De Haan TR, Van Den Akker ESA, Porcelijn L, Oepkes D, Kroes ACM, Walther FJ. Thrombocytopenia in hydropic fetuses with parvovirus B19 infection: incidence, treatment and correlation with fetal B19 viral load. BJOG: An International Journal of Obstetrics & Gynaecology. 2007;115(1):76–81.
38. Pistorius LR, Smal J, de Haan TR, Page-Christiaens GCML, Verboon-Maciolek M, Oepkes D, et al. Disturbance of Cerebral Neuronal Migration following Congenital Parvovirus B19 Infection. Fetal diagnosis and therapy. 2008;24(4):491–4.
39. Isumi H, Nunoue T, Nishida A, Takashima S. Fetal brain infection with human parvovirus B19. Pediatric Neurology. 1999;21(3):661–3.
40. Courtier J, Schauer GM, Parer JT, Regenstein AC, Callen PW, Glenn OA. Polymicrogyria in a fetus with human parvovirus B19 infection: a case with radiologic-pathologic correlation. Ultrasound in Obstetrics & Gynecology. 2012;40(5):604–6.
41. Dembinski J. Neurodevelopmental outcome after intrauterine red cell transfusion for Parvovirus B19-induced fetal hydrops. BJOG: An International Journal of Obstetrics and Gynaecology. 2002;109(11):1232–4.

42. Nagel HTC, de Haan TR, Vandenbussche FPHA, Oepkes D, Walther FJ. Long-Term Outcome After Fetal Transfusion for Hydrops Associated With Parvovirus B19 Infection. Obstetrics & Gynecology. 2007;109(1):42–7.
43. De Jong EP, Lindenburg IT, van Klink JM, Oepkes D, van Kamp IL, Walther FJ, et al. Intrauterine transfusion for parvovirus B19 infection: long-term neurodevelopmental outcome. American Journal of Obstetrics and Gynecology. 2012;206(3):204.e1-.e5.
44. Lassen J, Bager P, Wohlfahrt J, Bottiger B, Melbye M. Parvovirus B19 infection in pregnancy and subsequent morbidity and mortality in offspring. International Journal of Epidemiology. 2013;42(4):1070–6.
45. Stavec T. Posledice okužbe s parvovirusom B19 v nosečnosti [PhD Thesis]. Ljubljana: T. Stavec; 2015.
46. Anderson MJ, Higgins PG, Davis LR, Willman JS, Jones SE, Kidd IM, et al. Experimental Parvoviral Infection in Humans. Journal of Infectious Diseases. 1985;152(2):257–65.
47. Beersma MFC, Claas ECJ, Sopaheluakan T, Kroes ACM. Parvovirus B19 viral loads in relation to VP1 and VP2 antibody responses in diagnostic blood samples. Journal of Clinical Virology. 2005;34(1):71–5.
48. Bredl S, Plentz A, Wenzel JJ, Pfister H, Möst J, Modrow S. False-negative serology in patients with acute parvovirus B19 infection. Journal of Clinical Virology. 2011;51(2):115–20.
49. Enders M, Helbig S, Hunjet A, Pfister H, Reichhuber C, Motz M. Comparative evaluation of two commercial enzyme immunoassays for serodiagnosis of human parvovirus B19 infection. Journal of Virological Methods. 2007;146(1–2):409–13.
50. Enders M, Weidner A, Rosenthal T, Baisch C, Hedman L, Söderlund-Venermo M, et al. Improved Diagnosis of Gestational Parvovirus B19 Infection at the Time of Nonimmune Fetal Hydrops. The Journal of Infectious Diseases. 2008;197(1):58–62.
51. de Haan TR, Beersma MFC, Oepkes D, de Jong EP, Kroes ACM, Walther FJ. Parvovirus B19 infection in pregnancy: maternal and fetal viral load measurements related to clinical parameters. Prenatal Diagnosis. 2006;27(1):46–50.
52. Adams LL, Gungor S, Turan S, Kopelman JN, Harman CR, Baschat AA. When are amniotic fluid viral PCR studies indicated in prenatal diagnosis? Prenatal Diagnosis. 2012;32(1):88–93.
53. 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 in Obstetrics and Gynecology. 2001;18(3):232–6.
54. Bernstein DI, Sahly HME, Keitel WA, Wolff M, Simone G, Segawa C, et al. Safety and immunogenicity of a candidate parvovirus B19 vaccine. Vaccine. 2011;29(43):7357–63.
55. Jeon J, Victor M, Adler SP, Arwady A, Demmler G, Fowler K, et al. Knowledge and Awareness of Congenital Cytomegalovirus Among Women. Infectious Diseases in Obstetrics and Gynecology. 2006;2006:1–7.
56. Vossen A, de Vries J, van der Zeijst B. The 2008 congenital cytomegalovirus conference, 5–7 November, Centers for Disease Control and Prevention, Atlanta. Euro Surveill 2009;14:37–38. [cited 2014 May] Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19136.
57. Society of Obstetricians and Gynaecologists of Canada (SOGC) clinical practice guideline. Parvovirus B19) Infection in Pregnancy. Guideline No. 316 (Replaces No. 119), J Obstet Gynaecol Can2014;36(12):1107–1116.
58. Parvovirus B19 Infection in Pregnancy. Journal of Obstetrics and Gynaecology Canada. 2002;24(9):727–34.
59. Practice Bulletin No. 151. Obstetrics & Gynecology. 2015;125(6):1510–25.
60. UK National Screening Committee: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). June 2014. [cited 2017 May 1] Available from: https://legacyscreening.phe.org.uk/parvovirus.
61. Geršak K, Fras Z, Rems M. Ali vemo, kakšne morajo biti dobre klinične smernice? Zdrav Vestn. 2016;85(1):6–14.