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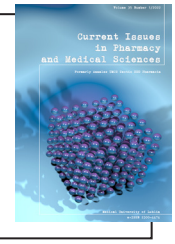

Parvovirus B19 infection during pregnancy

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ABSTRACT

Parvovirus B19 (B19V) is a widespread pathogen causing infection that occurs mostly in children. Even though infection of B19V is mainly asymptomatic, it can bring about a few conditions that may require medical intervention, including erythema infectiosum (fifth disease), slapped cheek syndrome, papular-purpuric gloves and socks syndrome (PPGSS), as well as other disorders related to the hematological system. Despite the fact that the most common route of transmission is through the respiratory system, B19V can be also transmitted transplacentally from mother to foetus. Vertical transmission may lead to myocarditis, thrombocytopenia, neural manifestations, and foetal hydrops, which may be life-threatening conditions to both mother and foetus. Detection of B19V infection is based mostly on molecular and serological screening and it is performed after suspected exposure to pathogen or exhibition of symptoms. Currently, there is no specific medication against B19V infection, therefore, treatment is based on the elimination of symptoms. New therapies are, however, under development.

INTRODUCTION

Parvovirus B19, a member of the *Parvoviridae* family, is widely spread and causes infections at a global scale [1,2]. It only affects humans, with the majority of adults having seropositive status by the age of 40. Indeed, around 90% of the elderly people demonstrate detectable antibodies against B19V. The B19V infection commonly occurs in school-aged children and it is believed that most people will be infected by the age of 15 [3,4]. It is mostly spread through respiratory droplets and blood products, as well as vertically from mother to child during pregnancy [4-6]. Viremia is responsible for the occurrence of symptoms in patients and once it resolves, the IgM antibodies can be detected. After approximately one week, the IgG antibodies are synthesized, and this occurs simultaneously with the appearance of a rash. After the viremia is cleared out, patients cannot spread the virus anymore [3,4]. The occurrence of B19V infections usually happens from late winter to early summer [4,7]. The B19V is highly infectious, however, the course of infection is mainly asymptomatic and if the symptoms appear, they are usually mild and nonspecific [3]. Parvovirus B19 infection is responsible for the erythema infectiosum (Fifth disease), slapped cheek syndrome, and papular-purpuric gloves and socks syndrome (PPGSS) as well as chronic anaemia and other haematological disorders [8]. During early pregnancy, the infection does not usually cause foetal defects, however, in later stages of pregnancy it might have a more severe impact on the foetus, including non-immune hydrops fetalis (NIHF) and foetal heart failure and death [7].

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Virus characteristics

The human parvovirus B19 is a part of the *Parvoviridae* family, and is comprised of 2 subfamilies: *Parvovirinae* (which infects vertebrates) and *Densovirinae* [9]. The B19V is a non-enveloped virus with linear, single-stranded DNA (4). The lack of lipid envelope results in its resistance to heat or chemical detergents [3,10].

It is known that parvovirus B19 can only infect humans and there are no other identified hosts. B19V infects cells with high proliferative potential, as its replication is dependent on the host cells, their cellular response to erythropoietin (Epo) and hypoxia [1,11]. Virus recognizes the P antigen that is present on erythroid progenitor cells, which are present in bone marrow, peripheral blood, as well as the liver of the foetus and the umbilical cord [3,7]. Hence, humans that show specific p-phenotype may show resistance to B19V infections [7].

After entering the cell, the viral genome is translocated to the nucleus, replicated and transcribed. Then, the mature virions are assembled and released in the lysis process.

The viral DNA contains sequences encoding two structure viral proteins (VP1 and VP2) and a non-structure protein (NS1), and is flanked on both ends by inverted terminal repetitive sequences. The genetic material of B19V has a positive or negative polarity and is equally distributed into newly synthesized virions. VP1 and VP2 are capsid proteins that differ by the length of the reading frame, with VP2 being the predominant capsid protein. NS1 protein contains highly conservative areas and it is important in gene expression, in addition to viral DNA synthesis, and is responsible for causing a cytotoxic effect on host cells [1,7,10]. Its cytotoxicity is associated with response to DNA damage, as well as induction of apoptosis, and can temporarily stop erythropoiesis, leading to erythroid aplasia [11]. After B19V infection, we can observe giant pronormoblasts in bone marrow with enlarged cell nuclei and displaced chromatin [1,7].

Route of transmission

The highest seropositivity occurs at an older age, and it is estimated that around 90% of elderly people have previously been infected with B19 at a younger age and have antibodies against the virus. In compliance with that, the lowest seropositivity occurs at a young age. Subsequently, the risk rises to 50% during adolescence and it is estimated that most people will be infected by the age of 15. After puberty, the risk remains at lower rates throughout adulthood [2,3,7,10].

Parvovirus B19 can be transmitted through four different ways: respiratory droplets, blood products, organ transplantation, and vertically from mother to foetus. The primary transmission route is by the respiratory system through saliva droplets, especially after close person-to-person contact, hence B19V may easily spread throughout the population [11,12]. As parvovirus infection is common in children, the groups with increased risk include day-care workers and schoolteachers where the transmission rate is around 30%. Another group with an increased risk of infection is those who live with an infected person, especially mothers of school-aged children, where the transmission rate increases up to 50% [3,13]. The virus can be also spread through blood-related products, including pooled factor VIII and IX concentrates, albumins and immunoglobulins [3,10].

Analyses of blood donors reveal that they show seroprevalence of 60% – which it corresponds to the general population. There is a greater risk that blood donors might be infected at the time of donation. There are no requirements for testing for parvovirus B19 infection of blood donors. It is estimated that new parvovirus infections among blood donors are up to 1% per year. As the infections are usually asymptomatic, interviews with donors do not provide information about seroprevalence and infection status. When it comes to blood recipients, it was expected that the prevalence might be similar to blood donors. However, it has never been confirmed that transmission of cellular blood products may lead to parvovirus B19 infection as the symptoms are often nonspecific and frequently associated with transfusion. For example, young patients who were prolongedly treated with coagulation factor concentrate for haemophilia A have shown a higher prevalence of antibodies against B19 parvovirus [7].

Another parvovirus B19 infection route includes the vertical transmission from mother to foetus. Infected mothers usually exhibit mild symptoms or are asymptomatic, and B19V infection does not affect the foetus. However, the infection might spread through the placenta and can lead to severe defects in the foetus. The severity of malformations depends on the developmental stage of the foetus, as well as maternal and foetal immunocompetency. The foetus is most susceptible to B19V infection during the second trimester, since the erythrocytes show shorter viability and the virus infects foetal liver, which is the main organ responsible for the hematopoietic process [5,11,13-16].

Diseases associated with the infection and clinical symptoms

Infections caused by parvovirus B19 in most cases are asymptomatic or are mild and self-limiting due to immune response. However, the infection can cause more severe manifestations and may require the administration of drugs. Currently, used therapies are nonspecific and targeted towards specific symptoms rather than the cause of infection [7,11,12,17]. The severity of infection depends on age and immunocompetency. Hence, a more serious course of illness can occur in older and immunodeficient individuals. B19V infection may give symptoms similar to acute HIV infection [12]. The most common manifestation of B19V infection in children is erythema infectiosum (known as the Fifth disease), foetal anaemia, and nonimmune hydrops fetalis (NIHF) [4,13,17]. In adults, the most common presentation of infection is arthropathy, however, it may also cause papular-purpuric gloves and socks syndrome (PPGSS), myocarditis, vasculitis, glomerulonephritis, as well as chronic anaemia and aplastic crisis in patients with immunodeficiency or haemolytic disorders [7].

***Erythema infectiosum* (*fifth disease, slapped cheek syndrome*)**

Infection of B19V can cause erythema infectiosum, a common childhood infection that can also occur in adults. The most frequent symptoms observed in children are malaise, mild fever, muscle sores, headache and nausea. After several days, the most characteristic "slapped cheek" facial rash appears caused by the formation of antigen-antibody complexes localized in skin and joints [1,7]. The rash may spread to extremities and the trunk and is transient, but it may reoccur after physical activity, exposure to the sun, or during stress and strong emotions. Slapped cheek syndrome can be mistaken for rubella and it might be difficult to notice the rash in people of colour [1,13,18]. In adults, the rash is less characteristic, with arthralgias and inflammations of the joints being much more frequent [7,13,18].

***Papular-purpuric gloves and socks syndrome* (*PPGSS*)**

Papular-purpuric gloves and socks syndrome is a rare presentation of B19V infection, and only a few cases have been described in the literature. Even though most of the cases are due to B19V infection, some cases have been caused by other factors, such as viral and bacterial infection, as well as therapy with specific antibiotics. The most characteristic symptoms are painful and itchy skin lesions,

mostly presented on hands and feet. Other manifestations include fever, oral lesions, petechiae and oedema [19,20].

Transient aplastic crisis* (*TAC*) *and chronic anaemia

Since parvovirus B19 has an affinity to hematopoietic stem cells, the infection may cause haematological symptoms, especially in patients with underlying haematological diseases such as hereditary spherocytosis, haemolytic anaemia, acute haemorrhagia and iron deficiency. Clinical manifestations of TAC include aplasia of erythrocytes and reticulocytopenia, and they last about a week, as haemoglobin level is slightly decreased. TAC can also cause anaemia in patients with low haemoglobin levels. Bone marrow in patients with TAC lacks maturing erythroid precursors, but it contains giant pronormoblasts. The most serious consequence of TAC is bone marrow necrosis – which can lead to the patient's death - however, in most cases, it is self-limiting [1,7,13].

B19V infection may lead to red cell aplasia in immunocompromised patients and may cause prolonged anaemia. Chronic anaemia can affect patients with immunodeficiency such as HIV-infected patients, patients undergoing immunosuppression or chemotherapy. These patients fail to develop a proper immune response that would allow the elimination of the virus from their system [21].

Rare manifestations of parvovirus B19 infection

In rare cases, infection of B19V can cause manifestations in other organs such as the heart, liver and kidneys, and it can also affect the nervous system. While in the past adenoviruses and enteroviruses were responsible for most cases of myocarditis, in recent years we observe a change towards parvovirus B19 and human herpesvirus. Although, nowadays, B19V is the most common cause of viral myocarditis, especially among children, there is not enough scientific data regarding the pathomechanism of the disease. Myocarditis caused by viral infection is responsible for a high rate of mortality among both children and adults. Contrary to other viruses, B19V infects coronary endothelium rather than cardiac muscle cells. The course of B19V myocarditis is different from myocarditis caused by other viruses, as the damaged endothelial cells cause myocardial ischemia and cardiac dysfunction [22-24].

Another rare presentation of infection is hepatitis, however, in literature, only a few cases have been described. B19V infection can lead to a wide range of symptoms in the liver, leading to acute hepatitis and fulminant liver failure. Even though the cases included all the age groups, the most affected group were children as they had a more severe course of the disease than adults [25].

In the past few years, more research data has been published regarding the correlation between B19V infection and neurological symptoms. Even though it can cause several neurological manifestations, the most common are encephalopathy and acute encephalitis. Infection of B19V is rarely considered to be the cause of encephalitis since it does not have any distinguishing features from other viral-associated encephalitis and the diagnosis towards B19V is done only after other viruses are excluded as a possible cause [26,27].

Due to the deposition of immune complexes, as well as direct infection of glomerular endothelial cells, B19V infection may lead to kidney damage and glomerulonephritis. One of the most common pathological features of renal injury due to B19V infection is endocapillary proliferative glomerulonephritis. Others can include hypocomplementemia and acute nephritic syndrome [28].

Infection during pregnancy – prevalence, infection process, clinical symptoms

Although parvovirus B19 infection seems to occur commonly in the general population, it is estimated that infection of B19V may affect pregnant women to 1-5% extent, but during epidemics, this level may increase up to 20% [29-31], and historically, the susceptibility of pregnant women reaches around 40% [32,33]. Diagnostic towards B19V during pregnancy is crucial as the infection may have serious consequences to both mother and foetus. It is recommended that every pregnant woman should consult an obstetrician to discuss her individual risk of infection during epidemics and whether she should take medical leave [30]. Most of the cases of B19V infection in pregnant women are asymptomatic or manifest as polyarthralgia or rush. This does not differ from healthy individuals. Symptomatic infection of B19V presents with fever, myalgia, and headache and it is followed by joint inflammation within 1-3 weeks [31,32].

Consequences of infection for foetus and new-born, risk of vertical transmission, prognosis

Parvovirus B19 is a common infection in pregnant women, and it may also affect the foetus, however, most of the pregnancies have a normal outcome. As the placental trophoblastic cells express the P antigen that is recognized by the virus, the infection may spread to the foetus. The highest risk of vertical transmission is observed during the first trimester of pregnancy and is estimated to be up to 33% [5,13,30]. However, in 60% of all cases, it is not diagnosed.

Even though the infection may not cause any symptoms, it can impact the foetus in several ways. Foetal infection may be associated with several clinical manifestations including thrombocytopenia, non-immune hydrops fetalis (NIHF) (known as foetal hydrops), intrauterine foetal death (IUFD), as well as neurological presentations and myocarditis [6,8,13]. Since B19V infects erythroid progenitor cells (or equivalent cells in the foetus), the foetus is the most vulnerable within the second trimester. During this period, the hematopoietic process takes place mostly in the liver, leading to transient cell cycle arrest [5,30,31].

The infection of B19V during pregnancy is a relevant cause of foetal death, and spontaneous miscarriage or stillbirth can occur, especially during the second half of pregnancy, when other causes are uncommon [30]. It is estimated that the spontaneous pregnancy loss rate after the infection of B19V during the first 20 weeks of pregnancy is around 15%, however, after 20 weeks it decreases to around 2,3%. The most probable cause of miscarriages is multiorgan foetal damage [13,30,34]. Most cases of intrauterine foetal death (IUFD) associated with parvovirus B19 infection occur within the second trimester of pregnancy, and even though

there were no symptoms during pregnancy, the autopsy of the foetus usually shows placental oedema, hydrops, serous effusion and erythroblastosis [35].

One of the consequences of infection of B19V is non-immune hydrops fetalis, known as 'foetal hydrops', which is caused by the accumulation of the fluids in foetal cavities, including pleural, abdominal, subcutaneous and pericardial. The risk of hydrops fetalis induced by infection of B19V is around 4%, but peaks at 7% during the hepatic stage. One of the possible pathomechanisms of hydrops arises from the incidence of foetal anaemia, as the virus attacks the liver and erythrocytes show a shorter half-life, leading to cardiac failure and therefore, to NIHF [6,30,31,34]. Since foetal hydrops has a harmful effect on the foetus, they can lead to death in utero or at birth. During ultrasound examinations, the foetus affected by hydrops may exhibit pericardial effusion, cardiomegaly, as well as ascites. In more serious cases, oedema and hydropic placenta can occur. These may lead to the development of maternal mirror syndrome with pre-eclampsia, anaemia, hypertension, oedema and proteinuria.

It is believed that mirror syndrome reflects the symptoms of the foetus. In cases of persistent hydrops fetalis, it may be an indication to terminate the pregnancy as it is a life-threatening condition to the mother [6,31,33,36]. Hydrops fetalis can lead to foetal thrombocytopenia, which has been reported mostly in the second trimester. This can occur in 15 to 54% of all cases, and it is thought to be caused by the cytotoxic effect of B19V on megakaryocytes, which leads to haemorrhage and increased risk of foetal loss related to procedures such as foetal blood sampling and intrauterine transfusion of red blood cells [13,31,37].

Even though there have been a few case reports about myocarditis and central nervous system anomalies, parvovirus B19 does not seem to cause serious congenital defects and it is not considered highly teratogenic [30,33,34].

Diagnostics of infections in pregnant women, foetus and new-born – and rules of conduct as well as recommendations

Diagnostic of the B19V infection is based mainly on clinical symptoms that are specific only in one-quarter of all patients. In others, the course of the infection may be non-specific or even asymptomatic. Currently, there are no recommendations for routine serological screening for B19V, as there are no effective methods against infection. Generally, the diagnostics of parvovirus B19 infection take place after developing typical symptoms, however, in pregnant women, it is suggested to run the test towards B19V infection in three situations: after a known exposure, during symptomatic infection, as well as after miscarriage of unknown cause or in case of foetal hydrops [13,33,34,36]. When clinical symptoms are nonspecific, they can be mistaken for rubella, measles or flu, and it is indicated to perform tests to differentiate B19V infection from other viral infections [14,34,36].

Maternal infection can be detected using molecular or serological methods. In the first case, viral DNA is detected using methods based on the amplification of nucleic acids or direct *in situ* hybridization, with the most common molecular diagnostic method being real-time polymerase chain reaction (real-time PCR) for detecting individual copies of the virus in the blood and serum. This allows measuring quantitatively the viral load, as well as monitoring the course of the infection enabling differentiation of infections that are clinically significant and nonsignificant [5,36,38].

Serological methods are based on the detection of specific antibodies against B19V (IgG and IgM) with the use of enzyme-linked immunosorbent assay (ELISA) and Western-blot assay. Parvovirus B19-specific IgM is produced within the first week after exposure and can be detected for up to 6 months. IgG appears after IgM is already being produced and they are usually present for life – preventing reinfection. When IgG is present and IgM absent, the patient is considered to be immune. If the woman is immune, then there is no risk of transmission to the foetus. If a pregnant woman has only IgM present, it can indicate a recent infection and the test should be repeated in the following week. If the woman was recently exposed to the virus, she may be in a serological window and should be tested again every 2-4 weeks. The presence of both IgG and IgM antibodies indicates recent infection and there is a probability of transmission of B19V to the foetus. Differentiation of past and recent B19V infection may be done via epitope type-specificity immunoenzymatic assays [5,13,30,33,34,38].

An additional test to detect the B19V infection is a cytological assessment of bone marrow. In patients who are immunocompetent, it is possible to run both molecular and serological diagnostics. However, in patients with immunosuppression, serological methods do not give reliable results as their immune response may be impaired [36,38].

Detection of recent B19V infection in pregnant women is an indication for referring women to special care to assess the risk of complications in the foetus [13,30,36,39]. Some researchers have observed that foetal infection is associated with increased levels of alpha-fetoproteins in mothers' blood serum, however intrauterine B19V infection can only be confirmed with the use of invasive methods such as the detection of viral DNA in amniotic fluid or foetal blood via PCR. It is observed that the concentration of DNA in amniotic fluid is higher than in maternal sera and is comparable to the viraemic DNA levels in the foetal serum. As it is only possible to detect infection during the viraemic stage, foetal diagnosis may be difficult. Since the foetus starts producing IgM around 22 weeks of gestation, the tests may give false-negative results even though the infection is present. After pregnancy loss, the infection of parvovirus B19 can be detected using histological methods or electron microscopy [5,13,30,34,39].

Management of B19V infection

The course of B19V infection is usually mild and self-limiting and there is no need for therapeutic intervention. However, the patients may require treatment and hospitalizations, especially in cases of haematological manifestations [11,31]. Currently, there is no specific antiviral drug for B19V infections, and the treatment is based mostly on the elimination of symptoms. Therapeutic management depends on immunocompetency, underlying conditions and clinical manifestations of B19V infection [4,40]. As the symptoms are mainly transient, immunocompetent individuals usually

do not require therapy. When symptoms require medical intervention, there are a few treatment options: administration of non-steroidal anti-inflammatory drugs (NSAIDs), blood transfusions, or intravenous immunoglobulin (IVIG) [31]. A few cases have been reported in the literature of treatment with the use of erythropoietin in B19V infection, however, the researchers observed deterioration in patients' condition, most likely due to increasing red blood cell progenitors - which are the target for B19V (10). NSAIDs are used to reduce inflammation when arthritis and arthralgias are present [4,11].

One of the main solutions to stabilizing the anaemia in infected patients is a blood transfusion. However, there is a need to assess the ability to produce neutralizing antibodies by the patient's immune system, which may interfere with other treatments, including chemotherapy, immunosuppressive therapy and antiretroviral treatment. Red blood cell transfusion can be administered especially for patients with aplastic crisis [4,11,40]. Another available method is the intravenous administration of immunoglobulins, especially in cases of severe anaemia and when the immune system is not able to produce its own antibodies against the virus.

Even though IVIG does not eliminate the virus until the development of the patient's immune response, it is considered to be a beneficial treatment option for infected patients [10,11,40]. The clinical response to the treatment is associated with increased levels of haemoglobin and reticulocytosis and decline in viral load, and the monitoring of B19V infection is based on the evaluation of their levels. It is also possible to measure the quantity of B19V DNA as an early indicator of relapse, however, the decrease of viral DNA in the blood is not the aim of the treatment and is used to confirm that B19V infection caused the symptoms. The purpose of the treatment is not to generate a negative PCR result but to normalize haematocrit and reticulocytosis [10,40]. What is more, creatinine levels in serum should be evaluated when intravenous immunoglobulins are administered [10].

As there is no treatment that prevents the transmission of B19V, from mother to child, pregnant women with confirmed infection should be closely monitored [4,33]. Since the risk of transmission to the foetus is moderate, it is recommended to monitor the child with ultrasonography so as to detect the possible hydrops at the earliest possible moment. Anaemia is detected using Doppler ultrasound examination of the middle cerebral artery peak systolic velocity [11,13,30,33]. As hydrops may be caused by anaemia, the foetus may require cordocentesis to measure the levels of haemoglobin and reticulocyte count, and intrauterine transfusion may be begun. This has been proven to significantly decrease the mortality among infected foetuses. If the hydrops and severe foetal anaemia occur in late pregnancy, induction of early delivery should be considered to perform blood transfusion in the infant [6,13,30,31,34].

Nowadays, researchers are looking for new therapeutic options for B19V infection. One of the studied drugs is hydroxyurea (HU), which is a DNA synthesis inhibitor and is already registered for sickle cell disease therapy. Another drug, cidofovir (CDV), is also FDA-approved. This is a nucleotide analogue that has been proven to inhibit B19V replication. What is more, a modified form of CDV, brincidofovir (BCV), has shown antiviral activity against B19V. There are also studies in developing a possible vaccine against parvovirus B19 [11,31].

SUMMARY

Even though vertical transmission from mother to foetus happens relatively rarely and usually leads to the normal outcome of pregnancy, B19V infection can cause serious consequences for both mother and her new-born baby, especially in the case of foetal hydrops. Hence, infected pregnant women require special care and monitoring of the course of infection and its impact on the foetus. Since there is no specific treatment and medication, novel therapies are still in demand.

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