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Parvovirus B19 infection during pregnancy: a problem not only for the gynaecologist

Zakażenie parwowirusem B19 w okresie ciąży – problem nie tylko dla ginekologa

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Abstract

Parvovirus B19 (B19V), which belongs to the *Parvoviridae* family, is one of the smallest viruses causing infections in humans. It is estimated that approximately 60% of the population will have a parvovirus B19 infection at some point in their lives based on B19V-specific antibody detection rates. The frequency of infections increases with age. Asymptomatic B19V infections are relatively common both in adults and in children. Parvovirus B19 is an aetiological factor for numerous diseases such as, for example, arthritis, erythema infectiosum, gloves and socks syndrome or haematological disorders. B19V infection is particularly dangerous during pregnancy due to the risk of maternal-foetal transmission; the estimated risk of virus transmission during pregnancy is 17–33%. The majority of infected foetuses have a good prognosis and experiencing intrauterine infection does not result in permanent sequelae; however, B19V infection during pregnancy can cause spontaneous abortion, hydrops fetalis or intrauterine death, among others; there are also single cases reported of congenital defects in the foetuses. In every pregnant woman with a suspected parvovirus B19 infection, assay of virus-specific IgM and IgG antibodies should be performed. If primary B19V infection is detected in a pregnant patient, she should be referred to a referral centre and undergo close observation with periodic foetal ultrasound examination. Children who have a history of parvovirus B19 infection during foetal life require specialist follow-up after birth. To date no specific method for B19V infection treatment has been developed. In addition, there is no vaccine against this virus.

Keywords: human parvovirus B19, *Parvoviridae* infections, pregnancy

Streszczenie

Parwowirus B19 (B19V), należący do rodziny *Parvoviridae*, jest jednym z najmniejszych wirusów wywołujących zakażenia u ludzi. Szacuje się, że około 60% populacji przejdzie w ciągu życia zakażenie parwowirusem B19, na co wskazuje wykrywanie przeciwciał swoistych dla tego wirusa, przy czym częstość zakażeń wzrasta wraz z wiekiem osób badanych. Bezobjawowa infekcja B19V jest zjawiskiem stosunkowo często obserwowanym zarówno u dorosłych, jak i u dzieci. Parwowirus B19 jest czynnikiem etiologicznym wywołującym liczne schorzenia, takie jak np. zapalenie stawów, rumień zakaźny, zespół rękawiczek i skarpetek czy zaburzenia hematologiczne. Zakażenie B19V jest szczególnie niebezpieczne w czasie ciąży ze względu na możliwość przeniesienia zakażenia z matki na płód; ryzyko transmisji wirusa w okresie ciąży szacuje się na 17–33%. Większość zainfekowanych płodów cechuje się dobrym rokowaniem, a przebycie zakażenia wewnątrzmacicznego nie pozostawia trwałych następstw, jednak zakażenie B19V podczas ciąży może spowodować m.in. poronienie samoistne, uogólniony obrzęk płodu czy zgon wewnątrzmaciczny; opisywane są także pojedyncze przypadki występowania wad wrodzonych u płodów. U każdej ciężarnej z podejrzeniem zakażenia parwowirusem B19 należy wykonać oznaczenie swoistych przeciwciał IgM i IgG, skierowanych przeciwko antygenom tego wirusa. W przypadku wykrycia pierwotnej infekcji B19V w czasie ciąży pacjentkę należy skierować do ośrodka referencyjnego i poddać ścisłej obserwacji z okresowym badaniem ultrasonograficznym płodu. Dzieci, które przeszły infekcję parwowirusem B19 w wieku płodowym, wymagają specjalistycznej kontroli po urodzeniu. Do tej pory nie udało się opracować swoistego leczenia zakażeń B19V, nie istnieje również szczepienie przeciw temu wirusowi.

Słowa kluczowe: ludzki parwowirus B19, infekcja parwowirusowa, ciąża

VIRUS CHARACTERISTICS

Parvovirus B19 (B19V) belongs to the family *Parvoviridae*, genus *Erythrovirus*[1]. This virus is one of the smallest viruses causing infections in humans (hence the part *parvo-* in the name from *parvus* meaning "small, fine" in Latin). The diameter of the virus is 22–24 nm, while its genome comprises a single-stranded DNA, composed of 5,600 base pairs[2]. In B19V structure there is a capsid protein VP1 (which plays the main role in immune response) and VP2 (which determines viral tropism), and a non-structural protein NS1 responsible for the death of an infected cell. Virus multiplication takes place in erythroid precursor cells in the bone marrow. The virus also displays tropism for the cells of other organs, e.g. hepatocytes, fibroblasts, myocytes, megakaryocytes or endothelial cells[3]. The virus has affinity to rapidly dividing cells, particularly erythropoiesis progenitor cells (for this reason, the name *erythrovirus* is sometimes used)[4]. B19V is a pathogen which causes infections only in humans (it is species-specific); one cannot contract it from animals and humans cannot transmit it to animals[5].

Parvovirus B19 was accidentally discovered in 1975 by Yvonne Cossart during screening of blood donors for hepatitis B and its name comes from the designation of a serum sample: number 19, plate B[6]. Research has shown that there are 3 main types of the B19 virus, i.e. genotypes 1, 2, 3, which differ in approximately 10% between one another. Genotype 1 is considered to be the most common, present all over the world, while genotype 2 is rarely detected in Europe. Genotype 3 is endemic for Ghana; sporadic cases have also been reported for France and Brazil[7].

IMMUNOLOGY AND EPIDEMIOLOGY

The first days after contracting the virus are the peak of viral multiplication. The level of viraemia rises rapidly, as high as up to 10^{12} geq/mL (genome equivalents/mL); no antibodies are detected at this point. Immunoglobulins M (IgM) antibodies appear between day 7 and 14 after infection, while the level of viraemia starts to fall during this period. IgM are detected in the blood up to 6 months after the original infection. IgG antibodies appear approximately 3 weeks after infection and are probably detectable until the end of one's life[8]. A high IgM count usually indicates a fresh infection, while an elevated IgG level without an increase in IgM count is usually a sign of immunisation in the past. It is estimated that approximately 60% of the population will have a parvovirus B19 infection at some point in their lives based on B19-specific IgG antibody detection rates. The frequency of infections increases with age. This means that as many as 40% of women may be at risk of primary B19V infection during pregnancy[9]. Parvovirus B19 epidemics are observed every 3–4 years. Every year in Poland, there are approximately 400,000 pregnant women; therefore, it may be estimated that approximately 6,000 of them contract B19V and approximately 3,000 transmit the virus to the foetus. As a result, one can expect significant complications of parvovirus B19 infection in approximately 300 foetuses in Poland annually[3].

The diagnosis of the infection is based on indirect methods (serological: ELISA, immunofluorescence or Western blot) or direct methods (viral DNA detection). It is also possible to detect the virus using an electron microscope[3,10].

The virus is passed mainly through droplet transmission, as a result of contact with respiratory secretions. There have also been reports of virus transmission through blood product transfusion. Another route of transmission is from the mother to the foetus via the placenta at the time of viraemia. The risk of placental transmission is not fully known, however, it is estimated to be as high as up to approximately 50%[9,11]. Infection transmission is more common in the case of long-term, everyday contact with an infected person, particularly a child (with a risk as high as 50%). Women who have three or more children and preschool and crèche workers are at the highest risk. The majority of infections during pregnancy are asymptomatic, while in 3% of cases pregnancy complications occur[12].

CLINICAL MANIFESTATIONS

Asymptomatic B19V infection is relatively common both in adults and in children. It is estimated that approximately 33% of adult cases are asymptomatic. In some patients **influenza-like symptoms** or a **rash** are observed[9,13].

Parvovirus B19 causes **erythema infectiosum**, a childhood disease which may also occur in adults. Initially, it manifests with low-grade fever, headaches and influenza-like symptoms. After a few days these manifestations start to subside, but a rash occurs. Initially, bright red skin eruptions occur on the face (often resembling the shape of a butterfly), which sometimes become blue red. For this reason, the name "slapped-cheek syndrome" is sometimes used in the literature. After a few days the rash spreads to the torso and upper and lower extremities, usually sparing the skin of the palmar and plantar surfaces. Skin changes on the torso and the extremities are usually paler than those observed on the face. At the time when the rash subsides, it assumes a characteristic, lace-like appearance caused by the changes starting to pale down from the centre towards the outside. The rash usually does not cause pruritus, although there are cases of pruritus reported, particularly in children below 10. The changes usually subside after 1–3 weeks; at this time, new eruptions may occur. Cases of bullous rash have also been reported. When rash is present, usually influenza-like symptoms or fever are no longer observed. Individuals who currently have erythema infectiosum can also develop other manifestations such as lymph node enlargement, eye redness, sore throat, diarrhoea and, more

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commonly in adults, arthritis and arthralgia. Arthritis associated with B19V infection in children is estimated to occur in 8% of cases[14,15].

Arthritis and arthralgia are the most common clinical manifestations of a primary B19 infection among adults. It occurs in approximately 60% of affected women and approximately 30% of affected men. Dermatological manifestations are rare in adults and are non-specific for B19V infection. The cause of arthritis is probably linked to the immune system: it is associated with antibodies circulating in the blood. The most commonly affected joints are metacarpophalangeal joints (75%), knees (65%), carpal joints (55%) and ankles (40%). No articular degeneration is observed in association with B19V infection[16]. Acute arthritis, which is diagnosed in 30–60% of patients, can even last more than 2 months in approximately 20% of individuals infected with B19V[13].

Parvovirus B19 infection is also a possible cause of **gloves and socks syndrome**, which is most common in young adults. It is characterised by pain, erythema and oedema of the hands and feet. After some time this condition becomes exacerbated: petechiae, purpura and even vesicles and bullae occur with subsequent skin desquamation. Sharp, linear demarcation of the lesions at wrists and ankles is a characteristic feature of the disease. Other areas of the body may also be affected such as the cheeks, knee and elbow areas and genitals. Patients can also report weakness, joint pain and fever. One needs to bear in mind that gloves and socks syndrome may also be caused by other factors such as hepatitis B virus, cytomegalovirus and Epstein–Barr virus infection or occur as an adverse reaction to medicines[17].

Parvovirus B19 infection can also cause haematological sequelae such as **thrombocytopenia** and **leukopenia**[18]. In children, transient erythroblastopenia of childhood (TEC) has been reported, which was probably caused by parvovirus B19 infection, although the aetiology of this syndrome has not been fully explained. TEC is characterised by occurrence at the age between 3 and 4 years. Its signs include anaemia, reticulocytopenia and a decreased number of red blood cell precursors in bone marrow aspirate[16].

Parvovirus B19 is a possible aetiological factor for **myocarditis** and **pericarditis**: a few cases with B19V aetiology have been reported in children and adults. In the literature, there are also reports of **hepatitis** and **neurological disorders** caused by B19V such as encephalopathies, meningitis and muscle atrophy[16].

In individuals with compromised immunity B19V is a possible aetiological factors for such diseases as chronic pure red cell aplasia (**PRCA**), acute lymphoblastic leukaemia (**ALL**) and virus-associated haemophagocytic syndrome (**VAHS**). B19V may also cause **transient aplastic crisis**; individuals with increased red blood cell breakdown or decreased red blood cell production are at the highest risk[16,19,20].

There is no causal treatment for parvovirus infection. Only symptomatic treatment is possible such as, for example, using anti-inflammatory drugs, analgesics and antipyretics (acetylsalicylic acid is not administered to children) and increasing fluid intake[14].

INFECTION DURING PREGNANCY

The first reports of abnormal course of pregnancy in patients infected with parvovirus B19 appeared in 1984. At the time at least 20 dead foetuses were reported in whose tissues the presence of B19V was detected. The virus multiplies to the greatest extent in progenitor cells responsible for erythropoiesis due to their quick division. This may lead to profound anaemia and circulatory failure in the foetus[21]. It is estimated that as many as 70% of women who have B19V infection during pregnancy are and will remain asymptomatic[22].

The risk of virus transmission from the mother to the foetus is estimated to be 17–33%. It is believed that the majority of children who contract the virus *in utero* have a good prognosis and intrauterine infection does not cause any permanent sequelae in them. In women in whom primary parvovirus B19 infection contracted during pregnancy is transferred to the foetus, intrauterine foetal death occurs in approximately 4–30% of cases. In the first trimester of pregnancy the risk of miscarriage is estimated to be 10%. The risk of miscarriage is probably the highest when the infection is transmitted between week 12 and 17 of pregnancy since the processes of erythropoiesis are the most intensive at this time. It is estimated that spontaneous miscarriage before week 20 of gestation occurs in total in approximately 14% of cases of foetal infection and after week 20 the rate falls to approximately 2%. The possible cause of miscarriage is multiorgan damage in the foetus. The risk of miscarriage decreases in the second trimester; complications of infection are rare in the last 2 months of pregnancy[12,23,24].

B19V circulating in maternal blood may bind to globoside, a specific viral receptor whose presence has been demonstrated both in the cytotrophoblast and in the syncytiotrophoblast, and subsequently enter foetal circulation via this route. It has been demonstrated that the level of globoside expression is the highest in the first trimester of pregnancy and gradually falls as the pregnancy progresses, which correlates with a decreased risk of foetal infection at later stages of pregnancy[25].

A case of parvovirus B19 infection complications occurring in only one of the foetuses in a dichorionic diamniotic twin pregnancy has been reported. The mechanism of intrauterine infection relevant to this case has not been fully discovered; the immune response may have been different between the two foetuses, the virus may have entered via just one of the placentas or the infection may have been asymptomatic in the other foetus[26].

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The occurrence of **non-immune hydrops fetalis** is one of the most frequently reported manifestations suggesting parvovirus B19 infection during pregnancy; it is estimated that B19V infection accounts for as many as up to 27% of all cases of hydrops fetalis. Hydrops fetalis is probably associated with severe foetal anaemia caused by the shorter life of infected red blood cells, consequent hypoxia and circulatory failure. A possible cause of hydrops fetalis may also be direct damage to cardiomyocytes and hepatocytes inflicted by B19V. Hepatocyte damage may also have an indirect cause: the formation of haemosiderin deposits in hepatocytes and Kupffer cells, which results in their fibrosis and necrosis. As a consequence, the liver produces a lower amount of albumins, which reduces oncotic pressure. Foetal oedema and accumulation of fluids in body cavities are probably caused by a combination of the effects of foetal anaemia, heart failure and direct vessel damage induced by hypoxaemia. Hydrops fetalis occurs usually when haematocrit drops below 15%; however, hydrops has also been reported in cases of moderate anaemia. Hydrops is usually diagnosed in the second trimester of pregnancy, 1–17 weeks (4–6 weeks in the majority of cases) after the onset of infection symptoms in the mother. The risk of foetal oedema and subsequent death falls in the third trimester, which is probably due to higher maturity of the foetal immune system. There are reports in the literature of single cases of **congenital defects** in foetuses infected with B19V such as nervous system, viscerocranial and eye defects; however, no direct link to B19V infection has been demonstrated[24,27,28].

In the first trimester and in the early second trimester placentomegaly can be observed on ultrasound examination, which occurs relatively frequently as a sign of B19V infection. Hydrops fetalis cases have also been reported for this period of pregnancy. On foetal ultrasound, one may also observe intrauterine growth restriction, the presence of fluid in the pleural cavities, generalised skin oedema and a widened cardiac silhouette. There are also reports of increased nuchal translucency, which is most probably the effect of foetal circulatory failure. It is suspected that a significant proportion of miscarriages associated with B19V infection in the first trimester is not possible to diagnose using ultrasound. In the second and third trimester, ultrasound examination may reveal ascites, the presence of fluid in the pleural cavities and in the pericardial sac, skin oedema of >5 mm, polyhydramnios, placentomegaly and foetal hypokinesia as well as hydrops fetalis[28]. Other ultrasound manifestations of intrauterine B19V infection include mitral regurgitation, tricuspid regurgitation and hepatic hyperaemia[29].

Macé et al. demonstrated that hydrops fetalis can also occur as isolated ascites and co-occur with effusion in other body cavities, most frequently in the pericardium and much less commonly in the pleural cavities. Ultrasound also revealed signs of myocarditis, which most commonly manifested with cardiomegaly; in addition, decreased myocardial contractility was observed. It was also observed that upon diagnosis of parvovirus B19 infection, in 10 foetuses the length of the femur was below the 5th percentile[30].

Congenital B19V infections are relatively rare, although they may be more common during an epidemic. The actual prevalence of B19V infections is unknown and infection in the mother is usually asymptomatic. For this reason, foetal ultrasound may contribute to determining the right diagnosis and choosing the appropriate management[31].

INFECTION MANAGEMENT DURING PREGNANCY

In every pregnant woman with a suspected parvovirus B19 infection, assay of B19V-specific IgM and IgG antibodies should be performed.

Laboratory test results IgM(−), IgG(+) mean that the patient has probably had the infection in the past, has an acquired immunity and there is no risk of infection for the foetus. A current infection may only be excluded using a molecular biology method (B19V DNA detection with real-time PCR). However, it is believed that it is only primary infection during pregnancy that carries a risk for the developing child.

Based on the results IgM(+), IgG(−), a fresh parvovirus B19 infection may be diagnosed and the patient should be managed accordingly. The pregnant woman should be referred to a referral centre and undergo careful observation with foetal ultrasound being performed every week or every 2 weeks for at least 8–12 weeks. This is due to the fact that hydrops fetalis may appear with a delay and the precise time of its potential occurrence is unknown. A primary positive result for IgM must be confirmed by demonstrating seroconversion and/or detecting B19V DNA. If the baseline results for both immunoglobulin classes are negative: IgM(−), IgG(−), follow-up testing for B19V-specific immunoglobulins should be performed after 2–4 weeks. During the window period the only diagnostic tool able to confirm the infection is a B19V DNA test. If the result of follow-up specific antibody testing is negative, B19V infection may be excluded and diagnostic investigation may be concluded. Thus, if the result of follow-up testing is positive: IgM(+) or IgM(+) and IgG(+), the patient should be considered to be having a fresh infection and should be appropriately managed[3,23,27]. In patients with compromised immunity, the diagnosis of parvovirus B19 infection should not be based on immunoenzymatic methods, since they may lead to inadequate results. In such cases the diagnosis should be determined using a viral DNA detection method[3].

The diagnosis of intrauterine infection in the foetus is possible only after invasive procedures have been performed such as amniocentesis, cordocentesis or chorionic biopsy. This type of management is not used routinely; the diagnosis of infection in the mother is not an indication for invasive diagnosis in the foetus. However, intrauterine infection may also be diagnosed based on amniotic fluid, foetal

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serum or placental fragment assessment using polymerase chain reaction (PCR) (viral DNA assay) or electron microscopic detection of viral particles. One needs to bear in mind that the presence of the virus is possible to detect only at the time of viraemia. Foetal blood antibody testing is also not a commonly used method since the foetus starts to produce IgM antibodies only after week 22 of gestation; such a test conducted at later stages of pregnancy also yields a relatively high rate of false negative results[9,32].

If foetal anaemia associated with B19V infection is suspected, a blood sample should be drawn for haemoglobin, platelets, reticulocytes and B19V DNA in order to confirm the transmission of infection from the mother to the foetus[3].

If hydrops fetalis occurs, the mother should be referred to a tertiary perinatal care referral centre and both the mother and the developing foetus should be closely observed. It seems reasonable to perform cordocentesis with foetal haematocrit and reticulocyte testing in order to determine whether there are indications for intrauterine transfusion. If hydrops fetalis occurs in full-term pregnancy, ending the pregnancy may be considered the best course of action to take. If hydrops fetalis is diagnosed in preterm pregnancy, steroid prophylaxis may be used in accordance with current recommendations in order to accelerate foetal lung maturation and prevent other complications of prematurity. Currently, there are no clear criteria for the management of hydrops fetalis. Authors recommend that Doppler ultrasound be used to assess foetal circulation focusing on the umbilical artery (UA) and middle cerebral artery–peak systolic velocity (MCA-PSV)[12,23,33].

Intrauterine transfusion seems to be a controversial method in the management of hydrops fetalis requiring further research and the determination of detailed indications. In a study of 539 cases of hydrops fetalis caused by parvovirus B19 infection during pregnancy Rodis et al. demonstrated a 30% mortality rate when no intrauterine transfusion was used; 6% of cases ended with intrauterine death following intrauterine transfusion. Among the observed pregnancies 34% ended successfully without intervention, i.e. hydrops resolved without transfusion, 29% of pregnancies with hydrops fetalis developed normally following transfusion and 1% of the pregnancies were ended[34].

Hellmund et al. evaluated the results of intrauterine transfusion performed in 55 foetuses before week 20 of gestation in whom severe anaemia caused by parvovirus B19 infection was diagnosed. Hydrops fetalis was diagnosed in 38.2% of cases; the condition increased the risk of intrauterine death. After intrauterine transfusion, the survival rate was 80%[35].

Supporting treatment with digoxin may be considered for foetuses with severe hydrops fetalis, cardiomegaly and signs of circulatory failure[3].

To date, no specific method for parvovirus B19 infection treatment has been developed. In addition, there is no vaccine against this virus, although efforts are being made to develop one. There are reports in the literature of attempts to treat B19V infection during pregnancy by administering immunoglobulins IgG-B19 to the amniotic sac; however, there are no clearly defined indications, outcomes are uncertain and there is no approved formulation for such a therapy[36].

At this point, the recommended method for the prevention of complications caused by B19V infection during pregnancy is avoiding contact with infected individuals.

All children who had parvovirus B19 infection during foetal life should be carefully observed after birth, particularly in terms of neurological health (some of them develop psychomotor disturbances and neurological delay probably associated with direct brain tissue damage caused by the virus or severe anaemia during foetal life). There are also reports of hepatic impairment, anaemia and myocarditis in such children[23,32,37,38].

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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