

Parvovirus infection in fetal life. Case report and recent literature updates

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ABSTRACT

Background. The parvovirus B19 (B19V) belongs to the Parvoviridae family, genus Erythrovirus, and is a virus that causes a common childhood disease called erythema infectiosum, also largely known as the fifth childhood disease. The clinical appearance is marked by the "slapped cheek" facies and an erythematous rash localized mainly on the extremities and on the trunk. Most people gain immunity during childhood, and when it occurs in pregnancy in non-immunized women, there are some serious complications for the fetus that can occur. B19V infection in pregnancy can conduct to fetal loss or severe hydrops fetalis, due to the risk of vertical transmission to the fetus and the virus tropism for the erythropoietic fetal stem cells with subsequent cell destruction and fetal anemia. Invasive treatment, as intrauterine fetal transfusion, is necessary for the cases of severe fetal anemia with good survival rates afterwards. The purpose of this review is to update the current knowledge regarding the best management of severe fetal anemia and other complications related to B19V infection in pregnancy, based on the latest data from literature and guidelines.

Methods. Electronic research for relevant articles published in the last years was made, with the usage of PubMed, Medline, Cochrane Data Base, and the current international guidelines promoted by the Obstetrics and Gynecology Societies.

Results and conclusions. The importance of prenatal detection of non-immunized women by serologic testing for parvovirus B19 should not be overlooked, and subsequent follow-up should be recommended in order to lower the incidence of fetal complications associated with developing the disease in pregnancy, especially during epidemics. In case of P19V infection in pregnancy, serial ultrasounds and lab tests should be performed in order to determine the impact on the fetus and the apparition of fetal hydrops. The future moms who are not immunized to B19V should be advised about the risk of vertical transmission and the associated fetal sequelae that can occur. Assessment for maternal disease and for fetal impairment has to become a priority when there are signs of primary infection in pregnancy.

Keywords: parvovirus B19, infection, pregnancy, fetal anemia, hydrops

INTRODUCTION

Parvovirus B19 (B19V) is a widespread infectious agent causing the erythema infectiosum, also known as the fifth childhood disease after an old classification of skin rash diseases in children, after measles, scarlatina, rubella and Dukes disease [1]. The Parvoviruses were accidentally discovered in 1975 while investigating the hepatitis B surface antigen using electron microscopy [2]. These viruses are described as the smallest DNA viruses, and they affect all the organisms from invertebrates to humans. Parvovi-

rus B19 belongs to the subfamily of Parvovirinae, genus Erythrovirus [1]. The virus has tropism for the erythroid progenitor cells, the B19V infection causing deficiency of erythropoiesis, with subsequent anemia, thrombocytopenia, and generalized inflammation. P antigen, which is the cell receptor for the B19V is found on erythrocytes, erythroid stem cells, megakaryocytes, placenta, endothelial cells and the fetal heart and liver, so there is a limited tropism of the virus. Because the virus doesn't have the ability to control the DNA cell synthesis

and the replication of the virus depends on it, the virus can infect only those cells with frequent cellular division [1,3]. The virus is considered stable, with rare mutations, so the immunity once gained, it usually persists for life [1].

The symptoms of the fifth disease are generally mild in children and immunocompetent adult and include a specific face rash (“the slapped cheek” appearance) and a second rash affecting the trunk, arms and legs, and non-specific manifestations as fever, runny nose, and headaches. About 50% of the adult infections can be entirely asymptomatic [1]. The infection in adults can also affect the joints, more frequently the women, which develop the Poly arthropathy syndrome, especially in the knees, feet or hands and can produce transient aplastic crises in specific cases. The joint pain generally resolves spontaneously in maximum 3 weeks, with rare exceptions which can take up to months [4]. The incubation period of the virus is about a week, with a time range between 4 days to 14 days [1,4].

Between 50% to 75% of women at childbearing age are estimated to be immunized to B19V since childhood. From the pregnant women, the infection can affect 1-5%, with a higher rate during epidemics (approximately 20%). The infection occurs mostly in winter and early spring. Following maternal infection, the vertical transmission to the fetus happens in 33-51% cases. The pregnancy outcome is largely normal, but in some cases the infection can result in serious fetal morbidity, namely fetal anemia, and non-immune hydrops fetalis, and even fetal loss [1,5,6].

METHODS

Electronic research for relevant articles published in the last years was taken, using PubMed, Medline, Cochrane Database and also the current international guidelines promoted by the Obstetrics and Gynecology Societies. The infection with parvovirus B19 during pregnancy and its fetal impact were discussed, along with the importance of the best management and follow-up in this particular case, in order to obtain the best outcome for the mother and for the fetus. Search words were *parvovirus B19, infection, pregnancy, fetal anemia, hydrops*. The publications used in order to make this content are entirely presented in the references section and can be found below.

EPIDEMIOLOGY

Being a common disease that occurs in childhood, erythema infectiosum is rare in the adult population. More than 80% of the adult population is

estimated to be immunized and test seropositive for B19V IgG [7]. The available data regarding the seroprevalence of women that can acquire the infection in the first months of pregnancy have similar values around the world, ranging between 26% and 43.5% [7,8,9]. The way of transmission is mainly respiratory, through sputum, saliva, or mucus, disseminated by an infected person when coughing or sneezing [4,7]. Also, the virus can be transmitted through blood and there have been cases documented of contaminated blood products. The vulnerable patients, who are at risk for critical complications due to B19V, such as the immunocompromised one or the pregnant population, should be given safe blood products [7,11]. Among susceptible pregnant women, 1-5% of them will catch the infection during the gestational period and in 33-51% of the cases vertical transmission to the fetus will occur, with the highest rate if the infection is caught in the first trimester [1,7]. Even though it is well known the implication of B19V in fetal loss, a correct evaluation of the exact percent of miscarriages induced by the virus is difficult to determine because of the absence of routine monitoring of this infection during pregnancy [10]. Based on the existing data, it is estimated that 3 % to 12 % of the pregnancy present with a poor fetal outcome due to maternal B19 infection [11].

PATHOGENESIS OF PARVOVIRUS B19 FETAL INFECTION

The B19V circulating in the maternal blood, binds to a specific receptor in the placental endothelium, called the globoside, and it multiplies at this level, being afterwards disseminated into the fetal circulation. Once present in the fetal organism, it binds and infects the erythroid progenitors and replicate in these cells, process which conducts to the destruction of the erythroid cells, blockage of the erythropoiesis and to subsequent fetal anemia, non-immune hydrops fetalis and even fetal loss. The greatest risk for vertical transmission is in the first trimester of pregnancy when the globoside receptor is expressed in a high percentage in the villous trophoblast, expression which decreases along with the growth of gestational age [12,13,14].

CLINICAL PRESENTATION OF B19V INFECTION

Maternal

The maternal symptoms and the gravity of this infection in pregnancy are similar to those noticed in the general adult population, with no comorbidities associated. The disease can be totally asymptomatic in a large percentage of cases (55-76%) or the infected women can experience initially a classic

prodromal syndrome of viral infection, which can include headache, fever, malaise, myalgia, followed in the next 1-3 weeks by pain in the joints (polyarthralgia) and/or an erythematous rash. The rash can be easily mistaken with the one that occurs during rubella infection or measles, and sometimes lab tests are indicated to determine the correct diagnosis. The joints frequently affected are the knees, the wrists, the ankles and the hands, and the pain usually disappears in a few weeks [7,11,15].

Fetal

The vertical transmission and the fetal damage can be observed between 1 to 20 weeks after the maternal infection. The most common fetal complications are anemia, non-immune hydrops fetalis and fetal loss. There have been also described some case reports of anomalies of the nervous system, craniofacial, gastrointestinal, or musculoskeletal defects, but they are considered to be coincidentally and there is no evidence that can link the B19 infection with congenital fetal anomalies [1,15,17]. The assessment of fetal complications can be made using serial sonographic exams, that highlight the existence of hydrops, with accumulation of fluid in different compartments of the fetal body. The signs of hydrops that can be seen during the ultrasound exam are skin oedema, ascites, pericarditis, pleural effusion and edema of the placenta [1]. When sonographic signs of hydrops can be identified, usually the fetal anemia is already severe, lower than 20% of the normal range. Taking this in consideration the best way to assess the fetal impairment is by using ultrasound Doppler velocimetry and measuring the peak systolic blood flow in the middle cerebral artery (MCA). An increase of this velocity value has good correlation with the developing fetal anemia, and additional cordocentesis to correctly identify the fetal hematocrit must be made. If the diagnosis of severe fetal anemia or hydrops is confirmed, intrauterine transfusion is the right treatment [1,16,18]. Along with the anemia, fetal thrombocytopenia is a common finding with an incidence estimated between 38-64% and it can conduct to serious risks associated with the invasive intrauterine procedures (blood transfusion or cordocentesis). As a result of severe fetal anemia, damage to the fetal circulation and heart failure can conduct to fetal demise, with the highest incidence when the vertical viral transmission happens in the first 20 weeks (16%). On the other hand, hydrops is reported usually when the maternal infection appears in the second trimester, with a rate of occurrence between 3 to 12%, slightly variable depending on the criteria and the groups included in different studies [15,16,17].

MANAGEMENT OF THE B19V INFECTION DURING PREGNANCY

Diagnosis

The diagnosis is mainly serologic by identifying the levels of IgM and IgG in the maternal blood and by detecting the viral DNA in plasma or serum. The diagnosis can be difficult to make due to the existence of false negative results of antibodies. Moreover, because the fetus can show signs of damage 20 weeks after the mother's infection with B19V, the detection of IgM can misguide showing a negative result [7,19]. When there is sonographic proof of hydrops fetalis or anemia, and the maternal infection is suspected, an invasive procedure is necessary to determine the viral DNA existent in the cord blood or in the amniotic fluid. The detection of IgM or IgG in the fetal blood is not reliable because it is considered that a negative IgM can result from the immature immune response of the fetus and a high level of IgG can be acquired by transplacental crossing from the mother [11,20].

Treatment

In a case of a non-immunized pregnant woman who gets infected with parvovirus B19, the symptoms are generally mild, with rapid recovery, without any treatment needed. In rare cases, when the disease is more severe, hospitalization and anti-inflammatory drugs may be of use, along with blood transfusion if severe maternal anemia develops. There are no specific antivirals for B19V, but the latest data suggest that cidofovir and hydroxyurea have anti-B19V activity [7,21,22]. Several attempts have been made to obtain a vaccine over the years which dramatically failed, and a new attempt is currently in the research process [23].

When fetal impairment, as in severe anemia or hydrops, is established by increased values of the peak systolic velocity of the middle cerebral artery (MCA-PSV) or by sonographic signs of hydrops, the recommended treatment is represented by intrauterine transfusion (IUT). The perinatal outcome is good, with survival rates ranging between 67-85% [7]. Because fetal thrombocytopenia is also a common finding, available platelets are required when doing the IUT, to minimize the risk of postinterventional hemorrhage [16]. An alternative therapy is the intrauterine administration of immunoglobulins (IVIg), that has been performed with satisfactory results [24]. The invasive treatments described above are indicated only in patients with severe fetal hydrops or anemia, for the mild forms expectation being the most reasonable option. Spontaneous resolution of this non-severe cases is quite frequent, and the follow up should include serial ultrasound examinations, with determination of the MCV-PSV [7].

Prophylaxis

Since there is no available vaccination or specific drugs that can counteract the infection with parvovirus B19, the careful prevention represents the only way to diminish the risk of acquiring the virus. Personal hygiene measures (washing the hands correctly, limiting the interaction with sick individuals, avoiding to touch the eyes, nose or mouth, using protection when coughing or sneezing) are the only ones that can reduce the viral transmission [4]. It remains to be seen if a vaccine will finally be obtained against parvovirus B19 infection [23].

CONCLUSIONS

Close consideration must be paid to parvovirus B19 infection in pregnancy because of the impor-

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