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Parvovirus B19 infection in pregnancy

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ABSTRACT

Parvovirus B19 infection is the most common cause of non-immune hydrops in fetuses. The risk of congenital infection is highest in the 1st and 2nd trimester and there are no current recommendations regarding screening of low-risk pregnancies. Recent exposure of the mother and ultrasound findings of fetal anemia or hydrops should include parvovirus B19 infection investigation.
Adequate monitoring through ultrasound and Doppler determine the fetal and perinatal outcome as interventions as intrauterine blood transfusions are the main treatment.

Keywords: pregnancy, infection, parvovirus B19

INTRODUCTION

It is difficult to estimate the burden of parvovirus B19 infection during pregnancy because of the cultural and behavioural contrasts within countries [1]. About 1 to 2% of women are affected during pregnancy and 60-75% of them have protecting antibodies [2]. Coinfections with *Toxoplasma gondii*, herpes simplex virus, cytomegalovirus are common and should be considered during initial investigations [3].

Parvovirus B19 is a single-stranded DNA virus, which belongs to the genus Erythrovirus and spreads through respiratory droplets or hand to mouth contact [4,5], blood-derived products and trans-placentally during pregnancy [5]. This virus affects the fetus causing non-immune hydrops as well as children and adults causing erythema exanthema infectiosum.

Red cells progenitors from the bone marrow, hepatocytes and myocardium, are the main targets of the virus causing a self-limited transient aplastic crisis, hepatitis and myocarditis [6]. Affecting mainly children and young adults, seroprevalence increases with age, reaching 40-60% for adults of 20 years of age [7].

It is a common childhood disease, also known as erythema exanthema infectiosum. Primary infection is the first exposure to the virus and usually evolves without symptoms but it can also have a biphasic evolution [5]. The incubation period is between 4 and 14 days after exposure [2]. The initial contagious phase consists of mild symptoms as pyrexia, malaise, myalgia and itchiness, 7 days post-infection, and IgM antibodies response 10-12 days after infection, lasting for 3-6 months [5,8]. These pseudo-influenza symptoms accompany a respiratory viral excretion and a rethyculocytopenia, manifested as mild anemia in adults which lasts for 1 week, and transient moderate lymphopenia, thrombocytopenia and neuthropenia [8]. The second phase, non-contagious, with rash, itchiness or arthralgia mimicking rheumatoid arthritis begins 17 days post-infection, concurrent with IgG production present for life [5,8].

An immunocompetent infected person is contagious before the onset of symptoms, 5-10 days after exposure [9] and for another 7 days during the viremia phase [6]. During pregnancy, infection can manifest without symptoms (30%-50%) [10] or associate symptoms as arthralgia (46%), rash

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(38%) and fever (19%) [11]. Maternal symptoms, such as arthropathy, tended to have a better correlation with the incidence of fetal loss comparing to no symptoms (9% vs. 5.3% incidence of fetal loss) [12].

The seroconversion rate is higher during epidemics every 3 to 4 years (late winter and spring) between 1 and 3% to 20-30% in daycare centers and schools and 50% through exposure to own children [5]. Seroprevalence in pregnant women depends on the background risk and varies between countries, exposure to children within different work categories, 35% to 65% of them having past immunity to future parvovirus B19 infection [13]. A susceptible population are daycare workers, especially seronegative women trying to conceive or during the first and second trimester, which need precaution measures like washing hands more often in order to decrease the risk of infection [14]. The risk of infection in seronegative pregnant women is 55% from their own children comparing to 6% with occupational exposure. Determining the immunological status in the first trimester in pregnant women who are mothers of preschool-age children, workers at daycare centers and school teachers, could be an option [15]. Reactivation of the virus occurs only in immunocompromised, but without evidence of fetal infection [16].

The rate of vertical transmission is 17% to 33% of pregnant women exposed to the virus and the risk of fetal infection is higher if seroconversion appears before 20 weeks of gestation [4]. The earlier the infection occurs (1st and 2nd trimester of pregnancy), the more severe the consequences are. The transplacental passage takes place during the viremia peak, 1 week after maternal infection [17]. Fetal parvovirus B19 infection is the most common cause of non-immune fetal hydrops with great perinatal mortality and morbidity. Direct inhibition of early stages of hematopoesis, with fetal anemia, causes damage to the fetus with complications such as miscarriage or stillbirth (11-15% before 20 weeks gestation) and hydrops (3% before and 1% after 20 weeks gestation) [4,17] . Detection and treatment are important in order to decrease the rate of cardiomyopathies, hepatic failure and neurodevelopmental sequelae which are long term consequences [4]. There is no evidence that parvovirus B19 infection is teratogenic [2].

DIAGNOSIS AND MANAGEMENT OF PREGNANT WOMEN EXPOSED TO PARVOVIRUS B19 INFECTION

Systematic screening is not recommended in low-risk pregnancies. In case of exposure or symptoms of parvovirus B19 infection (mostly arthritis and rash), testing for specific IgM and IgG is recommended [15].

Negative IgM and IgG should encourage counseling for preventive measures. In case of a recent exposure to the virus, repeating IgM and IgG every 2 to 4 weeks is recommended, especially if the exposure is ongoing. Additional confirmation methods through B19 parvovirus DNA should be considered if IgM levels have dropped below detection limit, but with careful interpretation, as DNA could persist in low levels for several months after acute infection [15]. In cases of fetal hydrops, detection of B19 parvovirus DNA in maternal blood comes with a high sensitivity for diagnosing maternal infection [18].

For women with negative IgM and positive IgG, immunity as an evidence of previous exposure exists and they are not at risk of fetal infection [9]. Depending on the individual risk, minimizing exposure at work and at home, washing hands more often are advisable [15].

Positive IgM and IgG may signify a recent infection and should encourage checking past serologies, if available, to confirm seroconversion or repeat IgG. In case of recent infection, IgG titer increases. A constant IgG value may indicate an infection up to 6 months earlier [15]. Measurement of IgG avidity enhances the precision of diagnosis in pregnancy and a high avidity value excludes an infection in the last 12 weeks [18]. This finding could decrease the ultrasonographic surveillance period [17]. Serial ultrasound and middle cerebral artery (MCA) Doppler assessment are needed [15].

Positive IgM with negative IgG status indicates a possible recent infection or a false-positive result and needs repeating serologies after 1 to 2 weeks to detect an increase in IgG level if infection has occurred and referral to obstetrician with serial ultrasound and MCA Doppler assessment and monitoring fetal movements for advanced gestations [9,15].

DIAGNOSIS AND MANAGEMENT OF FETAL PARVOVIRUS B19 INFECTION

Perinatal outcome and mortality are determined by the presence of hydrops [3]. In the absence of any intervention, 29% of hydropic fetuses will die comparing to 5.5% of non-hydropic fetuses, especially before 20 weeks of gestation [2]. The risk of intrauterine fetal death following maternal infection varies depending on gestational age, ranging between 17.2% at 0-8 weeks, 9.9% at 9-12 weeks,

12.7% at 13-16 weeks and 5,7% at 17-20 weeks. The reported incidence of hydrops was 7.3% at 13-16 weeks, 7% at 17-20 weeks and 5.2% at 21-24 weeks [3,12].

Serial ultrasound assessment in tertiary care centers should begin 4 weeks after maternal exposure/infection and achieved every 1 to 2 weeks up to 12 weeks after infection looking for signs of hydrops and fetal anemia [2]. Maternal fetal medicine specialists should search for signs of ascites, pleural and pericardial effusions, 1st trimester increased nuchal translucency, placental thickening, cardiomegaly, echogenic bowel, meconium peritonitis, amniotic fluid abnormalities, impaired fetal growth and measure the middle cerebral artery peak systolic velocity (MCA PSV) [9,15]. Assessing the MCA PSV following certain rules [19] is of great clinical importance, as cases of mild or severe anemia (Hb level under 3 g/dl) or pregnancies over 35 weeks gestation could influence the measurements and not correlate with the degree of fetal damage. A cut-off value of 1,5 MoM has been established with a 79% sensitivity and 73% specificity, to diagnose fetal anemia and reduce invasive procedures [2].

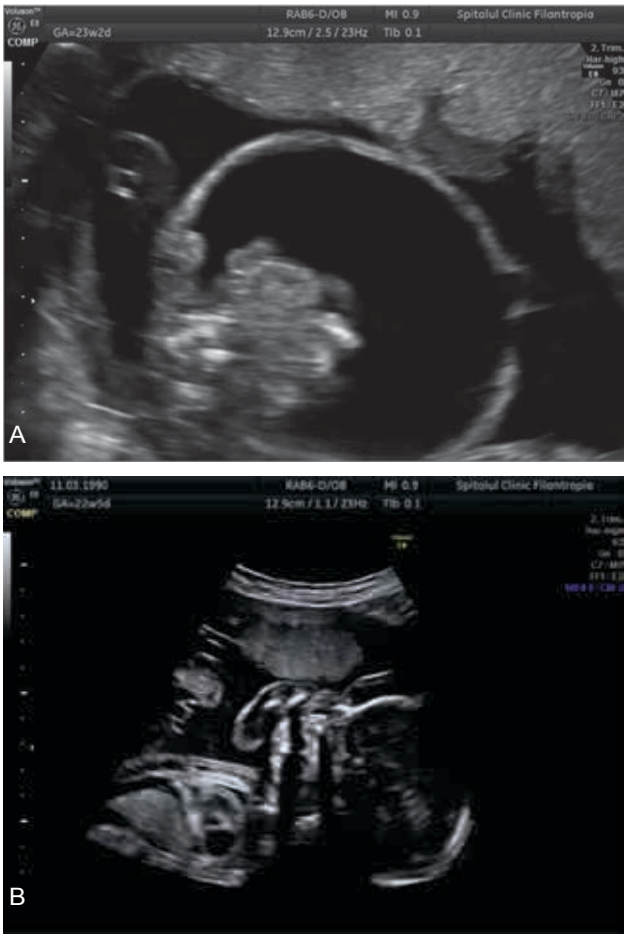

***FIGURE 1**. A. Fetal ascites. B. Hydrops fetalis in a fetus with parvovirus B19 infection (Filantropia Hospital Collection)*

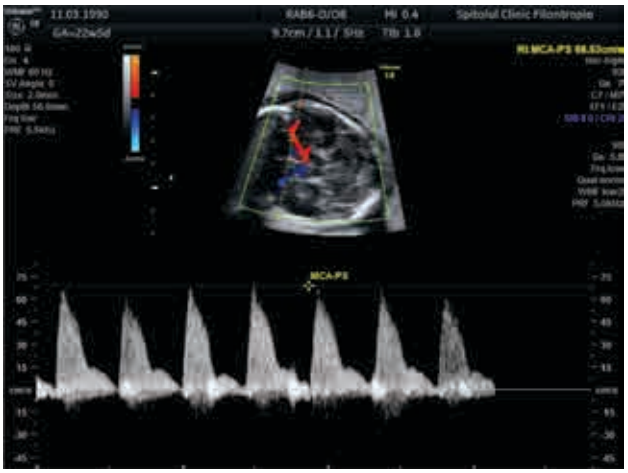

***FIGURE 2**. Measuring MCA-PSV in a fetus with parvovirus B19 infection (Filantropia Hospital Collection)*

Invasive testing, through amniocentesis and cordocentesis are the only methods to diagnose fetal infection. Determining the presence of parvovirus B19 DNA in the amniotic fluid or cord blood is not a routine and is performed in cases of severe fetal anemia and hydrops when intrauterine transfusion (IUT) is required [2].

Middle cerebral artery PSV over 1.5 MoM and fetal hydrops or ascites indicate the need of fetal blood sampling to confirm and treat fetal anemia through an IUT reducing the risk of intrauterine fetal death [2]. There is no fixed gestational age limit for IUT, as 1 to 3 procedures are usually required, depending on the resolution of anemia or hydrops [15]. Almost 95% of hydropic transfused fetuses have thrombocytopenia and some have considered transfusing platelets but with a possible risk of fluid overload [2,20]. After IUT hydrops resolves in 55% of cases, usually in 3 to 6 weeks after procedure, with persistent fetal ascites for another several weeks [2]. The survival rate is reported between 77% and 89% depending on the severity of hydrops and gestational age at IUT. The underlying organic and functional heart disorder in parvovirus B19 infection limits the target hemoglobin level at IUT considering further monitoring and repeating IUT [21]. Concurrence of anemia and thrombocytopenia indicate a future recurrence of anemia and repeated interventions. There are reported cases of mirror syndrome in pregnant women that reveal a persistent, severe fetal anemia [21].

Relying upon the gestational age and severity of hydrops, obstetricians should think about delivering a fetus near term after using corticosteroids for lung maturation. Delivery should take place in a tertiary care center and neonatologists be prepared to treat an anemic or hydropic neonate. Ex-

pectant management could be considered at earlier gestational ages in cases of mild or improving anemia or hydrops [15].

NEONATAL OUTCOME AFTER INTRAUTERINE PARVOVIRUS B19 INFECTION

With improving perinatal survival there is a raising concern about the short and long-term outcome of children from pregnancies affected by parvovirus B19.

Prematurity is one of the most important factors influencing the outcome of affected fetuses and its effects are difficult to discriminate. The possibility of congenital infection due to parvovirus B19 infection with other consequences on the fetus has also been discussed. Within case reports or small series of cases, fetuses with ocular disorders (microphtalmia, dysplastic changes of the retina, cornea, choroid, sclera or lens), cleft lip or palate, hydrocephalus, webbed joints, musculoskeletal defects, hepatocellular injury, hepatomegaly, cardiac disorders (myocarditis, congenital cardiomyopathy), placentomegaly, edema and angioedema, have been described as non-specific aspects of congenital infections [6].

A cerebral MRI needs to be planned either at 32 weeks or in the neonatal period in fetuses with hydrops or severe anemia (hematocrit at IUT under 15%) [21,22], lesions as migratory abnormalities, calcification in cerebral cortex and basal ganglia being reported [23]. The rate of severe neurodevelopmental sequelae varies within studies between 2.3% and 11% as parvovirus B19 infection affects the developing fetal brain either through hypoxic-ischemic injury to cerebral palsy or encephalitis, due to direct injury [24]. There is no clear correlation between the severity of fetal anemia or acidemia and neurodevelopmental outcome and 19% of the fetuses treated through IUT have been discovered with a delayed psychomotor development (cerebellar abnormalities) [25] with difficulties in testing at a very young age [23].

CONCLUSIONS

There are no current recommendations regarding a systematic screening of parvovirus B19 infection, but serial ultrasound assessments are the main tool to monitor women with a recent exposure to parvovirus B19 infection. In case of ultrasonographic findings of infection, viral serologies are necessary, including other infectious diseases, as TORCH.

Treatment through intrauterine blood transfusions have a good prognosis if there is an early intervention before the fetus develops generalized hydrops.

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