Parvovirus B19 during pregnancy: a review

Elsa Giorgio[1]
Maria Antonietta De Oronzo[2]
Irene Iozza[3]
Angela Di Natale[1]
Stefano Cianci[3]
Giovanna Garofalo[3]
Anna Maria Giacobbe[1]
Salvatore Politi[3]

[1] Policlinico Universitario "G. Martino", Department of Obstetrics and Gynecology, University of Messina, Italy
[2] Department of Gynecology, University "Campus Biomedico", Rome, Italy
[3] Santo Bambino Hospital, Department of Microbiological and Gynecological Sciences, University of Catania, Italy

Corresponding author:
Elsa Giorgio
Policlinico Universitario "G. Martino", Department of Obstetrics and Gynecology, University of Messina
email address: elsagiorgio@virgilio.it

Summary

Several infections in adults warrant special consideration in pregnant women given the potential fetal consequences. Among these is parvovirus B19 deserves special attention since the harmful effects on the pregnant woman and fetus. It can then cause fetal anemia, non-immune fetal hydrops and fetal death. Among cases with fetal demise, B19 is found in significant numbers, especially in the second and third trimesters of pregnancy. There is no specific treatment or prophylaxis available against B19 infection, but counseling of non-immune mothers and active monitoring of confirmed maternal infections with intervention to correct fetal anemia is likely to decrease mortality.

Key Words: Parvovirus B19, fetal, infection, hydrops, anemia

Introduction

Parvovirus B19 is a widespread infection that may affects 1-5% of pregnant women, mainly with normal pregnancy outcome (1,2). The prevalence of infection is higher during epidemics - between 3 and 20% with seroconversion rate of 3-34% (3,4). Infection during pregnancy can cause a variety of other signs of fetal damage. The risk of adverse fetal outcome is increased if maternal infection occurs during the first two trimesters of pregnancy but may also happen during the third trimester. It is a significant cause of fetal loss throughout pregnancy, but has a higher impact in the second half of pregnancy when spontaneous fetal loss from other causes is relatively rare. Parvovirus infection can cause severe fetal anemia as a result of fetal erythroid progenitor cells infection with shortened half life of erythrocytes, causing high output cardiac failure and therefore nonimmune hydrops fetalis (NIHF). The P antigen expressed on fetal cardiac myocytes enables the Parvovirus B19 to infect myocardial cells and produce myocarditis that aggravates the cardiac failure. Although there are several reports of major congenital anomalies among offspring of mothers infected by Parvovirus, the virus does not seem to be a significant teratogen. Since Parvovirus B19 infection can cause severe morbidity and mortality, it should be part of the routine work up of complicated pregnancies. Risk assessment for maternal infection during pregnancy is especially important during epidemics when sero-conversion rates are high (4).
Infection with parvovirus B19 is associated with a wide range of clinical presentations and outcomes. Effects may range from an uncomplicated pregnancy to severe hydrops fetalis or intrauterine foetal death. Maternal symptoms may be aspecific and may delay early diagnosis (5).

1. Spontaneous abortion
The spontaneous loss rate of fetuses affected with parvovirus B19 before 20 weeks' gestation is 14.8% and after 20 weeks' gestation is 2.3% (6,7-9). The reason is uncertain but may be related to multisystem organ damage (10).

2. Congenital anomalies
Though there have been case reports of central nervous system (10,11), craniofacial (10,11) and eye anomalies (10,11). In other species with other strains of parvovirus infection, congenital anomalies have been reported (10,11). However, is not demonstrated an association between parvovirus infection in pregnancy and increased risk of congenital anomalies in human fetus (10,11).

3. Hydrops
Association between parvovirus infection in pregnancy and hydrops fetalis has been clearly demostred (6-8, 12-16). Possible mechanisms are fetal anemia (due to the virus crossing the placenta) combined with the shorter half life of fetal red blood cells, leading to the severe anemia, hypoxia and high output cardiac failure. Other possible causes are fetal viral myocarditis leading to cardiac failure, and impaired hepatic function caused by direct damage of hepatocytes and indirect damage due to hemosiderin deposits (6-8, 12-15). When the infection

was acquired before 19 to 20 weeks' gestation (14.8%) (6-8,16), there is a higher fetal loss rate compared to that after 20 weeks (2.3%) (6-8,16). The ultrasound signs in a fetus with hydrops, include ascites, skin edema, pleural and pericardial effusions and placental edema (10).

Diagnosis of fetal anemia

Middle cerebral artery peak systolic velocity in high-risk pregnancies and in presence of some fetal pathology is a very important marker of fetal anemia (17).
Middle cerebral artery peak systolic velocity (MCA-PSV) is a high sensitive non-invasive means for determining the degree of fetal anemia; use of MCA-PSV into management of pregnancies at risk for fetal anemia enable to reduce the number of invasive procedures. This parameter should not yet be considered the global standard of care for diagnosis of fetal anemia because incorrect use by an unexperienced operator may cause more harm than good. However, if there is a reasonably close medical center with sonographers tranined to assess the MCA-PSV, patients at risk for fetal anemia should be reffered to this center (18). There is an inverse correlation between MCA PSV measurements and hemoglobin values in fetuses at risk for anemia due to maternal blood group alloimmunization and fetal parvovirus B19 infection. The MCA PSV is a reliable method for the prediction of severity of anemia in fetuses before the first intrauterine transfusion and in those which have undergone one or more transfusions, with good sensitivity and specificity in both groups of fetuses at ris (19).

Long-term neonatal outcome

There have been few studies of the long-term effects on children of maternal parvovirus B19 infection (7,9,16,20-27). The neonatal complications of maternal parvovirus B19 infection have been reported, including hepatic insufficiency (9,24,25), myocarditis (20,22,26), transfusion dependent anemia (10,11), and central nervous system abnormalities (20,9,25). However, incidence of congenital anomalies, overall learning disabilities, or neurologic handicaps[16]. Through a questionnaire survey, Miller et al.[7] found no increased risk of adverse outcome in children of mothers with parvovirus infection in pregnancy at one year (182 children) and 7 to 10 years (129 children) of age. Most children born to mothers who develop parvovirus B19 infection in pregnancy do not appear to suffer long-term sequelae, but further studies are needed (21). Parvovirus B19 itself does not seem to cause long-term neurologic morbidity, but severe anemia may be an independent risk factor for long-term neurologic sequelae (27).

Exposure/infection in pregnancy

The first thing to do for management of Parvovirus B19 is the study of parvovirus B19-specific IgG and IgM. A pregnant woman what is exposed to or develops signs or symptoms of parvovirus B19 infection should perform both parvovirus B19-specific IgG and IgM., one should determine if she is immune (see figure) (21,28). Parvovirus B19 IgM usually appears within 2 to 3 days of acute infection and may persist up to 6 months. Parvovirus B19 IgG appears a few days after IgM appears and usually remains present for life (21).

1. IgG+ IgM-
If a pregnant woman has presence of B19-specific IgG and absence of parvovirus B19-specific IgM she can be considered immune. It will most likely contracted the infection about six months before. If the woman is immune, she can be reassured because she will not have adverse consequences in the pregnancy because only the primary infection in pregnancy may cause fetal harm (21).

2. IgG- IgM+
The presence of parvovirus B19 IgM antibodies with the absence of parvovirus B19 IgG antibodies suggests either a very recent infection or a false positive result. In this situation, the pregnant woman must repeat the dose parvovirus B19 IgG and IgM in 1 to 2 weeks. If the IgG is positive, it suggests a recent infection. If both parvovirus B19 IgG and IgM are negative, the woman is not immune so she is therefore susceptible to infection (21). If she has had a recent exposure to the virus, and may be incubating the infection, it is suggested that the IgG and IgM tests be repeated 2 to 4 weeks later. If exposure is ongoing, one may wish to repeat serology every 2 to 4 weeks. If testing reveals both parvovirus B19 IgG and IgM to be present, this may suggest recent infection (21). If stored blood is available from the woman, testing may confirm seroconversion. If stored blood is not available, repeat blood work should reveal an increasing parvovirus B19 IgG titre if recent infection has occurred. If the titre is not increasing, this may represent an older infection (up to 6 months prior). Serologic diagnosis with parvovirus B19 IgM alone for recent infection may be difficult due to lab sensitivity for IgM being positive up to 6 months after acute infection. Women who is not immune need to be assessed with regard to their exposure risk so she should perform these measure: hand washing, infact this measure decreases infection (12). During an outbreak, parents of preschool and school children as well as employees should be informed of the risk of infection and its management. Each woman should be counseled about her individual risk, based on her risk of infection, gestational age, and other obstetrical considerations. The decision to leave work to try to minimize the risk of infection during an outbreak of parvovirus B19 infection should be made by the woman after discussion with her physician, family members, public health officials, and employers, taking into account her specific risk. As there is no evidence that susceptible women reduce their risk of infection by leaving work, and one study demonstrated no difference in infection rates between susceptible pregnant school teachers who left the workplace and those who stayed (29), it is not recommended that policies be pursued to routinely send home women susceptible to infection (12).
If the woman has developed a recent infection, the virus may be transmitted to the fetus and may cause nonimmune hydrops. Therefore, it is recommended that these women be referred to an obstetrician or maternal-fetal medicine specialist and that these women have serial

ultrasounds to detect evidence of hydrops for 8 to 12 weeks after infection, as the development of hydrops may be delayed (7,11,21,29,30). There are no randomized trials of the frequency of ultrasounds required; however, most maternal-fetal medicine specialists perform ultrasonographic assessment weekly or every 2 weeks (30).
These follow-up ultrasounds could be limited to assessment of amniotic fluid volume and evidence of hydrops (level II ultrasound with documentation). As fetuses with hydrops tend to move less, women should also be instructed to monitor fetal movement daily (21). If there is a delay in establishing the woman's immunity status, one may wish to obtain serial ultrasounds for the detection of hydrops, until this information regarding immunity is available (31).

Diagnosis of fetal infections

Parvovirus B19 cannot usually be cultured in regular culture media. It can be identified histologically by characteristic intranuclear inclusions or by the presence of viral particles by electron microscopy (10). Viral DNA may also be identified by polymerase chain reaction (PCR) of amniotic fluid or fetal blood by cordocentesis. The most reliable way to diagnose acute fetal infection is to detect in amniotic fluid or fetal serum viral DNA by PCR or viral particles by electron microscopy. Clinical use of these tests remains to be evaluated. Although there is the possibility of diagnosing parvovirus B19 infection through PCR on amniotic fluid obtained by amniocentesis, invasive diagnosis of this condition is not required for all suspected or confirmed maternal infections. If amniocentesis is performed for a fetal indication, a PCR for parvovirus B19 can be requested as part of the workup. The presence of viral particles, however, can only be seen during the viremic stage. The presence of parvovirus B19 IgM in fetal blood cannot be depended upon to make the diagnosis of fetal infection (32), as the fetus does not begin to make its own IgM until 22 weeks' gestation. There have been false negative results even when the fetus is beyond 22 weeks (33). Elevated maternal serum alpha fetoprotein (MSAFP) levels have been associated with fetal parvovirus B19 infection in several case reports (34,35); but one study found the association between MSAFP and fetal infection weak and thus it cannot be used as a reliable marker of fetal parvovirus B19 infection (36).

Management of fetal hydrops

Every pregnancy identified with fetal hydrops should be referred to a tertiary care centre with a maternal-fetal medicine specialist.
The current management of hydropic fetuses due to parvovirus B19 infection is somewhat controversial. The primary management tool is cordocentesis to assess fetal hemoglobin and reticulocyte count. If necessary intrauterine transfusion must be performed (11). If the fetus is term or near term, delivery should be considered (11). If delivery is not imminently required, amniocentesis for lung maturity evaluation may be considered. Use of corticosteroids to accelerate lung maturity is not controindicated. For fetuses at younger gestational ages or with pulmonary immaturity, the management options of expectant management or intravascular transfusion (11, 21) have been proposed. There are no randomized trials to evaluate the best management for fetal hydrops caused by parvovirus B19 infection. The upper limit of gestational age for transfusion is case and centre dependent. Due to myocarditis, the degree of hydrops may not correlate with fetal hemoglobin. Preliminary information has suggested a role for Doppler assessment of umbilical venous and middle cerebral artery flow velocities in the assessment of fetal anemia (37-40). A summary of case reports of intravascular transfusion for fetal hydrops due to parvovirus B19 infection revealed a fetal mortality rate of 11%. In all 18 cases, the fetal hemoglobin was less than 8 g/dL, and most had severe hydrops. Twenty cases were treated expectantly, with serial ultrasounds noting a fetal mortality of 26%. In those cases managed expectantly, this management was chosen based on the fact that the hydrops appeared to be mild or improving (based on ultrasound and/or cordocentesis). Failey et al. (41) compared outcomes of expectant management with intravascular transfusion, controlling for severity of hydrops and gestational age, and found a greater than 7-fold reduction in fetal death with intravascular transfusion. In a survey of maternal-fetal medicine specialists involving 539 cases of parvovirus B19-induced hydrops, death occurred after intravascular transfusion in 6% of cases, and in 30% of cases without intravascular transfusion (30).

Conclusion

Most women with B19 infection in pregnancy had a satisfactory outcome, but there is nevertheless a substantial risk of fetal loss and non immune hydrops in the second trimester. An early diagnosis of fetal anemia due to parvovirus infection is possible. If a maternal infection is suspicted the woman should be referred to a terziary center of fetal maternal medicine.

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