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Case Report

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Non immune hydrops fetalis due to Parvovirus B19 infection. A case report

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Abstract

Backround: The term "hydrops fetalis" refers to excessive accumulation of pathologic serous fluid within the fetal soft tissues and body cavities. There are two categories, the immune and the nonimmune hydrops (NIHF). Currently 90 percent of cases of hydrops are nonimmune, because of the decrease of incidence of immune with the advent of anti-D immune globulin.

Case presentation: We present a case of Parvovirus B19 (PB19) infection that resulted in NIHF. Fetus had severe ascites, mild pericardial effusion and mild myocardial dilation, that appeared during the 30th gestational week. Fetal evaluation with sonography was repeated every week and the fetal growth curves, Dopplers and amniotic fluid index were normal. Each week there was a gradual recession of the effusions until the 36th gestational week, when they eventually resolved without any treatment. After delivery, the neonate was symptom – free.

Conclusions: The cause of NIHF is identified in at least 60 percent prenatally and in more than 80 percent postnatally, while only 40 percent of pregnancies with NIHF result in a liveborn neonate. The prognosis is heavily dependent on etiology. Diaplacental transmission of PB19 on second trimester can cause fetal complications like hydrops, premature rapture of membranes, even fetal loss in about 30 percent. These cases should be closely followed in a Fetal Medicine Unit, especially if there is evidence of fetal anemia or hydrops.

Key words: Nonimmune hydrops fetalis, edema of the fetus, parvovirus.

Backround

The term "hydrops fetalis" refers to excessive accumulation of pathologic serous fluid within the fetal soft tissues and body cavities. With sonography, hydrops has become a prenatal diagnosis. It is defined as at least two fetal effusions, which include ascites, pleural effusion, pericardial effusion and generalized skin edema (skin thickness more than 5mm).[1] Placentomegaly and hydramnios may accompany this

condition.[2] There are two categories of hydrops. If found in association with red cell alloimmunization, it is termed immune, otherwise, it is nonimmune (NIHF). Nowadays, 90 percent of hydrops cases are nonimmune because of the prevention of Rh D alloimmunization with the anti-D immune-globulin.[2] The prevalence estimate of NIHF is 1 per 1700 – 3000 pregnancies.[4] Only 40 percent of pregnancies with NIHF result in a liveborn neonate and for these the neonatal survival rate is about 50 percent.[1]

Perigestational Parvovirus B19 infections affect 1 percent of pregnancies.[6] Most cases follow exposure from the pregnant women's own children. If acute Parvovirus infection complicates pregnancy, diaplacental transmission rates are up to 50 percent. Intrauterine infection may cause spontaneous abortion during the first trimester, or NIHF during the second trimester.[6] Even after vertical transmission, the overall risk of serious disease remains very low. Miller et al. report a 9 percent risk of fetal loss in a prospective cohort study of 427 pregnant women with confirmed B19 infection.[7] The spontaneous resolution of hydrops and the following delivery of symptom free newborns at term have been repeatedly reported, especially after intrauterine red cell transfusion.[8]

Case presentation

A 26 years-old G0P1 woman was committed in the Fetal Medicine Unit of The First Department of Obstetrics and Gynecology at 30^{+4} gestational weeks due to hydrops fetalis. Until the 30^{th} gestational week, the woman was followed in a provincial hospital of the island she lived. Her personal medical history was free. Her routine blood tests and first and second – trimester ultrasounds were normal. Indirect Coombs tests were all negative so far. The laboratory test for cystic fibrosis (80% of mutations) was negative. The screening for congenital infections revealed only a high IgG antibody titer for Parvovirus B19, while IgM titer was very low.

During physical examination, she was normotensive, afebrile and without any symptom of infection. She referred a respiratory infection three months ago. She recovered without any treatment. In the ultrasound, the fetus had severe ascites, mild pericardial effusion and mild myocardial dilation and thickening. No structural anomalies were identified. Fetal growth curve was in the 90^{th} percentile and fetal movements were normal. MCA Doppler velocimetry was normal as well as amniotic fluid index. Amniocentesis was performed for fetal karyotype and PCR for PB19. We recommended a fetal echocardiography by a pediatric cardiologist and reevaluation in our Department in a week.

A week later, the patient returned with a normal molecular karyotype testing and a positive PCR for PB19. Fetal heart ultrasound revealed mild pericardial effusion and mild myocardial thickening. In the following ultrasound, the ascetic fluid was less, the pericardial effusion was absorbed and Dopplers were normal. Each week there was a gradual recession of the effusion until the 36^{th} gestational week, when the ascites totally resolved without any intervention.

One week later, she delivered a male fetus (37^{+1} gestational week), by cesarean section due to the history of hydrops fetalis. The neonate weighted 3290 gr and had an Apgar score of 8 at the 1^{st} minute. It remained in the Neonate Unit for 5 days and then discharged. The newborn had not anemia at birth and did not

Table 1. Newborn's laboratory findings

	1ST DAY	2ND DAY	3RD DAY	4TH DAY
Hct	53,9	54,9	54,5	
Hb	18,7	18,8	18,6	
WBCs	10800	15900	12400	
PLTs	286000	270000	324000	
Total Bil		4	3,84	2,88
Direct Bil		1,39	1,47	1
CRP		0,9	0,5	
LDH				551

require neither phototherapy nor transfusion. No neurological complication was observed. The brain, heart and abdominal ultrasounds were normal and the short-term neonatal outcome was excellent. (Table 1)

Discussion

The etiology of NIHF varies and differs between the trimesters. There is no identifiable cause in about 20 percent of cases.[4] If hydrops is detected during the 1st trimester, the most common cause is the aneuploidy (nearly 50 percent). Etiologies of NIHF include cardiovascular defects, cardiomyopathies, tachyarrhythmias, chromosomal syndromes, hematological problems, infections (TORCH), thoracic abnormalities, lymphatic anomalies, placental, twin and cord abnormalities, kidney and urinary tract malformations or obstructions, gastrointestinal causes, tumors and other rare disorders.[6]

Diagnostic evaluation of NIHF should include targeted sonographic and laboratory characteristics and findings.[1] Women carrying hydropic fetuses should be referred to Fetal Medicine Units for their follow – up and treatment. Initial evaluation include indirect coombs test for alloimmunization. If this test is negative, immune hydrops is excluded. Sonographic fetal and placental examination should include detailed anatomic survey, in order to identify structural anomalies, MCA Doppler velocimetry to assess fetal anemia and fetal echocardiography. In addition, amniocentesis should be performed for fetal karyotype and PCR for the detection of B19 parvovirus, CMV and toxoplasmosis. Specific gene mutations should be considered for testing, such as a-thalassemia genes and errors of metabolism. If anemia is suspected, Kleihauer – Betke test should be performed for the assessment of fetomaternal hemorrhage.[5]

Parvovirus B19 is a small single stranded DNA virus that is spread by respiratory secretions. It can also be transmitted vertically from mother to fetus during pregnancy. PB19 can infect the placenta and fetal erythroid precursor cells and as a result it can cause complications including fetal anemia, NIHF and intrauterine fetal demise.[9] PB19 has many pathogenic cellular receptors. The most clinically important is P-antigen (P-Ag). P-Ag is present on haematopoietic precursors as well as endothelial cells, fetal myocytes and placental trophoblasts. This antigen is responsible for the clinical syndromes of the infected fetus.[10] Specific B19V IgM antibodies appear 7 to 12 days after infection and usually disappear within 3 to 4 months.[10] IgG antibodies offer lifelong immunity, so if a pregnant woman is IgG positive at the time of exposure, she is immune and is not at risk of fetal transmission of PB19.[10] Infection is asymptomatic in 25-50 percent of cases. Approximately 85 percent of the elderly show serologic evidence of past infection.[9] The risk of PB19 infection during pregnancy is almost 1 percent.[6] Diaplacental transmission occurs one to three weeks after maternal exposure.[11]

PB19 is not teratogenic.[11] Haematopoietic cells of the liver, myocardium, endothelial cells, platelets, megakaryocytes and fibroplasts express the P-Antigen viral receptor, so they are susceptible to PB19 damage. Fetal liver acts as the primary haematopoietic organ from 9 to 24 weeks gestation.[10] During the 2nd trimester the red blood cells increase more than 30-fold and their half – life time is 45 to 70 days. As a result, the fetus is very vulnerable to the attack against its red cell production by PB19. This risk is greatly decreased in the third trimester, when fetal haematopoiesis happens in bone marrow and the lifespan of red blood cells is increased. The risk of NIHF is 3.9 - 11.9 percent, with a peak incidence at 21 – 24 gestational weeks.[11] The interval between infection and NIHF is 2-6 weeks.

Screening of PB19 serological status during pregnancy is not recommended. A positive IgM result means recent infection, but at the time of NIHF, IgM levels may have already become low or even undetectable.[13] The diagnosis of fetal infection is made by amniocentesis for PCR of PB19 DNA.[10]When maternal infection is diag-

nosed or NIHF exists, referral for specialist assessment is necessary. Serial measurements of the peak systolic velocity of the fetal middle cerebral artery (MCA PSV) can detect fetal anemia.[1] If MCA PSV is more than 1.5 MoMs from 18 to 35 gestational weeks, fetal anemia is present.[14] Early signs of fetal anemia include ascites and cardiomegaly. In more serious cases, generalized edema and placentomegaly may exist. Other signs of PB19 infection include echogenic bowel, meconium peritonitis, first trimester increased nuchal translucency, amniotic fluid abnormalities and myocardial dysfunction.[10] Fetal myocarditis and thrombocytopenia are also known complications.

There is no treatment of fetal PB19 infection. If there is evidence of severe fetal anemia (elevated MCA PSV or NIHF) in a preterm fetus, evaluation with fetal blood sampling is necessary. If fetal hematocrit is less than 30 percent (in hydrops is usually less than 15 percent), intrauterine transfusion is indicated. The target hematocrit is 40 to 50 percent. The RBCs type is O, Rh D negative and the transfusion can be intravascular into the umbilical vein or peritoneal, when early-onset hemolytic disease develops.[1] Subsequent transfusions take place every 2 to 4 weeks and MCA PSV after the first transfusion, is not as sensitive as before in detecting severe anemia.[15] Intrauterine platelet transfusion can be performed in severe thrombocytopenia, but there is a great risk of thrombosis and cardiac failure.[16] Intrauterine intravenous immunoglobulin (IVIG) therapy also has been described as a successful treatment of hydrops. The prophylactic administration of IVIG in PB19 infected women to prevent fetal transmission has not been yet evaluated.[17] These treatments should be performed in Fetal Medicine Units.

Congenital anomalies from PB19 infection are extremely rare, but exist. Several case reports refer hyperechogenic bowel, meconium peritonitis and hypoplasia of abdominal muscles in newborns that suffered hydrops. In addition, ocular malformations have been reported. Myocarditis is a main symptom in hydropic fetuses but it is not accompanied by anatomical anomalies. Some cases of hydrocephalus and cerebellar hemorrhage have been referred. There is insufficient data for the neurodevelopmental outcome of infected children that suffered hydrops fetalis. There are some studies that refer neurodevelopmental delay.[18] Children with neurodevelopmental problems had hydrops fetalis and were transfused. In summary, permanent fetal abnormalities from PB19 infection are extremely rare. Fetal anemia and cardiac failure seem to be responsible for these cases. Possible effects of PB19 on fetus brain need further evaluation.[18]

Conclusions

Transplacental PB19 infection occurs in 30-50 percent of acutely infected women, but most neonates are normal. Fetal infection can cause fetal anemia, hydrops fetalis, myocarditis, intrauterine death and rarely neurodevelopmental delay. PB19 is not teratogen.

Routine screening for PB19 immunity during pregnancy is not indicated (ACOG). Screening for PB19 infection should be performed only after exposure or after identification of NIHF or placentomegaly with ultrasonography. In case of positive IgM antibodies, serial ultrasounds should be performed every 1 to 2 weeks for 12 weeks after exposure. Doppler measurement of the MCA PSV can detect fetal anemia. If fetal anemia is suspected, PCR of amniotic fluid can diagnose PB19 infection. Fetal blood hematocrit can be determined by cordocentesis and intrauterine transfusion is performed in severe anemia.

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