Parvovirus B19 Infections in Pregnant Women and Neonates: Review

Gebe Kadınlarda ve Yenidoğanlarda Parvovirus B19 Enfeksiyonları

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ABSTRACT Parvovirus B19 was discovered by Cossart et al. in 1975 incidentally while screening sera for hepatitis B surface antigen by electron microscopy. Parvovirus B19 is a nonenveloped, small, single-stranded DNA virus with an icosahedral capsid. It infects erythroid precursor cells in bone marrow. The main receptor of the virus is globoside or P antigen, which is present on erythrocytes, endothelial cells, placental trophoblast, and fetal hepatic and myocardial cells. Parvovirus B19 infection called "erythema infectiosum" usually causes a febrile illness but may be a problem especially in patients with chronic hemolytic anemia and pregnant women. Close and frequent contact with young children is a major risk for acquiring parvovirus B19 infection during pregnancy. In pregnant women, the virus passes through placenta. The transplacental transmission of the virus can be in all trimesters but more frequent in the first trimester. Acute parvovirus B19 infection in pregnancy is associated with fetal anemia, hydrops fetalis, and intrauterine fetal death. The transmission rate to fetus is about 33%, and the risk for fetal death is 9% when a pregnant woman has acute parvovirus B19 infection. If a pregnant woman gives a history of exposure to parvovirus B19, specific IgM and IgG antibodies should be investigated. The pregnant woman with IgM positivity should be followed up with ultrasonography (USG) weekly for at least 12 weeks. This virus should be considered when a hydropic fetus is detected by USG although the mother does not give a history of an infection.

Key Words: Hydrops fetalis; parvovirus B19

ÖZET Parvovirus B19, Cossart ve ark. tarafından 1975 yılında, hasta serumlarında elektron mikroskop ile hepatit B yüzey antijeninin araştırılması esnasında tesadüfen keşfedilmiştir. Parvovirus B19, zarfsız, küçük, ikozahedral kapsidli, tek-iplikli bir DNA virusudur. Bu virus kemik iliğindeki eritroid öncül hücreleri enfekte eder. Virusun esas reseptörü eritrositler, endoteliyal hücreler, plasental trofoblastlar, fetal hepatik ve miyokardiyal hücrelerde bulunan globosid veya P antijenidir. "Eritema enfeksiyozum" olarak isimlendirilen parvovirus B19 enfeksiyonları genellikle ateşli bir hastalıktır, ancak özellikle kronik hemolitik anemisi olan hastalarda ve gebe kadınlarda sorunlara neden olabilir. Küçük çocuklarla yakın ve sık temas gebelik süresince parvovirus B19 enfeksiyonuna yakalanma için büyük bir risk oluşturur. Gebe kadınlarda, virus plasenta aracılığıyla bebeğe geçer. Virusun plasenta yoluyla geçişi tüm trimesterlarda olabilir, ancak geçiş ilk trimesterda daha sıktır. Gebelikte geçirilen akut parvovirus B19 enfeksiyonu fetal anemi, hidrops fetalis ve intrauterin fetus ölümü ile ilişkili olabilir. Gebe bir kadın akut parvovirus B19 enfeksiyonu geçirdiğinde fetusa geçiş oranı %33, fetal ölüm oranı ise %9'dur. Eğer gebe bir kadın parvovirus B19 ile temas öyküsü verirse, parvovirus B19'a özgül IgM ve IgG antikorları incelenmelidir. IgM pozitifliği saptanan gebe kadın en az 12 hafta süresince haftalık ultrasonografi (USG) takibine alınmalıdır. USG incelemelerinde hidropik bir fetus saptandığında, anne enfeksiyon öyküsü vermese de bu virus akla gelmelidir.

Anahtar Kelimeler: Hidrops fetalis; parvovirus B19

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VIRAL CHARACTERISTICS OF PARVOVIRUS B19

Parvovirus B19 was first discovered by Cossart et al. in 1975 while screening sera for hepatitis B surface antigen by electron microscopy.[1] They detected some particles other than hepatitis B virus and then they

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understood that they were in fact parvovirus. They called it parvovirus B19 because the virus was found in sera on panel B and specimen 19.[2]

Parvovirus B19 is a nonenveloped, small, single-stranded DNA virus with an icosahedral capsid. Its genome encodes for three major proteins. These are, two structural proteins (VP1 and VP2) which make up the capsid and one non-structural protein (NS-1) which is responsible from viral replication, activation of viral gene transcription and inducing apoptosis.[3,4]

Parvovirus B19 infects erythroid precursor cells in bone marrow. The main receptor of the virus is globoside or P antigen, which is present on erythrocytes, endothelial cells, placental trophoblast, and fetal hepatic and myocardial cells.[5,6] Parvovirus B19 is a widespread human pathogen. Parvovirus B19 infection called "erythema infectiosum" usually causes a febrile illness but may be a problem especially in patients with chronic hemolytic anemia and pregnant women.[7,8] Transmission is mainly through respiratory droplets but possible by transfusion of infected blood products.[9] In pregnant women the virus passes through placenta.[10] In 1984, the relation of parvovirus B19 infection in pregnancy and hydrops was reported.[9,11] Acute parvovirus B19 infection in pregnancy is associated with fetal anemia, hydrops fetalis, and intrauterine fetal death.

CLINICAL MANIFESTATIONS AND TRANSMISSION OF PARVOVIRUS B19 INFECTION IN PREGNANCY

The incubation period of the infection is 4-14 days. Viremia occurs approximately 7 days after inoculation and persists for up to 4 days, and rash appears by the 16th day. The patients are infectious until the characteristic exanthema develops.[9] The rash causes a "slapped cheek" appearance on the face. The rash is more common in children than adults. Arthritis may be seen in 10% of children and in more than 50% of adults.[8,9] One-fourth to one-third of the infected adults are asymptomatic.[12,13] In pregnant women asymptomatic infection rate is reported as 25%.[14] In a study from Japan, Chisaka et al. reported that half of the parvovirus B19 infections in pregnant women are asymptomatic.[15]

It is reported that 30-60% of adults are seropositive. But seropositivity rates vary within different countries and reported as 20-81%.[16] The prevalence of IgG antibodies in the population is reported as 2-15% in 1-5 years, 15-60% in 6-19 years, 30-60% in adults and more than 85% in geriatric population.[17] The highest incidence of the infection is between 5-15 years.[2] Secondary attack rate of households is as high as 50%, and the infection risk of a seronegative student is reported as 20-30% in the event of an ill student is in the same classroom.[18] The seropositivity rate of pregnant women is reported as 50-70%. The annual parvovirus B19 IgG seroconversion rate among women of childbearing age is estimated as 1.5% during nonepidemic periods and 13% during epidemic periods.[19]

Close and frequent contact with young children is a major risk for acquiring parvovirus B19 infection during pregnancy.[20] The risk of infection is reported as approximately 50% from close, frequent interaction with an infected child, for example living in the same home.[21] Most infections during pregnancy are due to exposure from a woman's own children. Some literatures report that no significant differences were found in maternal infection from occupational exposures.[13,22] Although some literatures report the occupational exposure risk of parvovirus B19 is equal or lower than the exposure risk in the community and household, some literatures report that some certain occupations are at risk of exposure. In one study, it is reported that infection is more likely transmitted by house-hold contacts than school contacts.[6,8,10] Valeur-Jensen et al. reported that to have only one child increases the risk of infection 3-fold and to have 3 or more children increases the risk 7.5 fold when compared with nulliparous women.[22] But contrary what is said above, it is reported that the highest infection rate is among school teachers, day-care workers and stuff.[23] Baseline serologic testing of pregnant women working as school teachers, day care workers and women living with school age children may be useful to determine their susceptibility to the infection.[8] In Germany, screening of parvovirus B19 antibodies of pregnant women working at schools and day

care centers are recommended although they do not give a contact history.[24] Some reports suggest seronegative pregnant women to avoid contact with parvovirus B19, but it is not possible to prevent transmission by excluding infected patients from their school and workplaces, because patients can transmit the infection before they are symptomatic of erythema infectiosum. The infectivity of immunocompetent patient is already finished at the time of clinical illness.[8] Therefore, avoiding a workplace environmental is individual.[3,8]

The transplacental transmission of the virus can be in all trimesters but more frequent in the first trimester.[25] Transmission is less frequent with increasing gestational age. In the first trimester, parvovirus B19 can cause spontaneous abortion in about 30% of cases. In the second trimester, hydrops fetalis and/or fetal death is seen in 12% of infected pregnant women. In the third semester, fetal death is reported in approximately 7% of infected pregnant women.[25,26] Fetal and maternal infection can also be asymptomatic.[25,27]

When a pregnant woman has acute parvovirus B19 infection, the transmission rate to fetus is about 33%, and the risk for fetal death is 9%. Puccetti et al. found transmission rate as 31.7% and among the infected fetuses 40% had hydrops.[9,28-31] It is reported that parvovirus B19 is responsible from 8-9% of non-immune hydrops fetalis.[30,32] However, there are some literatures that report higher rates. Carlsen reported the rate of parvovirus B19 infection among the fetuses with hydrops as 40%.[33] Brkic found asymptomatic acute parvovirus B19 infection rate as 22.72% among pregnant women with spontaneous abortion.[26] On the other hand, Enders et al. reported fetal hydrops risk as 4.2% after gestational parvovirus B19 infection.[34] Gratacos et al. reported the incidence of acute infection during pregnancy as 3.7% and the incidence of fetal loss caused by parvovirus as 1.66%.[35] The mother of any fetus with hydrops should be investigated for parvovirus B19 infection.[9]

OUTCOMES OF PARVOVIRUS B19 INFECTIONS IN PREGNANCY

The risk of fetal death is reported higher when infection occurs before 20 weeks of gestation.[30,32] The risk of fetal loss in pregnancies infected before 20 weeks is approximately 10% but after 20 weeks the risk reduces to 1%.[8] Enders et al. reported a higher risk of fetal hydrops in pregnancies affected by B19 between 9 and 20 weeks gestation.[34] In the early second trimester, the reason of increased fetal loss rate is due to the rapid hematopoietic system of the fetus.[36] Also at the second trimester, P antigen is present on the trophoblast layer in the placenta and allows the vertical transmission of parvovirus B19 from infected mother to the fetus. At this stage, hematopoiesis is located at fetal liver and the lifespan of the red blood cells is reduced as 45-70 days. Therefore, the fetus is very vulnerable to defects in hematopoietic system.[37,38] At the third trimester, hematopoiesis is at the bone marrow, and the lifespan of the red blood cells increases, and P antigen is not present. Therefore the risk of hydrops fetalis reduces by the third trimester.[12] But it is reported that parvovirus B19 still can be a reason of fetal death in the third trimester and these fetal deaths are usually non-hydropic.[39] Sarfraz et al. investigated 35 940 pregnant women in Norway and reported that, only four women had serological signs of acute parvovirus B19 infection in pregnancy, either presence of IgM antibodies in the first serum sample or seroconversion, among the 281 women who experienced fetal death.[40] Parvovirus B19 does not cause growth failure of the fetus.[41] Sarfraz et al. reported that past and present maternal parvovirus B19 infection was not significantly associated with birthweight or length of gestation in live born offspring.[40] Additionally, fetal infection is not thought to be teratogenic.[31]

DIAGNOSTIC METHODS IN PREGNANCY

IgM and IgG antibodies directed against parvovirus B19 should be investigated firstly in a pregnant woman who gives an exposure history with parvovirus B19 infection. If IgM is negative after 2 weeks of exposure, probably the woman is not infected with the virus.[3] The woman with only IgG positivity is immune to the virus. IgM and IgG positivity of a pregnant woman indicate infection within 7-120 days and this means that the fetus is at risk.[37] IgM antibodies are detectable within 7-10

days after infection and peak at 10-14 days, then decrease within 2-3 months.[42] IgM and IgG are both negative at the first 7 days which is called the window period after exposure and the tests should be repeated. When hydrops is detected at routine ultrasonography (USG) investigations, the IgM level of the pregnant woman can be very low or undetectable.[3] However, IgM may persist for several months.[43] IgG avidity testing may be useful in discriminating recent or past infection, when IgM and IgG antibodies are both positive. IgM positivity detected at early stages of pregnancy may be due to primary infection before conception.[24] Fetal IgM level can only be used after 22 weeks of gestation, because fetus can produce IgM after that period.[5]

For the evidence of the recent infection, parvovirus B19 DNA can be investigated in maternal blood.[44] Enders et al. reported significant decrease in viral load during the first 2 weeks of parvovirus B19 infection. In addition, they found that DNA levels did not differ in symptomatic or asymptomatic women. They suggested that the degree of viremia did not correlate with the clinical outcome.[24]

Investigating the parvovirus B19 DNA in fetal serum of cord blood or amniotic fluid by polymerase chain reaction (PCR) method is a valuable method in verification and exclusion of the infection.[3,12,16] It is reported that the sensitivities of IgM evaluation on fetal blood sample and DNA searching by PCR are 29%, and 100%, respectively.[10,45] However, it is suggested that, significant viral load in cord blood or amniotic fluid is not predictive to poor outcome of pregnancy.[3,26]

Most of the fetal complications occur within the 8-12 weeks of maternal parvovirus B19 infection.[10,24] Weekly USG follow-up is recommended for at least 12 weeks of a pregnant woman with a history of exposure or parvovirus B19 infection. Hydramnios, placentomegaly, pericardial or pleural effusions, ascites, and skin and scalp edema may be present of a hydropic fetus.[46] The first findings of the disease in the fetus are ascites and the increase of the fetal hearth thickness.[12] While investigating these findings, increased peak systolic velocity of middle cerebral artery should be evaluated as an indicator of anemia.[47] Hemoglobin value of a hydropic fetus could be evaluated and intrauterine transfusion can be performed simultaneously. An algorithm for parvovirus B19 infection in pregnant women with an exposure history is given in Figure 1.

In some cases, maternal alfa-fetoprotein (AFP) levels were detected high in sera of pregnant women and it is suggested that women who have high levels should be evaluated about parvovirus B19 infection. The source of AFP may be damaged liver cells and infected placental cells. But the association is weak because AFP is evaluated at 15 to 18 weeks of gestation and limited to the cases of women infected during the last first and early second trimester. Therefore AFP is not recommended to be used as a predictor of the risk.[8]

Despite all of these diagnostic methods, the etiology can be detected in only 50-80% of nonimmune hydrops fetalis cases.[48]

As we stated above, if an acute parvovirus B19 infection is detected in a pregnant woman, weekly USG investigations are recommended for at least 12 weeks.[8] Fetal hemoglobin level can be evaluated by cordosynthesis, and intrauterine blood transfusion can be performed in cases with low hemoglobin values or wait for the spontaneous resolve of the hydrops. Pregnancy termination is not recommended of a pregnant woman with an acute parvovirus B19 infection.[5,9] Also, amniocentesis is not recommended for diagnosis of asymptomatic intrauterine infection.[49] Several investigators have reported spontaneous resolution of nonimmune hydrop.[8] Gilbert reported that spontaneous resolution is probable in about one-third of cases.[49] This is because red blood cell destruction is self limited.[8] But, the mortality rate in fetuses managed expectantly is higher than the rate of the cases managed with intrauterine transfusion. The average time for hydrops resolution is 4 weeks after intrauterine transfusion.[9] Intrauterine transfusion is recommended in fetuses at less than 32 weeks gestation or with immature lungs, and delivery can be considered after 32-34 weeks of gestation when the lung maturity is verified.[8] Fetal blood sampling can be repeated after 3-4 weeks if intrauterine transfusion is performed.[36] It is reported that, timely intrauterine transfusion of fetuses with severe hy-

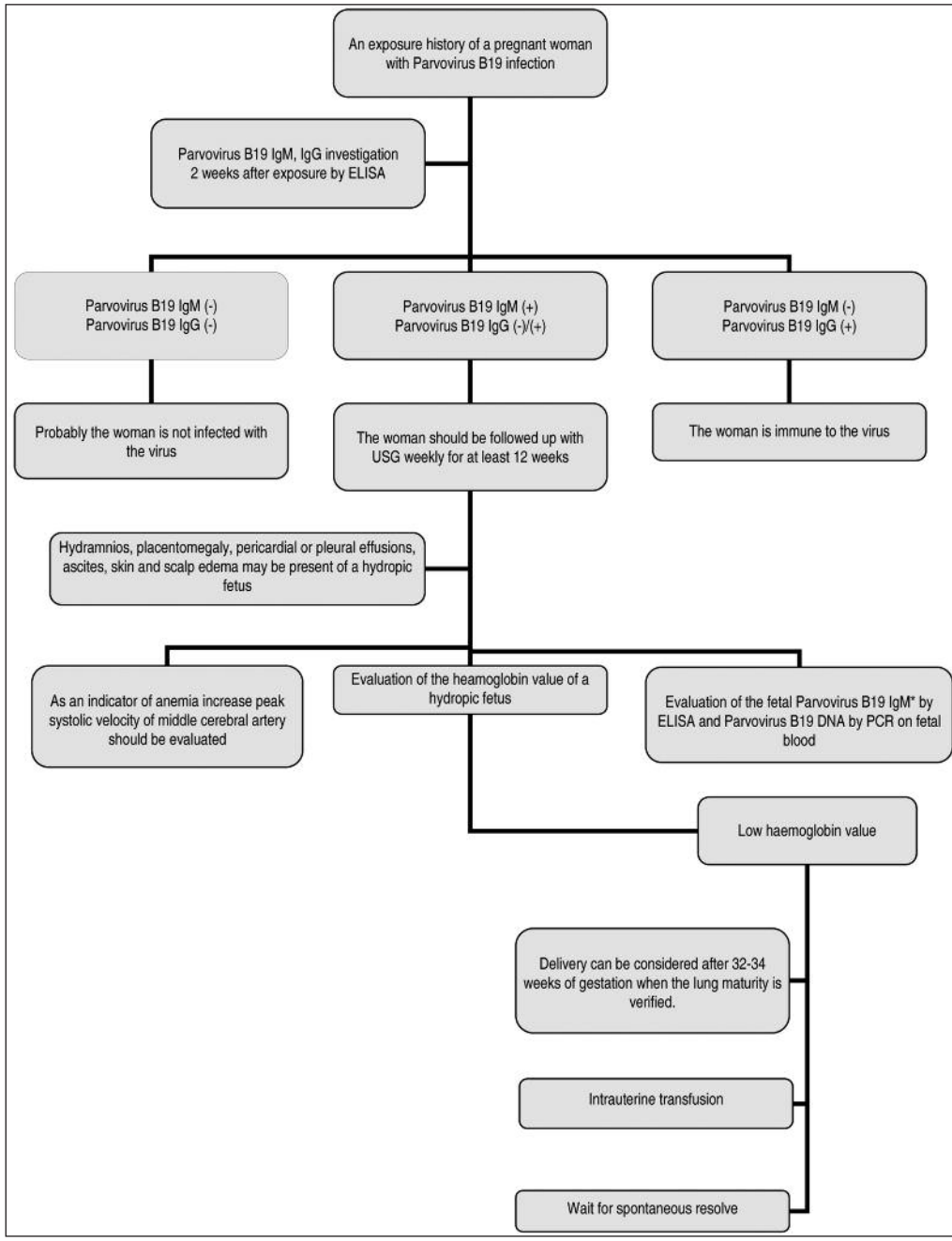

FIGURE 1: Algorithm for Parvovirus B19 infection in pregnant women with an exposure history.
*Fetal Parvovirus B19 IgM can be detected after 22 weeks of gestation.

drops reduces the risk of fetal death.[3] If severe intrauterine hydrops or anemia is diagnosed at weeks of gestation more than 28, delivery and extrauterine treatment is recommended in some literatures.[2,36]

Although parvovirus B19 infections are most commonly seen in children of school age, it can be found in all age groups. We know that it can affect the fetus when a pregnant woman has an acute parvovirus B19 infection. In the follow-up of a pregnant woman with a history of exposure to parvovirus B19, hydrops and anemia of the fetus should be evaluated. This virus should be considered in a pregnant woman when hydrops is detected in routine USG, although the woman does not give a history of exposure to the virus or a history of acute infection.

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