

# PRENATAL DIAGNOSIS AND PERINATAL MANAGEMENT OF MATERNAL-FETAL CONGENITAL PARVOVIRUS B19 INFECTION

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## SUMMARY

**Objective:** In nonimmune pregnant woman, the primary infection with parvovirus B19 may lead to transplacental transmission to the fetus with variable outcomes, including congenital anemia, hydrops fetalis, fetal death or spontaneous resolution.

**Case Report:** In the first case, a 28-year-old woman, gravida 2, para 1, whose fetus was found to have left-sided pleural effusion on a sonogram at 29 weeks of gestation. A sample of aspirated pleural fluid was positive for parvovirus B19 by polymerase chain reaction. Cordocentesis showed fetal hemoglobin level of 5.0 g/dL. Intra-peritoneal transfusion (IPT) was performed, because access to the fetal circulation was difficult. Thirty milliliters of group O, Rh-positive packed red cells were transfused into the peritoneal cavity. A non-hydrotic baby weighing 2,680 g was delivered at 33 weeks of gestation. The neonate's complete blood count examination showed a hemoglobin level of 16.3 g/dL. The newborn baby was discharged in stable condition. In the second case, a 31-year-old woman, gravida 2, para 1, whose fetus was found to have ascites, hypertrophic cardiomyopathy, and placentomegaly on a sonogram at 23 weeks of gestation. An amniotic fluid sample was positive for parvovirus B19 DNA by polymerase chain reaction. Fetal ascites and hypertrophic cardiomyopathy gradually resolved after maternal iron supplementation and 2 weeks of intrauterine digitalization therapy. A healthy infant weighing 3,198 g was delivered at 37 weeks of gestation. The neonate's complete blood count examination showed a hemoglobin level of 10.3 g/dL.

**Conclusion:** Termination of pregnancy is rarely indicated, because B19 virus is not teratogenic. Although intravascular transfusion offers obvious theoretical advantages, in some cases in which access to the fetal circulation is difficult or impossible, IPT should be performed combined with appropriate medical treatment. Thus, there is still a place for IPT in modern management of the severely anemic fetus, and this technique should not be neglected. [*Taiwan J Obstet Gynecol* 2007;46(4):417-422]

**Key Words:** hydrops fetalis, intraperitoneal transfusion, parvovirus B19

## Introduction

Fetal parvovirus B19 infection is a congenital disorder that is characterized by nonimmune hydrops, ascites, pleural effusion, hypertrophic cardiomyopathy,

placentomegaly, ventriculomegaly, and other findings caused by transplacental transmission of parvovirus to the fetus [1,2]. Congenital infection rates vary depending on the prevalence in the community. Approximately 50% to 75% of adult women are immune. Maternal infection with parvovirus B19 is estimated to occur in 0.25-6% of susceptible pregnancies [1]. Transplacental transmission can occur any time during pregnancy. The risk for congenital infection from an infected mother to her unborn baby is between 10% to 35% and is highest in the first and second trimesters [1,3].

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The average time from diagnosis to resolution is about 6 weeks [1].

We describe two cases of congenital fetal parvovirus infection that were timely diagnosed by sonography and viral DNA polymerase chain reaction (PCR) examination and managed successfully with intraperitoneal transfusion (IPT) and medical treatment.

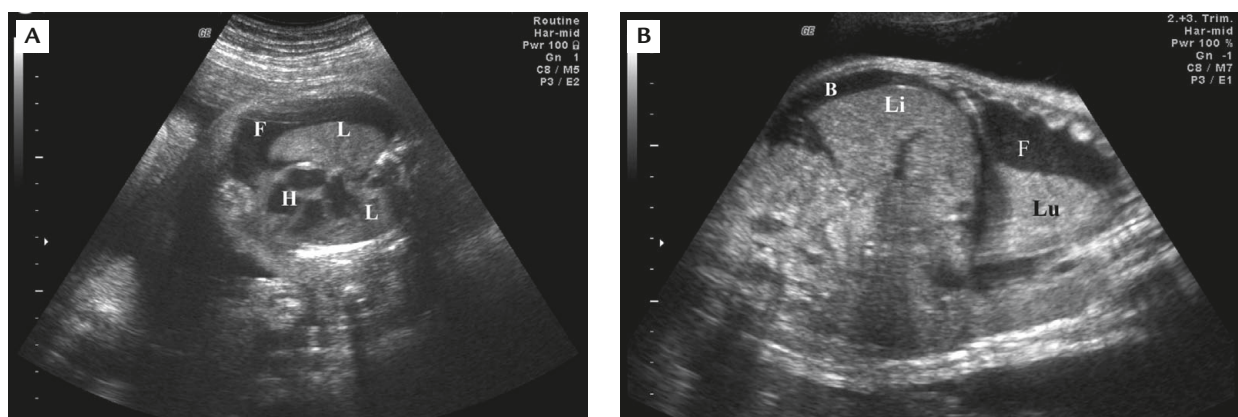
## Case Report

### Case 1

A 28-year-old woman, gravida 2, para 1, was referred to our hospital at 29 weeks of gestation because of fetal pleural effusion. Pertinent medical history and obstetric history included an alpha-thalassemia trait and recent flu-like symptoms transmitted from her 4-year-old febrile child. A Doppler ultrasonographic examination (Voluson 730 Expert; GE Medical Systems, Austria) showed a massive left-sided pleural effusion (Figure 1A), hydrocele, polyhydramnios (amniotic fluid index, 38 cm), and bulky placenta (5.54 cm). Venous Doppler waveform analysis revealed a high time-averaged velocity of 30 cm/s without ominous sign of absence or reversal of atrial systolic blood flow velocity in the ductus venosus. Thoracocentesis was performed, and 50 mL of blood-tinged pleural fluid was aspirated from the left pleural cavity. Pleural fluid examination showed red blood cells (RBCs) of 70,000/mm<sup>3</sup>, white blood cells (WBCs) of 24,300/mm<sup>3</sup> (lymphocyte/neutrophil ratio, 99:1), and Pandy's test of 4+. A sample of aspirated pleural fluid was positive for parvovirus B19 by PCR. The karyotype was 46,XY. Percutaneous umbilical blood sampling showed hemoglobin level of

5.0 g/dL. Maternal hemoglobin level was 6.9 g/dL (hematocrit, 23.7%). IPT was performed at 31 weeks of gestation, because access to the fetal circulation was difficult. The patient was sedated with an intravenous narcotic (pethidine) and a tranquilizer. After aseptic preparation, a 20-gauge percutaneous transhepatic cholangiography (PTC) needle (Hakko, Japan) was inserted into the fetal abdominal cavity under direct ultrasound guidance. Proper needle placement was verified by injecting a small amount of saline solution and observing fluid layering in the peritoneal cavity. Thirty milliliters of group O, Rh-positive packed RBCs were injected directly through the PTC needle in aliquots of 10 mL at an average of 5–10 mL per minute, taking 2 to 5 minutes for each aliquot (Figure 1B). Transient bradycardia was observed after 15 mL of RBCs were transfused, and the IPT was discontinued for 2 minutes before giving the full amount of blood calculated as necessary after the fetal heart rate returned to normal baseline level. The amount of pleural effusion was increased after IPT procedure. A repeat thoracocentesis was performed to decrease lung compression, and 70 mL of darkish pleural fluid was aspirated (RBCs, 290,000/mm<sup>3</sup>; WBCs, 15,800/mm<sup>3</sup>).

The patient received 1 week's intrauterine digitalization therapy with digoxin 0.25 mg 12 hourly (maternal digoxin, 1.51 ng/mL) for impending fetal heart failure signs. Preterm labor occurred at 33 weeks of gestation, and she spontaneously delivered a non-hydropsic male baby weighing 2,680 g with Apgar scores of 1 and 6 at 1 and 5 minutes, respectively. The neonate's complete blood count examination showed a hemoglobin level of 16.3 g/dL. The newborn baby was sent to the



**Figure 1.** (A) Hydrothorax associated with fetal parvovirus infection. Axial scan of the thorax at 29 weeks shows a large left pleural fluid collection which shifts the heart to the right. F=pleural fluid; H=heart; L=lung. (B) Sonographic image depicts intraperitoneal transfusion. Thirty milliliters group O, Rh-positive packed red cells were injected into the free peritoneal cavity, as shown by ultrasound outlining the hypoechoic shadow surrounding the liver and small bowel. B=red cells; F=pleural fluid; Li=liver; Lu=lung.

neonatal intensive care unit for further care. Thoracic tube was inserted for drainage of pleural fluid. The newborn baby was hospitalized for 2 weeks and was discharged in stable condition.

### Case 2

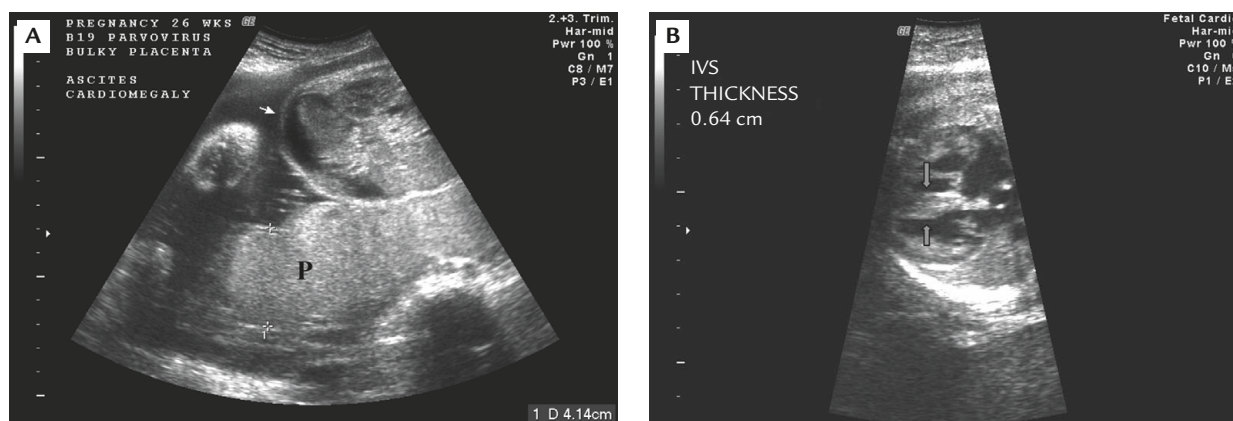
A 31-year-old woman, gravida 2, para 1, was referred to our hospital, because her fetus was found to have ascites, hypertrophic cardiomyopathy, and placentomegaly on a sonogram at 23 weeks of gestation. Pertinent medical history and obstetric history included recent flu-like symptoms transmitted from her 16-month-old febrile child. A Doppler ultrasonographic examination showed a small amount of ascites, hypertrophic cardiomyopathy with interventricular septum thickness measuring 6.4 mm, and bulky placenta (Figure 2). Intrahepatic portion of the umbilical vein was markedly dilated. The umbilical artery Doppler systolic/diastolic ratio measurement was 3.0 without pulsatile flow in the umbilical vein. An amniotic fluid sample was positive for parvovirus B19 DNA by PCR. The chromosome karyotype was a normal 46,XX. Intrauterine transfusion (IUT) was arranged but was halted, because the ascites and hypertrophic cardiomyopathy gradually resolved after maternal iron, folic acid and vitamin B complex supplementation therapy and 2 weeks of intrauterine digitalization therapy with digoxin 0.25 mg 12 hourly (maternal digoxin, 1.22 ng/mL).

A healthy female infant weighing 3,198 g was delivered vaginally at 37 weeks of gestation. The neonate's complete blood count examination showed a hemoglobin level of 10.3 g/dL (hematocrit, 31.2%) and platelet count of 383,000/ $\mu$ L. Neonatal echocardiography showed unremarkable finding except for the patent foramen ovale and patent ductus arteriosus. The newborn baby was hospitalized for 3 days and discharged in stable condition.

### Discussion

Erythema infectiosum (infectious redness) is also known as “slapped-cheek” disease or “fifth disease”. The name fifth disease stems from that when diseases causing childhood exanthemata (rashes) were enumerated, it was fifth on the list. Erythema infectiosum is caused by a virus called parvovirus B19. The virus is horizontally transmitted from one person to another via airborne droplets from the nose and throat, for example when coughing or sneezing. Parvovirus B19 infection is common in school-aged children and younger children who attend day-care facilities. Seropositivity rates are 5–10% among young children (aged 2–5 years), increasing to 50% by age 15 years and 60% by age 30 years. These results suggest that parvovirus B19 infection is an occupational risk for female teachers and day-care providers who have contact with greater numbers of ill children [4].

The parvovirus may be small, but they are mighty. The virus has a tropism for rapidly dividing erythrocyte precursors, particularly pronormoblasts and normoblasts, wherein they replicate to high titers, destroying infected cells [1,2]. Thus, no reticulocytes are available to replace abnormal short half-life aging or damaged erythrocytes, as they are cleared by the reticulo-endothelial system. The fetus may be especially vulnerable to anemia due to parvovirus B19 infection because of the short-lived RBCs and a possible ineffective immune response that can lead to chronic infection. Rare reports in the literature state that parvovirus B19 may infect other cell types, causing encephalitis and myocarditis [1,2,5]. Additionally, Nagel et al [6] reported abnormal neurodevelopmental status in five of 16 survivors that was not related to the severity of fetal anemia and acidemia. They hypothesized that fetal parvovirus B19 infection may induce central nervous



**Figure 2.** (A) Axial scan of the abdomen at 23 weeks shows a small amount of ascites (arrow) and mildly thickened placenta (P). (B) Four-chamber view shows thickened interventricular septum 0.64 cm (arrows) and hypertrophic ventricular wall.

system damage. Long-term postnatal investigation is warranted, especially in the presence of clinical symptoms or developmental delay.

Occasionally, the virus infects leukocytes (especially neutrophils) and megakaryocytes [2]. Although parvovirus B19 infection may manifest with pancytopenia, it is not believed to contribute significantly to true aplastic anemia. However, in patients with hemoglobinopathies or hemolytic anemias, in whom the duration of erythrocyte survival is decreased, a decrease in the reticulocyte count to less than 1% may precipitate an aplastic crisis. Parvovirus B19 is the only known infectious cause of aplastic crisis [2].

During the first trimester, fetuses with parvovirus B19 infection can present with increased nuchal translucency. In the second and third trimesters, fetal infection by parvovirus B19 can be suspected using ultrasound, with the presence of fetal hydrops, ascites, pleural or pericardial effusion, skin thickening, hypertrophic cardiomyopathy, hepatosplenomegaly, hydrocephalus, microcephaly, intracranial calcifications, placentomegaly, and amniotic fluid volume disorders [1]. Fetal anemia is associated with a hyperdynamic circulation; therefore, it can be predicted with Doppler measurement of the middle cerebral artery peak systolic velocity in pregnancies complicated by parvovirus B19 infection by increased values of velocities prior to the appearance of sonographic signs of hydrops [7]. Furthermore, cordocentesis allows precise assessment of fetal anemia, which can then be corrected by IUT. Absence or reversal of atrial systolic blood flow velocity in the ductus venosus and pulsatile flow in the umbilical vein offers the best prediction of perinatal critical outcomes due to end-stage heart failure and regurgitation secondary to tricuspid insufficiency. The outcome proved favorable in the majority of fetuses, even in those that were severely anemic. The overall rate of parvovirus B19-related fetal death has been estimated as between 4% and 17%, with a peak frequency before 20 weeks of gestation [1,3].

Specific diagnosis can be made by the following methods [2]. If a pregnant woman is exposed to parvovirus B19, obtain a serologic examination to test for maternal parvovirus B19-specific IgG and IgM as soon as possible. Positive IgG and IgM results indicate infection within the last 7–120 days (possible risk to fetus). Negative IgG and positive IgM results indicate acute infection (higher risk to fetus). Cordocentesis can be performed to test for fetal blood parvovirus B19-specific IgM. PCR is a more useful clinical tool to diagnose for infection and detects if any of the viral DNA is present in the blood, amniotic fluid and other body fluids on both fresh and paraffin-embedded

tissues. A positive result is indicative of viremia/infection. Electron microscopy can also identify parvovirus B19 virus in tissues.

Because the major fetal manifestation of parvovirus infection is anemia, IUT should be considered if a cordocentesis shows a fetal blood sample hemoglobin level of < 10 g/dL. In 1963, Liley successfully performed the first IPT on a severely sensitized erythroblastotic infant *in utero*, and in doing so, created new horizon in obstetric care [8]. For more than 20 years, the traditional method for performing transfusion *in utero* has utilized the IPT approach under direct ultrasound guidance [8–11]. Proper needle placed freely in the fetal peritoneal cavity should be verified by aspirating ascitic fluid in the hydropic fetus or by injecting a small amount of saline solution and observing the layering of fluid space in the peritoneal cavity in the non-hydropic fetus. Otherwise, injection into retroperitoneal tissue, abdominal viscera, soft tissues and so on, would be disastrous. Washed and irradiated group O, Rh-positive packed cells, which have been cross-matched against the mother's blood, are injected directly through the needle in aliquots of 10 mL at an average of 5–10 mL per minute, taking 2 to 5 minutes for each aliquot. The fetal heart rate should be monitored throughout the procedure. The fetus usually tolerates these infusion rates without difficulty. However, if persistent bradycardia or fetal cardiac irregularity is observed, IPT should be discontinued before giving the full amount of blood calculated as necessary. A second transfusion is given 10 to 12 days after the first transfusion, and subsequent transfusions are administered at intervals of 3 to 4 weeks until the fetus has reached 33 weeks of gestation or greater [8,10]. While IPT is of minimal hazard to the mother, it may pose a potential hazard to the fetus. In the Winnipeg ultrasound era, a traumatic-death-per-procedure rate of 3.7% was reported in severely erythroblastotic fetuses [10]. However, Watts et al [11] reported that no immediate transfusion-related death occurred for the 77 IPTs in 35 pregnancies.

The amount of transfused blood necessary to correct for fetal anemia was determined by the formula proposed by Rodeck et al [12]:  $V(Hct_3 - Hct_1)/Hct_2$ , where V = estimated fetoplacental volume,  $Hct_1$  = the pretransfusion hematocrit,  $Hct_2$  = the Hct of the transfused blood, and  $Hct_3$  = the desired Hct. Another transfusion volume formula is: gestation in weeks minus  $20 \times 10$  mL [8,9,11]. However, in case 1, we limited the volume to the smallest possible volume of 20–25 mL/kg of the estimated fetal body weight according to gestational age to minimize the stress to the fetal cardiovascular system, which could be aggravated by parvovirus B19 infective myocarditis [13]. The more severe the



hydrops, the lesser IUT will be well tolerated. Fetal transfusions are rarely carried out later than 33 to 34 weeks of gestation, as delivery during that gestation period carries a 95% chance of infant survival. The decision to manage case 2 conservatively was based on evidence of spontaneous resolution of ascites and hypertrophic cardiomyopathy after an appropriate medical therapy, when compared with the initial sonographic findings at the source of referral.

Erythrocytes injected into the fetal peritoneal cavity are absorbed intact via the subdiaphragmatic lymphatics, which drain into the right lymphatic duct and hence into the systemic circulation [8,10]. Absorption of red cells in the fetus without ascites takes 8 to 12 days. If hydrops is present, the absorption may be erratic. In some cases, it is excellent, while in others, it is poor; particularly in the moribund fetus with no breathing movement, the absorption is negligible. The reversal of hydrops may occur if absorption of red cells is adequate. First, the hemoglobin level rises to correct anemia. Second, erythropoietin production drops and hepatic erythropoiesis diminishes. This in turn causes a fall in portal and umbilical venous pressures and improves hepatic circulation and hepatocyte function with the resultant increase in albumin levels [8].

Since absorption of red cells from the peritoneum is erratic in the presence of ascites, fetal ascites should be aspirated before IPT is performed. Although the intravascular approach offers obvious theoretical advantages for these hydropic fetuses, for cases in which access to the fetal circulation is difficult or impossible because of technical reasons, IPT should be performed. Thus, there is still a place for IPT in modern management of the severely anemic fetus, and this technique should not be neglected.

There seem to be two different mechanisms involved in the pathophysiology of nonimmune hydrops fetalis: anemia and heart failure [14]. The low hemoglobin level was not significantly related to the outcome [6,14]. A simple fetal hematologic evaluation is unable to provide new insights on parameters that may be of prognostic value. Therefore, the role of IUT in the management of *in utero* parvovirus B19 infection may be different from that of immune hydrops. It is possible that parvovirus B19-induced myocarditis could be an associated deleterious event, leading even to heart failure and death. There is even a report of terminal cardiac heart failure in a third-trimester fetus, which had a successful transplant postnatally [5]. Therefore, Forestier et al [14] suggested that IUT should be considered only in fetuses with severe anemia (Hct < 15%), because the condition can be a cause of fetal death. Use of intrauterine digitalization therapy to treat fetal

hypertrophic cardiomyopathy has been attempted as a palliative treatment in our case with good effect [15,16]. Intravenous immunoglobulins therapy have been successfully used in postnatal patients. It has been shown to be effective in resolution of viremia and improvement in red cell indices [2]. Spontaneous resolution of fetal hydrops without intervention has also been documented [13]. In view of these therapeutic options, termination of pregnancy is rarely indicated, because parvovirus B19 is not teratogenic.

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