Discordant Outcomes in a Case of Parvovirus B19 Transmission Into Both Dichorionic Twins

Monika Schiesser,[1,2] Consolato Sergi,[3] Martin Enders,[4] Holger Maul,[2] and Paul Schnitzler[5]

[1] *Klinikum Traunstein, Germany*
[2] *Department of Obstetrics and Gynaecology, University Women's Hospital, University of Heidelberg, Germany*
[3] *Institute of Pathology, Medical University of Innsbruck, Austria*
[4] *Labor Prof. Enders und Partner, Institut für Virologie, Infektiologie und Epidemiologie e.V., Stuttgart, Germany*
[5] *Dept. of Virology, University of Heidelberg, Germany*

Maternal infection with parvovirus B19 during pregnancy can cause aplastic anemia in the fetus and may lead to nonimmune fetal hydrops and fetal demise. Twin pregnancies complicated by infection due to parvovirus B19 are very rare clinical events. We present a dichorionic, diamniotic, dizygotic twin pregnancy after in vitro fertilization with parvovirus B19 infection and viral transmission to both twins, but different outcomes. At 19 weeks gestation, hydrops fetalis was diagnosed for male twin A, female twin B did not show any abnormalities. At 22 weeks gestation an acute parvovirus B19 infection was detected and twin A was diagnosed with intrauterine fetal death (IUFD) by ultrasound at 23 weeks gestation. Viral DNA was detected in maternal blood as well as in placenta and liver tissue of this twin. Twin B was born at 35 weeks gestation asymptomatically and no signs of hydrops or other congenital anomalies but viral DNA was detected by PCR in serum. At the age of 2 years, both IgG titres against B19 and parvovirus DNA amplification copies were still positive in plasma of the surviving twin, but no clinical signs were detectable. It is remarkable that both twins were infected with parvovirus B19 early in pregnancy but showed a discordant clinical outcome. Our case report describes the rare occurrence of an intrauterine fetal death (IUFD) of one twin and the asymptomatic infection of the other in a twin pregnancy.

Keywords: parvovirus B19, pregnancy, hydrops fetalis, twin, intrauterine fetal death (IUFD)

Parvovirus B19 is a small single-stranded DNA virus that causes a common exanthematous disease in childhood, erythema infectiosum. Transient aplastic crisis, arthropathy in adults and persistent anemia has also been associated to parvovirus B19 infection (Young and Brown, 2004). The overall seroprevalence of B19 in serum from adult individuals in Germany is about 70% (Enders et al., 2007; Röhrer et al., 2008). Acute infection with parvovirus B19 during pregnancy can cause several serious complications in the fetus, such as anemia, hydrops, neurological complications, and fetal death (Anand et al., 1987; de Jong et al., 2006; Yaegashi et al., 1998). Parvovirus B19 infection associated with nonimmunologic hydrops fetalis (NIHF) was described for the first time in 1984 (Brown et al., 1984).

Early diagnosis and treatment of intrauterine parvovirus B19 infection is essential for preventing fetal complications. Testing maternal serum for IgM antibodies against parvovirus B19 and DNA detection by PCR can confirm maternal infection (Enders et al., 2006; Knöll et al., 2002; Török et al., 1992). Ultrasound investigation of the fetus is consequently applied for diagnosis of fetal hydrops. The highest rate of fetal hydrops is seen if maternal infection occurs in the first 20 weeks of gestation (Enders et al., 2004). Intrauterine transfusion might be effective for treatment of fetal anemia, the proportion of fetuses with severe hydrops that survive following fetal transfusion is about 85% (Enders et al., 2004).

Previous reports of twin pregnancies affected by parvovirus B19 have established a high mortality and morbidity in survivors (Graesslin et al., 2005). Although differential infection has been occasionally reported in dichorionic twins (Pustilnik and Cohen, 1994), in most cases both fetuses are affected. Nonimmune hydrops fetalis, myocarditis, polyhydramnios in the mother, and premature delivery have been described for twin pregnancies. In this report, we present a case of discordant outcome of parvovirus B19 in a twin pregnancy. This case report describes the occurrence of an in utero fetal death (IUFD) in one

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Address for correspondence: Paul Schnitzler, Department of Virology, University of Heidelberg, Im Neuenheimer Feld 324, 69120 Heidelberg, Germany. E-mail: Paul_Schnitzler@med.uni-heidelberg.de

Table 1

Diagnostic Procedures and Time Course of Parvovirus Infection in Mother and Twins

	Mother	Twin A	Twin B
19 weeks gestation	Increased alpha-fetoprotein	Hydrops fetalis	Asymptomatic
22 weeks gestation	Acute parvovirus infection B19 IgG positive B19 IgM positive serum B19 DNA positive		
23 weeks gestation		In utero fetal death (IUFD)	
35 weeks gestation	Delivery placenta B19 DNA positive	Amniotic fluid B19 DNA positive liver B19 DNA positive	B19 IgG positive B19 IgM negative, serum B19 DNA positive, asymptomatic
6 months			B19 IgG positive B19 IgM negative serum B19 DNA negative, asymptomatic
24 months			Antiparvovirus B19 IgG positive, IgM negative, B19 DNA positive, asymptomatic

twin associated with an asymptomatic B19 infection of the other twin. For the first time, a follow-up of the surviving twin up to the age of two years is presented.

Case Report

A 36-year-old Caucasian woman (G1, P0) at 22 weeks gestation was referred to the Department of Obstetrics and Gynaecology of the University of Heidelberg with the diagnosis of suspected parvovirus B19 infection during a diamniotic, dichorionic pregnancy. The pregnancy was uneventful until the 19th week of gestation, when a sonography performed in a gynaecological practice revealed signs of hydrops fetalis with abdominal ascites, pericardial effusion and integumentary thickening of Twin A, but normal appearance of Twin B. Increased values of the alpha-fetoprotein in maternal serum were found. However, she was not referred to our hospital until 22 weeks of gestation. Maternal rubella, cytomegalovirus, and herpes virus immunoglobulin (IgG) titres were positive, all suggestive of past exposure and no antibodies against *Toxoplasma gondii* were detectable. Maternal serum was found to be positive for parvovirus B19 IgG, IgM and B19 DNA (Table 1). To detect parvovirus B19 DNA, a highly sensitive nested PCR was employed. Two successive sets of amplification were performed and primers corresponding to the parvovirus B19 NS1 gene were applied (Clewley, 1993). No termination of the pregnancy was decided, but the twins were followed up to term of the pregnancy.

One day after admission to our hospital, Twin A was diagnosed with IUFD at 23 weeks gestation and intrauterine transfusion with erythrocytes was no more possible. However, no signs of hydrops ever developed in Twin B. At term with vaginal delivery female Twin B showed normal appearance, while opening of the amniotic cavity of male Twin A showed the appearance of a fetus papyraceus. Amniotic fluid from Twin A was tested also positive for parvovirus B19 DNA by PCR. Postmortem examination of Twin A was performed after delivery and revealed autolysis of fetal tissues and extensive necrosis of one part of the placenta. No congenital abnormalities were found and karyotypes were normal in both twins. Erythrocytes of the placental villous stroma and of the liver, as well as ghost liver cells showed enlarged nuclei with characteristic eosinophilic inclusion bodies. Liver iron content of a fresh sample was analysed by atomic absorption spectroscopy and was notably increased probably related to the destruction of the progenitor blood cells present in the liver. DNA sequences of the parvovirus B19 were detectable in the liver and in the placenta of Twin A as well as in maternal blood (Figure 1). Serum from the living newborn (Twin B) was found negative for parvovirus B19 IgM but positive for B19 DNA. The neonatal course of the surviving twin was uneventful, haemoglobin was in normal range and echocardiography did not reveal any abnormalities. The growth and development were normal and at the age of 6 months the infant showed normal psychomotoric development with successful fulfilment of the perinatal growth milestones. At this age, parvovirus B19 was not detected in the infant's serum. However at the age of 2 years, the child was tested positive for anti-parvovirus B19 IgG and B19 DNA suggesting an acute or persisting infection. To date, the living child is well and has not developed any cardiac dysfunction.

Discussion

During the second trimester of pregnancy, the fetus is particularly susceptible to B19 infection, at this stage erythroid progenitor cells derived from fetal liver are preferred targets of parvovirus B19. The characteristic feature of this infection is the presence of eosinophilic intranuclear inclusion bodies in circulating normoblasts and their precursors in fetal organs (Anand et

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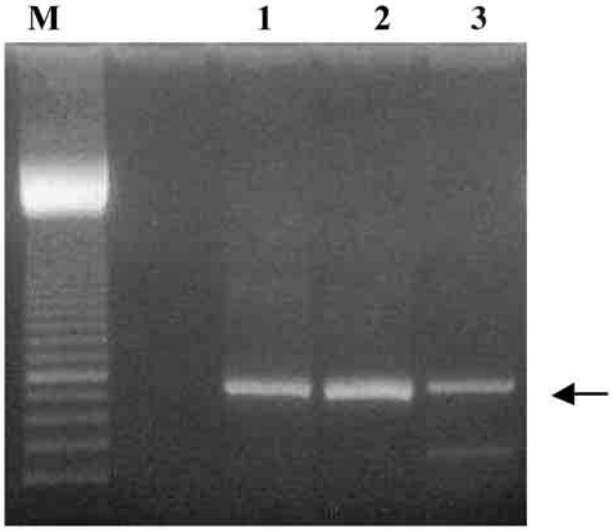

Figure 1

Detection of parvovirus B19 DNA by PCR.

Note: M = molecular weight marker, lane 1 = liver, lane 2 = placenta, lane 3 = maternal blood. Arrow indicates positive bands.

al., 1987). The histologic diagnosis is also feasible in macerated fetuses as shown in our case emphasizing the importance of post-mortem investigation of a fetus papyraceus. One week after maternal infection, peak viral load levels occur and peak IgM levels are observed after another week (Enders et al., 2007; de Haan et al., 2007). Vertical transmission occurs 1 to 3 weeks after maternal infection, suggesting that fetal infection occurs during the maternal peak viral load. B19-derived fetal hydrops occurs in 95% of cases within 12 weeks of maternal infection (Enders et al., 2004; Miller et al., 1998). At the time of B19-induced hydrops, detection of B19 DNA in maternal blood shows the best diagnostic sensitivity for identifying maternal B19 infection, as reported recently (Enders et al., 2008).

Twin pregnancies complicated by infection due to parvovirus B19 are very rare clinical events. Maternal infection with parvovirus B19 during pregnancy can cause aplastic anemia in the fetus and may lead to nonimmune fetal hydrops and fetal demise. In our case report, the pregnancy was uneventful up to 19 weeks' gestation, when hydrops fetalis was diagnosed for Twin A by ultrasound sonography and IUFD was observed in week 23. At this time point, the mother was tested positive for anti-parvovirus B19 IgG, IgM and B19 DNA. At delivery, B19 DNA was detected in amniotic fluid, liver and placenta. At birth, parvovirus B19 infection was detected in twin B, but this child remained asymptomatic. Very few cases of parvoviral infections in twin pregnancies have been reported previously. Pustilnik and Cohen (1994) described a dichorionic, diamniotic twin pregnancy with differential infection and immunological diagnosis in a 35-year-old white woman at 20 weeks gestation with IUFD of the affected twin. Zerbini et al. (1993) reported a twin pregnancy in which only one fetus developed a symptomatic infection with ascites and pleural effusion that spontaneously resolved. A case of differential fetal infection in a dichorionic twin pregnancy culminating in a dual live-birth has been reported recently (Dickinson et al., 2006). B19 IgM and B19 DNA were detected in the infected twin, but not in the other twin. Weiner and Naides (1992) described symptomatic survivors of congenital twin parvovirus infection, where both infants were affected. The diagnosis was performed by identification of virus particles using immunogold labeling electron microscopy, but maternal serum, fetal ascites, and cord sera were always negative for anti-B19 IgM and IgG antibodies. Infection with B19 of both twins had been reported for three other cases (Graesslin et al., 2005; Wolff et al., 1999; von Kaisenberg et al., 2007), in two of these cases a fatal outcome was described for one of the twins. Since failure to mount an appropriate antibody response to viral infection, the antenatal diagnosis of parvovirus B19 requires a multifaceted approach, including serology and detection of viral DNA by PCR. Although all these tests are usually sufficient for diagnosis of parvovirus B19, in some situations the PCR can be useful and is more sensitive than direct DNA hybridization (Török, 1992). A similar case to our case report with IUFD of one of the twins and asymptomatic presentation of the other twin was reported by Foster and Allen (2004). However, PCR of samples from the surviving twin was not performed, thus viral infection cannot be sufficiently ruled out. Differential viral infection is not a prerogative of parvovirus B19. Wang et al. (1990) described monozygotic twins born to a mother with rubella infection during pregnancy. One twin showed a positive rubella IgM titer at birth in conjunction with a persistent IgG titer, the other twin had a negative IgM titer but a positive IgG titer. PCR for rubella RNA was not performed in the IgM negative infant and viral infection is not ruled out with certainty. Our case showed differential clinical outcome after parvovirus B19 infection in a dichorionic, diamniotic twin pregnancy. In this case, both immunological and PCR tests indicated the infection of both twins.

The consequences of the IUFD also depend on the chorionicity, with an increased risk of premature birth in cases of dichorial pregnancy and with an increased risk level of ischemic visceral lesions in cases of monochorial pregnancy. Probably, the type of the placenta and the zygosity of the pregnancy also marked regressive alterations with dystrophic calcifications and might influence the differential clinical outcome in twin pregnancies. Another factor to keep in mind is the presence of specific vessel communications with differential placental blood flow. This factor plays a major role in the twin–twin transfusion syndrome where according to the damage pletora phenomena, acardia or feti papyracei can occur. Transmission of

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viral particles between twin fetuses may also depend on other factors, including host factors and genetic differences. In our case report one twin reacted with anemia and death while the other twin showed no clinical symptoms. Discordant outcomes in viral transmission into both dichorionic twins has been related to the viral load level at the time of viremia (Pustilnik and Cohen, 1994). The possibility of viral transfer from one fetus to another should also be considered. The major target cells for B19 are erythroid progenitors bearing the main cellular B19 receptor P blood group antigen globoside on their surface; B19 is cytotoxic for these cells. Furthermore B19 has been demonstrated to carry an apoptosis inducing factor and the ability to induce cell cycle arrest. The shortened life span of red blood cells during the hepatic stage of fetal hematopoiesis renders the fetus at this gestational age especially susceptible to severe anemia and hydrops fetalis. Finally, there is a chance of the infected fetus to survive without therapy.

In this report, we described a case of differential clinical outcome of parvovirus B19 infection in a twin pregnancy with both immunological and PCR findings indicative for viral infection in both twins. The surviving twin was followed-up for two years, but no clinical signs of the congenitally B19 infected child were detectable and no dysfunctions developed.

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