

# Discordant Fetal Infection for Parvovirus B19 in a Dichorionic Twin Pregnancy

Jan E. Dickinson,<sup>1</sup> Anthony D. Keil,<sup>2</sup> and Adrian K. Charles<sup>1,3</sup>

<sup>1</sup> School of Women's and Infants' Health, The University of Western Australia, Perth, Western Australia, Australia

<sup>2</sup> Department of Microbiology, King Edward Memorial Hospital for Women, Perth, Western Australia, Australia

<sup>3</sup> Department of Pathology, King Edward Memorial Hospital for Women, Perth, Western Australia, Australia

There are only a few reports of fetal parvovirus infection in the circumstance of a twin pregnancy. We report a case of differential fetal infection following maternal parvovirus B19 infection in a dichorionic twin pregnancy culminating in a dual live-birth. A 32-year-old woman was diagnosed with parvovirus infection following exposure to her infected child at 19 weeks' gestation in a dichorionic twin gestation. Maternal IgG seroconversion was documented and maternal blood parvovirus B19 DNA was detected by PCR testing. Fetal monitoring with serial ultrasound assessment was instituted. At 25 weeks' gestation Twin I (male) displayed minor ascites, small pericardial effusion, placentomegaly and oligohydramnios. Middle cerebral artery peak systolic velocity (MCA PSV) studies were abnormal. Twin II (female) was sonographically unremarkable. A single fetal intravascular transfusion for Twin I was performed (pretransfusion Hb 80 g/L). Twin I fetal blood parvovirus B19 DNA was detected by polymerase chain reaction (PCR) and serum demonstrated both B19 IgG and IgM. Following fetal transfusion the hydrops resolved, although the placentomegaly persisted. Two live infants were delivered at 37 weeks' gestation. Individual neonatal venepuncture detected B19 DNA by PCR in Twin I but not in Twin II. B19 IgM was present in Twin I but not Twin II. Both neonates had B19 IgG antibodies. Placental histopathology demonstrated mild edema for Twin I but no inclusion cells. The placenta of Twin II was unremarkable. This case demonstrates the ability for differential transplacental infection of this virus and the assistance of fetal MCA flow studies to guide therapy in a multiple pregnancy at risk of parvovirus infection.

Parvovirus B19 has been recognized as a pathogenic fetal virus for the past two decades (Brown et al., 1984). While the majority of maternal infections with this single-stranded DNA virus result in a live term fetus, maternal parvovirus infection prior to 20 weeks' gestation is associated with a fetal loss rate of approximately 10% (Miller et al., 1998). Parvovirus B19 has been associated with fetal hydrops, believed secondary to viral-mediated fetal red cell destruction, viral myocarditis or impaired liver function. The transplacental transmission rate of parvovirus B19 has been

estimated to be 33% (Public Health Laboratory Service Working Party on Fifth Disease, 1990), although the mechanisms of placental virus transfer are not well understood.

Differential parvovirus B19 infection in a multiple pregnancy has been rarely reported. In two case reports the infected fetus died prior to delivery (Foster & Allen, 2004; Pustilnik & Cohen, 1994). In a third case it was unclear as to the parvovirus B19 status of the nonhydropic fetus (Zerbini et al., 1993). We report a case of differential fetal parvovirus B19 infection of a twin pregnancy in which both fetuses survived and discuss the management strategies employed to optimize this outcome.

## Case Report

A 32-year-old woman with a known dichorionic twin pregnancy was referred to our institution at 21 weeks' gestation following parvovirus exposure and subsequent IgG seroconversion some 2 weeks prior. Maternal serum parvovirus B19 DNA was detected by polymerase chain reaction (PCR) testing, using an in-house real-time TaqMan assay with primers and probe directed to a target region within the parvovirus VP1 gene.

Serial ultrasound imaging was instituted and at 25 weeks' gestation, approximately 6 weeks postmaternal infection, Twin I was noted to have a pericardial effusion, small volume ascites and an elevated middle cerebral artery peak systolic velocity (MCA PSV) of 54 cm/second. Twin II was unremarkable to sonography and displayed a normal MCA flow velocity waveform pattern (MCA PSV = 27 cm/second). There was a fused placenta on the posterior uterine wall and a marked difference in placental thickness was evident, with that of Twin I being large and edematous in appearance. The sonographic appearances were consistent with fetal hydrops secondary to parvovirus B19 infection of Twin I. An intrauterine fetal transfusion

Received 10 October, 2005; accepted 23 March, 2006.

Address of correspondence: Dr Jan E. Dickinson, School of Women's and Infants' Health, The University of Western Australia, King Edward Memorial Hospital for Women, 374 Bagot Road, Subiaco WA 6008, Australia. E-mail: Jan.Dickinson@uwa.edu.au

was subsequently performed for Twin I. The opening fetal hemoglobin was 80 g/l with a hematocrit of 25% and a reticulocyte count of 14.9%. There was an associated moderate fetal thrombocytopenia of  $93 \times 10^9/l$ . Parvovirus B19 DNA was present on PCR analysis of the pretransfusion blood sample. Both parvovirus B19 IgG and IgM were present in the fetal blood of Twin I. An uncomplicated fetal intravascular transfusion of 46 mls was conducted with a closing hemoglobin of 123 g/l. Following the fetal transfusion the sonographic signs of hydrops resolved and the pregnancy continued in an uncomplicated fashion until elective cesarean delivery at 37 weeks' gestation. A live male (Twin I) and female (Twin II) infant were delivered with both vigorous at birth.

In the early neonatal period respiratory distress occurred and parvovirus serology and PCR were obtained from each baby at the time of medically indicated venepuncture. Twin I demonstrated the presence of parvovirus IgG and IgM with B19 DNA detected on PCR testing. Twin II demonstrated only parvovirus B19 IgG, without detectable IgM and a negative B19 DNA PCR.

Examination of the twin placentae showed a difference in the placental thickness (Twin I placental disc thickness measuring 3 cm and Twin II placental disc 1.5 cm). Histologically the villi of the placenta of Twin I were edematous and mildly immature. No viral inclusions were present in the placenta of Twin I. Histology of the placenta of Twin II was unremarkable.

## Discussion

Differential twin pregnancy parvovirus infection with dual term survivors has been rarely reported. A solitary case in 1993 of fetal hydrops secondary to parvovirus infection in a dichorionic twin pregnancy at 25 weeks' gestation has been reported (Zerbini et al., 1993). A single intrauterine transfusion was required with resolution of the hydrops, although in the third trimester meconium peritonitis occurred necessitating surgical resection of necrotic bowel in the neonatal period. The nonhydropic co-twin was parvovirus B19 DNA and IgM negative at birth. In apparent parvovirus infection with atypical features in a monochorionic diamniotic twin gestation parvovirus B19 was observed on electron microscopy of fetal ascitic fluid with confirmation by B19 monoclonal antibody immunogold labeling (Weiner & Naides, 1992). Maternal serologic studies were however persistently negative for parvovirus B19 IgG and IgM with neonatal sera only transiently positive at a low level for parvovirus B19 IgM, and no fetal anemia documented. Despite serial amnioreduction procedures in this case, the placenta was unremarkable despite persistent fetal hydrops.

There have been two prior publications of differential twin parvovirus infection in which the infected twin succumbed to an intrauterine death prior to birth (Foster & Allen, 2004; Pustilnik & Cohen, 1994). In the Pustilnik and Cohen (1994) case, fetal hydrops of

one twin was evident at 18 weeks' gestation and death occurred 2 weeks later, without fetal therapeutic intervention. Premorbid amniocentesis provided a positive culture for Parvovirus B19. The single survivor delivered at term and cord blood parvovirus B19 IgM was negative. In the Foster and Allen (2004) case the diagnosis of fetal parvovirus infection was made as part of a work-up for a single fetal demise in a twin pregnancy at 25 weeks' gestation. Amniocentesis of the hydropic deceased twin demonstrated the presence of parvovirus B19 on PCR testing. Delivery occurred at 29 weeks' gestation following maternal disseminated intravascular coagulation and the surviving twin had no parvovirus B19 IgM and a negative B19 PCR after birth. IgG antibodies were present for B19, consistent with transplacental maternal antibody transfer. The case under discussion in this manuscript was notable for a dual live-birth of healthy infants, an outcome yet to be published in the circumstance of differential twin parvovirus infection. This was most likely a result of the maternal diagnosis of parvovirus infection prior to the development of severe fetal hydrops. The serial ultrasound assessment of the pregnancy permitted the early detection of significant fetal anemia and specific therapeutic intervention that may have prevented intrauterine fetal demise or significant morbidity.

The availability of B19 DNA detection with PCR technology has been of great assistance in maternal viral infection, permitting the appropriate targeting of at-risk pregnancies for fetal sonographic surveillance. It has been estimated that 50% to 65% of reproductive age women have been exposed to parvovirus B19, as assessed by the presence of IgG antibodies (Cohen & Buckley, 1988; Valeur-Jensen et al., 1999). Maternal seroconversion during pregnancy is reported in 1 to 3% of nonimmune woman (Chorba et al., 1986). In this particular case, the pregnant woman contracted parvovirus B19 after exposure to her infected daughter. Whilst seroconversion was documented at approximately 19 weeks' gestation, it is most likely maternal infection was acquired in the preceding weeks, possibly at gestational age 15 to 16 weeks. This is the most common form of parvovirus acquisition in pregnancy, with a 50% risk of nonimmune women contracting the virus within their own home when exposed to a household member (Chorba et al., 1986).

Once a nonimmune pregnant woman is either exposed or identified with parvovirus B19 infection, blood for viral DNA using PCR technology should be conducted. Viral DNA is only present during maternal viremia and it is during this time that fetal infection may occur. In contemporary fetal medicine, evidence of maternal seroconversion and/or detection of maternal IgM antibody supplemented by detection of maternal viremia where available, prompts the conduct of serial ultrasound over an 8- to 12-week period for evidence of fetal hydrops (Enders et al., 2006; Rodis et al., 1998). Amniocentesis for amniotic fluid B19 DNA detection with PCR is not routinely

performed in susceptible pregnancies, rather this is reserved for more directed assessments. The primary aim of ultrasound in maternal parvovirus B19 infection is to assess the potentially infected fetus for evidence of hydrops, which occurs principally due to fetal anemia and viral myocarditis. The noninvasive assessment of fetal anemia with middle cerebral artery flow velocity waveform analysis has achieved widespread acceptance and appears a sensitive and specific test (Mari, 2000). Initially reported for use in red cell isoimmunization it has been used successfully in parvovirus B19 associated fetal anemia, as demonstrated in this case. It has been previously observed that the degree of fetal hydrops may not correlate with the fetal hemoglobin (Crane, 2002), and in our case the fetal hydrops was more severe sonographically than would have been expected with a hemoglobin of 80 g/l. This is presumed due to the impact of viral myocarditis and hepatic dysfunction. The middle cerebral artery peak systolic velocity discordance also served to reassure that Twin II was in no imminent jeopardy and did not warrant invasive assessment.

The neonatal laboratory investigations indicated Twin II did not sustain congenital parvovirus B19 infection, confirming the differential twin infection. However, to be completely certain Twin II is noninfected a later serologic assessment should be performed to document loss of transplacentally acquired maternal B19 IgG. Passively acquired maternal IgG antibodies may persist in the infant for 9 to 12 months (Trlifajova et al., 1982). It is assumed that the separate placentation of the dichorionic twin pregnancy influenced this viral infection discordance. Intraplental vascular anastomoses characterize monochorionic placentation and it would be predicted that concordance in infections would be expected due to hematologic interaction. This does not appear to be absolute, however, with a case report of differential infection with rubella virus in a monochorionic diamniotic twin pregnancy (Wang et al., 1990). This would suggest that nonplacental factors might also influence transplacental viral passage and subsequent fetal infection.

In conclusion, we present a case of discordant fetal infection and secondary hydrops due to parvovirus B19 in a dizygotic twin pregnancy. Fetal intravascular transfusion was associated with a resolution of hydrops, permitting continuation of the pregnancy culminating in a dual live-birth at term. Contemporary molecular technology and prenatal ultrasound were central in fetal surveillance and intervention in this case, permitting targeted intervention of the affected twin and expectant observation of the noninfected sibling.

### Acknowledgments

The authors wish to thank Dr Gerry Harnett, The Western Australia Centre for Pathology and Medical Research, Nedlands, Western Australia, for performing the parvovirus PCR assays.

### References

- Brown, T., Anand, A., Ritchie, L. D., Clewley, J. P., & Reid, T. M. (1984). Intrauterine parvovirus infection associated with hydrops fetalis. *Lancet*, 2, 1033–1034.
- Chorba, T., Coccia, P., Holman, R. C., Tattersall, P., Anderson, L. J., Sudman, J., Young, N. S., Kurcynski, E., Saarinen, U. M., & Moir, R. (1986). The role of parvovirus B19 in aplastic crisis and erythema infectiosum (fifth disease). *Journal of Infectious Diseases*, 154, 383–393.
- Cohen, B. J., & Buckley, M. M. (1988). The prevalence of antibody to human parvovirus B19 in England and Wales. *Journal of Medical Microbiology*, 25, 151–153.
- Crane, J. (2002). Parvovirus B19 infection in pregnancy. SOGC Clinical Practice Guidelines, No. 119. *Journal of Obstetrics and Gynaecology Canada*, 24, 727–734.
- Enders, M., Schalasta, G., Baisch, C., Weidner, A., Pukkila, L., Kaikkonen, L., Lankinen, H., Hedman, L., Soderlund-Venermo, M., & Hedman, K. (2006). Human parvovirus B19 infection during pregnancy: Value of modern molecular and serological diagnostics. *Journal of Clinical Virology*, 35, 400–406.
- Foster, R. T., & Allen, S. R. (2004). Differential transmission of parvovirus B19 in a twin gestation: A case report. *Twin Research*, 7, 412–414.
- Mari, G., & Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. (2000). Fetal blood flow velocity of the middle cerebral artery in the anemic fetus. *New England Journal of Medicine*, 342, 9–14.
- Miller, E., Fairley, C. K., Cohen, B. J., & Seng, C. (1998). Immediate and long term outcome of human parvovirus B19 infection in pregnancy. *British Journal of Obstetrics and Gynaecology*, 105, 174–178.
- Public Health Laboratory Service Working Party on Fifth Disease (1990). Prospective study of human parvovirus (B19) infection in pregnancy. *British Medical Journal*, 300, 1166–1170.
- Pustilnik, T. B., & Cohen, A. W. (1994). Parvovirus B19 infection in a twin pregnancy. *Obstetrics and Gynecology*, 83, 834–836.
- Rodis, J. F., Borgida, A. F., Wilson, M., Egan, J. F., Leo, M. V., Odibo, A. O., & Campbell, W. A. (1998). Management of parvovirus infection in pregnancy and outcomes of hydrops: A survey of members of the Society of Perinatal Obstetricians. *American Journal of Obstetrics and Gynecology*, 179, 985–988.
- Trlifajova, J., Pokorny, J., Svandova, E., & Ryba, M. (1982). Study of persistence of maternal antibodies to varicella-zoster virus by indirect haemagglutination, with result control by radioimmunoassay.

- Journal of Hygiene, Epidemiology, Microbiology, and Immunology*, 26, 65–73.
- Valeur-Jensen, A. K., Pedersen, C. B., Westergaard, T., Jensen, I. P., Lebech, M., Andersen, P. K., Aaby, P., & Pedersen, B. N. (1999). Risk factors for parvovirus B19 infection in pregnancy. *Journal American Medical Association*, 281, 1099–1105.
- Wang, L. N., Wang, Y. F., Horne, C. C., & Shiao, L. C. (1990). Congenital rubella infection: Escape of one monozygotic twin with two amnions, one chorion and a single placenta. *Journal of Formosan Medical Association*, 89, 30–33.
- Weiner, C. P., & Naides S. J. (1992). Fetal survival after human parvovirus B19 infection: Spectrum of intrauterine response in a twin gestation. *American Journal of Perinatology*, 9, 66–68.
- Zerbini, M., Musiani, M., Gentilomi, G., Venturoli, S., Gallinella, G., Gibellini, D., Morandi, R., Guerra, B., Bovicelli, L., & La Placa, M. (1993). Symptomatic parvovirus B19 infection of one fetus in a twin pregnancy. *Clinical Infectious Diseases*, 17, 262–263.
-