Clinical and virological aspects of human parvovirus B19 Infection during Gestation.

Haan, T.R. de

Chapter 6

Long-term outcome after fetal transfusion for hydrops associated with Parvovirus B19 infection
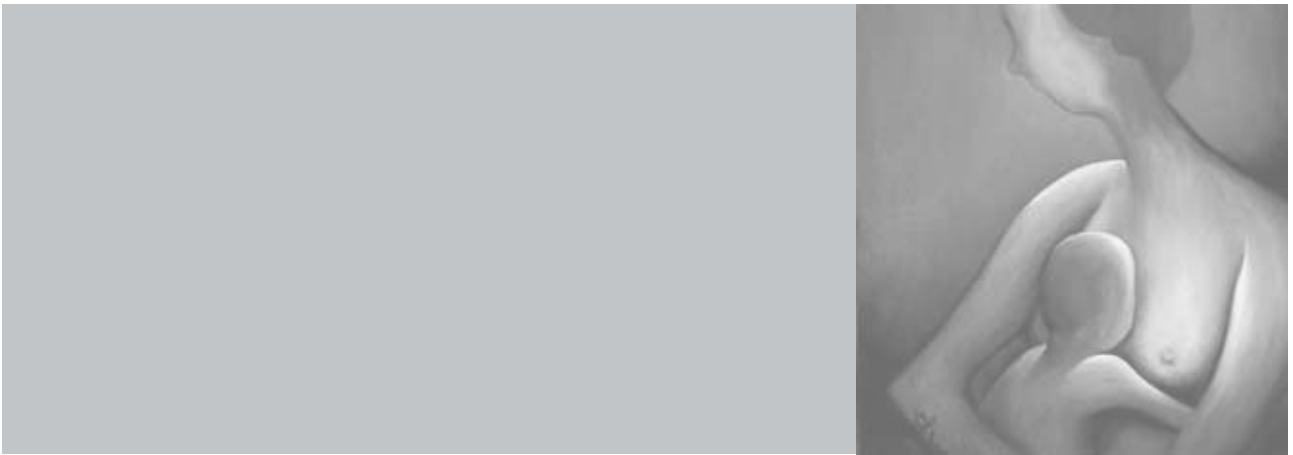
H.T.C. Nagel, MD*
T.R. de Haan, MD*
F.P. Vandenbussche, MD, PhD
D. Oepkes, MD, PhD
F.J. Walther, MD, PhD

*Both authors contributed equally to the work presented and should be considered joint first authors.

Abstract

Objective: To evaluate long-term neurodevelopmental status of children treated with intrauterine red blood cell and platelet transfusion (IUT) for fetal hydrops caused by parvovirus B19.

Methods: Maternal and neonatal records of all intrauterine transfusions for congenital parvovirus B19 infection in our center between 1997 – 2005 were reviewed. Congenital B19 virus infection was confirmed by the presence of Maternal B19V specific Immunoglobulin M or parvovirus B19 DNA in fetal blood samples. All children underwent a general pediatric and neurological examination. Primary outcome measure was neurodevelopmental status (developmental index by Bayley Scales of Infant Development or Snijders-Oomen test). Secondary outcome measure was general health status of surviving children.

Results: A total of 25 IUT sessions were performed in 24 hydropic fetuses. Median fetal hemoglobin concentration, platelet count, and blood pH before IUT were 4.5 g/dL (range 2.4- 11.4 g/dL), 79 x 10^9/L (range 37-238 x 10^9/L) and 7.36 (range 7.31-7.51), respectively. Sixteen survivors aged 6 months to 8 years were included in the follow-up study. Neurodevelopment was normal in 11 children (68%). Five children (32%) demonstrated a delayed psychomotor development with an abnormal neurological examination (mild delay n=3, severe delay n=2). Neurodevelopmental status did not correlate with with pre-IUT hemoglobin, platelet, or blood pH values. Growth and general health status was normal in all. Two children had minor congenital defects.

Conclusion: Neurodevelopmental outcome was abnormal in 5 out of 16 survivors and was not related to the severity of fetal anemia and acidemia. We hypothesize that fetal parvovirus B19 infection may induce central nervous system damage.

Introduction

The incidence of parvovirus B19 (B19V) infection among seronegative pregnant women is around 2.4% (1). Vertical transmission occurs in 33-51% of cases of maternal infection (2,3). Fetal infection is fatal in 9% of the cases (4). Fetal death occurs in more than half of the B19V cases with severe fetal anemia and hydrops (3,5-11). Management of B19V infection with intrauterine erythrocyte and platelet transfusion (IUT) significantly reduces the mortality and morbidity of B19V infection (12-16). However, severe fetal anemia or a prolonged hydropic state may also lead to delayed neurodevelopment in surviving children (17,18). B19V has also been associated with cases of prenatal stroke, leading to significant neurodevelopmental delay in surviving patients (19-21).

Few data are available concerning long-term neurodevelopmental outcome of patients surviving hydrops treated with IUT. Four groups studied the outcome in survivors of severe anemia due to red cell alloimmunization treated with IUT. The percentage of children with disabilities was between 4.5 and 10.5 percent (14,15,22,23). However, fetal hemolytic disease may not be fully comparable to B19V induced fetal hydrops.

Dembinski *et al* reported normal neurodevelopmental outcome in 20 survivors after B19V induced fetal hydrops treated with IUT (24). However, 11 other children in their series were lost to follow-up. Three children who received IUT for B19V described in two reports also had normal developmental outcome (8,10).

The main objective of our study was to evaluate the neurodevelopmental status of children who survived fetal hydrops caused by parvovirus B19 and treated with IUT in our center. Primary outcome measure was the neurodevelopmental status of surviving children. We also studied the correlation between neurodevelopmental outcome and the severity of fetal anemia, thrombocytopenia and acidemia. Secondary outcome measure was the general health status of surviving children.

Materials and methods

The Department of Obstetrics of the Leiden University Medical Center is the national referral center for intravascular fetal transfusion in the Netherlands. We searched our database for all intrauterine transfusions performed between December 1997 and December 2005 for cases of fetal hydrops and parvovirus B19 infection. Fetal hydrops was defined as excess fluid in two or more cavities of the fetal body. Diagnosis was confirmed by the presence of B19V specific IgM or B19V DNA in fetal blood samples. Fetal blood samples were assessed for hemoglobin concentration (g/dL), platelet counts (x 10^9/L) and blood pH before and after intrauterine red cell and platelet transfusion. In all cases blood samples were taken to exclude chromosomal abnormalities. The amount of transfused blood needed to correct for fetal anemia was calculated on the basis of the initial hematocrit and the estimated fetal weight according to the protocol by Rodeck *et al* (20). Results are

depicted as percentages of the estimated fetal blood volume (120 ml/kg estimated fetal weight) in Table 1.

The Institutional Review Board of the Leiden University Medical Center approved the follow-up study and all parents gave written informed consent for their children. A trained examiner assessed neurodevelopmental outcome using tests validated for each age category. The Bayley Scales of Infant Development (Second Edition-Dutch version :BSID-II-NL) was used for infants 1 to 42 months of age (25,26). It comprises three separate scales (mental scale, motor scale and behavioral rating). Mental and motor scale scores are converted to a mental developmental index (MDI) and a psychomotor developmental index (PDI) with a mean of 100 and a standard deviation (SD) of 15. Normal limits are defined as MDI and PDI values between 85 and 114. Values of 70-84 are defined as mildly delayed. A score of <70 is defined as severely delayed. For ages 2.5 to 7 years the revised Snijders-Oomen Non-Verbal Intelligence Test–Revised (SON-R 2.5-7) was used (27). This test consists of six basic subtests (Categories, Mosaic, Puzzles, Patterns, Situations and Analogies). Scores are calculated as performance scale (SON-PS) and reasoning scale (SON-R). Raw subtest scores are standardized with population and age specific scores with a mean value of 100 and a SD of 15. The SON-R has been validated for Dutch and Belgian children.

Data concerning parental ethnicity, parental education and socio-economic status were noted. A pediatrician performed a standardized general examination, including weight, length and head circumference to evaluate growth according to age-specific percentiles (28), and a standardized neurological examination according to the Touwen method (29). A recent medical history was taken from the parents or caretakers.

Statistical analysis was performed by SPSS statistics version 12 (SPSS inc., Chicago, IL, USA). A p-value of < 0.05 was considered to indicate statistical significance. Results are depicted as median values with ranges. A separate linear regression analysis was used to evaluate any correlation of neurodevelopmental status with each variable (fetal hemoglobin values, fetal bloodgas values and fetal platelet counts).

Results

Maternal symptoms

We retrospectively evaluated the occurrence of maternal symptoms due to the parvovirus B19 infection. The gestational age at which infection occurred had a median of 17 weeks (range: 10- 25 weeks). In one case this date could not be determined. All women reported a condition of general malaise. Fever of short duration (2-3 days) was reported by 4/16 women (25%). Generalized arthralgia was noted by 7/16 women (43%). A skin rash at the time of infection was reported by 3/16 women (18%). Three women reported two or

more symptoms. A total of 7/16 women (43%) experienced no symptoms at all and were referred because of a suspected parvovirus B19 contact during pregnancy.

The source of infection was unknown in two cases. In 14 cases the source of infection was a contact with children suffering fifth disease, either own children or by contact in school –or daycare centre. A total of 11/16 women (68%) reported reduced fetal movements at the time of infection persisting up until the IUT. Treatment by IUT invariably resulted in an immediate and persistent increase of fetal movements.

Table 1. Maternal, fetal and neonatal characteristics of the study population. Normal development group (n=11) versus abnormal development group (n=5). IUT: Intrauterine transfusion; TFV: transfused volume as % of fetal blood volume. Maternal ages in years; gestational ages in weeks; hemoglobin values in g/dl.; platelet values x 10^9.

	Normal development at investigation n=11 Median (range)	Abnormal development at investigation n=5 Median (range)
Maternal age at IUT (y)	28 (19-36)	28 (24-32)
Gravidity	3 (1-4)	2 (1-3)
Parity	2 (0-3)	1 (0-2)
Maternal symptoms		
Fever	n= 3	n=1
Skin rash	n= 2	n=1
Arthralgia	n= 3	n=4
Fetal movements		
Normal	n= 3	n=2
Reduced	n= 8	n=3
Gestational age infection	17 (14–25)	14 (10-23)
Gestational age IUT	22 (20–27)	20 (18-28)
Hemoglobin before IUT	5.4 (2.4-11.0)	4.4 (2.4-4.9)
Hemoglobin after IUT	12 (9.7–13.9)	11.8 (9.7-18.7)
pH before IUT	7.3 (7.3-7.4)	7.4 (7.3-7.5)
pH after IUT	7.3 (7.2-7.4)	7.3 (7.2-7.4)
Platelets before IUT	54 (37-238)	102 (79-137)
TFV	27 (6 - 42)	20 (17-87)
Birth weight (g)	3,145 (2,145-4,160)	3,170 (2,890-3,340)
Gestational age at birth	39 (32 - 41)	40 (37-41)
Current age in years	4 (0.5 - 8.0)	4 (0.4-8.0)
IQ –scores	104 (86-132)	76 (26-84)

IUT sessions

During the study period a total number of 690 IUT procedures were performed at our department. Twenty-five IUT procedures (3.5%) were performed in 24 fetuses to correct B19V induced hydrops and anemia. One fetus received two IUTs. One fetus died during the IUT session, six died in utero following the IUT sessions, and 1 infant died at birth (mortality rate: 33%). Sixteen of the 24 fetuses survived and all children were available for investigation at follow-up.

Maternal, fetal and neonatal characteristics are depicted in Table 1. In two cases, hemoglobin concentrations after IUT could not be determined due to needle displacement. Fetal blood pH measurements were obtained in 12 cases. All available blood pH values were within the normal range before and after IUT.

General outcome

One infant was delivered at 32 weeks of gestation by a spontaneous preterm delivery. There were no signs of an acute intrauterine infection and antenatal fetal heart rate monitoring was normal. He was ventilated for infant respiratory distress syndrome and experienced a good clinical recovery with normal development. All other infants were delivered at >/= 37 weeks. One infant was small for gestational age with a birth weight of 2,340 grams at 37 weeks of gestation, the other infants had a normal birth weight. Fifteen infants had a 5 minute Apgar score >7. One infant had a 5 minute Apgar score of 4, but a normal neurodevelopmental outcome.

Physical examination demonstrated a cardiac murmur in one child with a clinically insignificant mitral valve insufficiency and a corrected hypospadia in another child. No other signs of dysmorphology were noted in these children. All other children proved normal on examination. Weight, length, and head circumference were all within normal limits for age.

Table 2. Details of the 5 children with mild to severe neurodevelopmental delay. GA: gestational age; IUT: intrauterine transfusion; Hb: hemoglobin; TFV: transfused volume as % of fetal bloodvolume; DQ: developmental quotient; IQ: intelligence quotient; MDI: mental developmental index; PDI: psychomotor developmental index; SON-IQ: Snijders-Oomen Non-Verbal Intelligence Test–Revised.

	Current age (years)	Sex	GA at IUT (weeks)	Pre-IUT Hb (g/dL)	Pre-IUT platelets (x 10⁹/L)	Pre-IUT pH	TFV	GA at birth (weeks)	Birth weight (g)	DQ/IQ score CI
1	1.5	Girl	18	4.0	128	7.41	19	41	3,155	PDI:84
2	3.2	Boy	20	5.0	87	7.35	17	40	3,175	MDI:76
3	7	Boy	22	8.3	76	7.36	6	37	2,340	IQ:80
4	0.5	Girl	23	4.5	79	7.51	24	40	3,170	MDI:55
5	7.5	Boy	28	5.0	137	7.32	87	37	3,340	IQ:26

Neurodevelopmental outcome

Tests for neurodevelopment were performed in the outpatient clinic (n=13). One child was tested in the home situation because of inability to travel. Two children had recently been evaluated extensively elsewhere because of possible neurodevelopmental delay. Parents consented to retrieval of all clinical data, but declined visiting our clinic for repeat investigation.

Seven children were tested with the SON–R test and nine with the BSID-II-NL test. SON-IQ scores and BSID-II-NL mental scores were within the normal range in 11 children (68%). These children all had a normal neurological examination. The medical history of one child suggested a delayed motor development, but neurological examination and developmental testing revealed no abnormalities. He was later diagnosed with the Buschke-Ollendorff syndrome, an autosomal dominant disease consisting of osteopoikilosis and disseminated connective tissue nevi of elastic type, not associated with congenital B19 infection.

Five children (32 %) had a developmental score indicating delay. Three children had a mild delay (children # 1-3 in Table 2). Two children had a severe developmental delay (children # 4 and 5 in Table 2). All five children demonstrated signs of a neurological deficit on examination. One child had marked hypotonia of the lower extremities, two children experienced a delayed development of fine motor coordination, and one child suffered a marked hypertonia and hyperreflexia of the upper extremities suspect of developing diplegia. One of the two children with severe developmental delay (child #5) had strabismus convergens, ataxia and generalized hypotonia. Additional laboratory and metabolic investigations were unremarkable, but a cerebral MRI scan demonstrated atrophy of the cerebellar vermis.

Neurodevelopmental outcome data are depicted in Figure 1, details are presented in Table 2. Using linear regression analysis, no statistically significant correlations were found between neurodevelopmental status and fetal pre-IUT hemoglobin levels. The regression coefficient proved 0.548 (CI: -8.0 – 9.8, p=0.834). We were also not able to demonstrate a correlation between intrauterine pH and neurodevelopmental status (regression coefficient: -0.209, CI: -47.5 – 26.5, p: 0,537). No correlation was detected for pre-IUT Platelet count and neurodevelopmental status (regression coefficient: -0.184, CI: -0.450- 0.082, p=0.159).
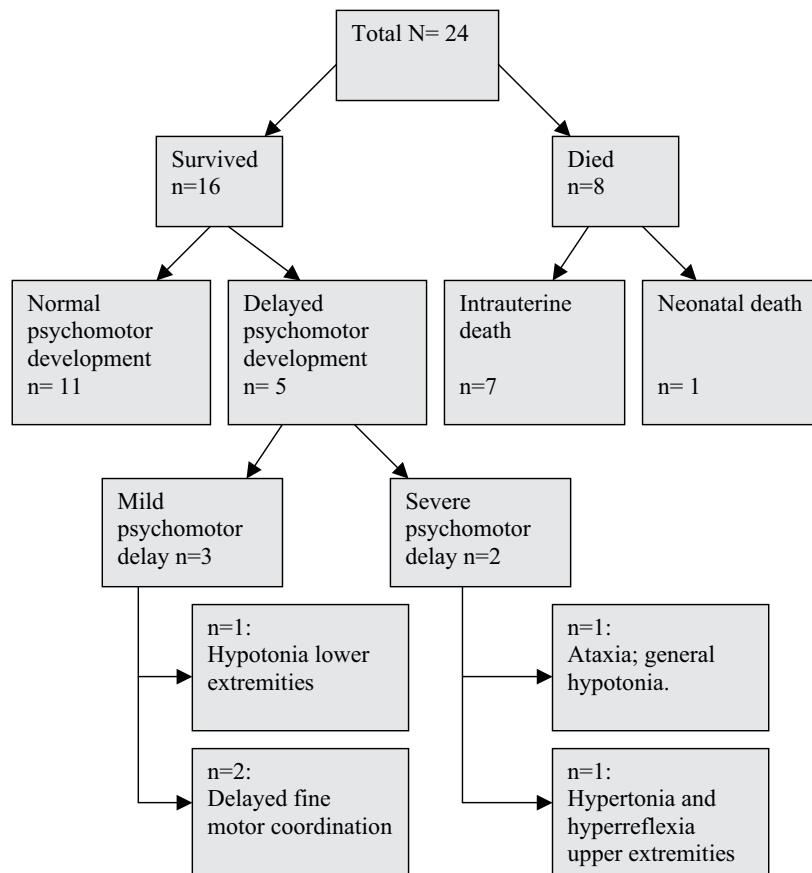
Figure 1. Psychomotor and neurological outcome in the study group.

Discussion

The objective of this study was to evaluate long-term neurodevelopmental outcome and general health status in children who experienced fetal hydrops due to intrauterine B19V infection. All children had been treated by IUT. We found abnormal neurodevelopmental outcome in one-third of the survivors of B19V infection. This is in contrast to the findings of the only other published large series of long-term follow-up in these patients. Dembinski and colleagues reported a good clinical outcome after IUT for B19V induced hydrops (24). However, they had a high loss to follow-up as only 20 out of 31 children (65%) were seen for testing. We agree with Wolke *et al* that the chances for adverse outcome are generally much higher in the group that is initially lost to follow-up (30). Miller *et al* described long-term outcome after parvovirus B19 infection in 427 pregnancies with 367 surviving infants, of whom 129 were followed up at 7- 10 years of age by sending questionnaires to obstetricians and general practitioners (8). However, only seven fetuses in this series

developed fetal hydrops and only 3 of them survived, of whom two underwent an IUT. These two survivors had a good neurodevelopmental outcome. Rodis *et al* investigated 108 children at a median age of 4 years following congenital B19V infection and 97 controls (10). Significant delays in motor, speech, or language development or significant attention deficits requiring special education were observed in 7.4% of the children in the study group versus 7.2% in the controls, cerebral palsy was detected in one patient of the study group (10). However, this study included only one hydropic fetus and outcome was assessed by sending a questionnaire to the caretakers (10). We consider it a strength of our study that all children were individually investigated and tested for neurodevelopmental outcome.

Our findings on the association of B19V with congenital anomalies are similar to those of previous reports. Miller *et al* described a case of ventricular septum defect (8) and an earlier cohort study reported hypospadias (31). We detected a case of mitral valve insufficiency and a case of hypospadias. Although some case reports suggest a possible teratogenic effect of B19V, a clear association of maternal B19V infection with congenital defects has not been proven (32-34). This is further supported by normal growth and general health status in our study population. Dembinski *et al* (24) reported a higher incidence of preterm births (9 out of 20 children) compared to our report (1 out of 16 births) and an average number of 4 IUTs. In contrast, all fetuses in our study received one IUT, except for one who received 2 IUTs. The higher frequency of IUT in the group of Dembinski et al (24) may explain the increase in the number of preterm deliveries. Average duration of gestation and hemoglobin levels at IUT were similar in both reports. We did not find any correlation between fetal hemoglobin levels or fetal blood pH and neurodevelopmental outcome. A limitation of our study is the small amount of study subjects. We may not have been able to detect any correlations because of the small number of study subjects. The wide confidence intervals are demonstrative of this fact.

One of our patients with a severe developmental delay had an abnormal MRI scan with atrophy of the cerebellar vermis. This is an interesting finding as two experimental studies on fetal B19V infection report cerebellar hypoplasia and ataxia as principal adverse outcomes (35,36). Clinical studies have confirmed the presence of cerebellar lesions on MRI scans following congenital B19V infection and support the possibility of prenatal stroke in these infants (19,37,38). We were not able to perform imaging studies in the other children as this was beyond the scope of this study. Future investigations should focus on the possibility of central nervous system damage following congenital B19V infection, especially in the presence of clinical symptoms or developmental delay.

A state of severe fetal hydrops may be prevented by timely referral and treatment of parvovirus B19 infection during gestation. As neurodevelopmental outcome is not clearly related to the measure of fetal anemia or acidemia, we speculate that B19V infection may cause central nervous system damage by itsself. The mechanism for this possible damage remains to be elucidated.

References

1. van Gessel PH, Gaytant MA, Vossen AC, Galama JM, Ursem NT, Steegers EA, et al. Incidence of parvovirus B19 infection among an unselected population of pregnant women in the Netherlands: A prospective study. Eur J Obstet Gynecol Reprod Biol 2006;128(1-2):46-9.

2. de Jong EP, de Haan TR, Kroes AC, Beersma MF, Oepkes D, Walther FJ. Parvovirus B19 infection in pregnancy. J Clin Virol 2006;36:107.

3 Corcoran A, Doyle S. Advances in the biology, diagnosis and host-pathogen interactions of parvovirus B19. J Med Microbiol 2004;53:459-75.

4. Prospective study of human parvovirus (B19) infection in pregnancy. Public Health Laboratory Service Working Party on Fifth Disease. BMJ 1990;300:1166-70

5. Enders M, Weidner A, Zoellner I, Searle K, Enders G. Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases. Prenat Diagn 2004;24:513-8.

6. Chisaka H, Morita E, Yaegashi N, Sugamura K. Parvovirus B19 and the pathogenesis of anaemia. Rev Med Virol 2003;13:347-59.

7. Norbeck O, Papadogiannakis N, Petersson K, Hirbod T, Broliden K, Tolfvenstam T. Revised clinical presentation of parvovirus B19-associated intrauterine fetal death. Clin Infect Dis 2002;35:1032-8.

8. Miller E, Fairley CK, Cohen BJ, Seng C. Immediate and long term outcome of human parvovirus B19 infection in pregnancy. Br J Obstet Gynaecol 1998;105:174-8.

9. Cameron AD, Swain S, Patrick WJ. Human parvovirus B19 infection associated with hydrops fetalis. Aust N Z J Obstet Gynaecol 1997;37:316-9.

10. Rodis JF, Rodner C, Hansen AA, Borgida AF, Deoliveira I, Shulman RS. Long-term outcome of children following maternal human parvovirus B19 infection. Obstet Gynecol 1998;91:125-8.

11. Schwarz TF, Roggendorf M, Hottentrager B, Deinhardt F, Enders G, Gloning KP, et al. Human parvovirus B19 infection in pregnancy. Lancet 1988;2:566-7.

12. Schild RL, Bald R, Plath H, Eis-Hubinger AM, Enders G, Hansmann M. Intrauterine management of fetal parvovirus B19 infection. Ultrasound Obstet Gynecol 1999;13: 161-6.

13. Fairley CK, Smoleniec JS, Caul OE, Miller E. Observational study of effect of intrauterine transfusions on outcome of fetal hydrops after parvovirus B19 infection. Lancet 1995;346:1335-7.

14. Doyle LW, Kelly EA, Rickards AL, Ford GW, Callanan C. Sensorineural outcome at 2 years for survivors of erythroblastosis treated with fetal intravascular transfusions. Obstet Gynecol 1993;81:931-5.

15. Hansmann M, Gembruch U, Bald R. New therapeutic aspects in nonimmune hydrops fetalis based on four hundred and two prenatally diagnosed cases. Fetal Ther 1989;4:29-36.

16. Halitsky V, Schwalb E, Krumholz BA, Gromisch DS, Schwartz P. Intra-uterine transfusions. Two interesting cases. Am J Dis Child 1967;113:245-50.

17. Janssens HM, de Haan MJ, van Kamp I, Brand R, Kanhai HH, Veen S. Outcome for children treated with fetal intravascular transfusions because of severe blood group antagonism. J Pediatr 1997;131:373-80.

18. van Kamp IL, Klumper FJ, Bakkum RS, Oepkes D, Meerman RH, Scherjon SA, et al. The severity of immune fetal hydrops is predictive of fetal outcome after intrauterine treatment. Am J Obstet Gynecol 2001;185:668-73.

19. Isumi H, Nunoue T, Nishida A, Takashima S. Fetal brain infection with human parvovirus B19. Pediatr Neurol 1999;21:661-3.

20. Rodeck CH, Nicolaides KH, Warsof SL, Fysh WJ, Gamsu HR, Kemp JR. The management of severe rhesus isoimmunisation by fetoscopic intravascular transfusions. Am J Obstet Gynecol 1984;150:769-74.

21. Kerr JR, Barah F, Chiswick ML, McDonnell GV, Smith J, Chapman MD, et al. Evidence for the role of demyelination, HLA-DR alleles, and cytokines in the pathogenesis of parvovirus B19 meningoencephalitis and its sequelae. J Neurol Neurosurg Psychiatry 2002;73:739-46.

22. Hudon L, Moise KJ, Jr., Hegemier SE, Hill RM, Moise AA, Smith EO, et al. Long-term neurodevelopmental outcome after intrauterine transfusion for the treatment of fetal hemolytic disease. Am J Obstet Gynecol 1998;179:858-63.

23. Hardyment AF, Salvador HS, Towell ME, Carpenter CW, Jan JE, Tingle AJ. Follow-up of intrauterine transfused surviving children. Am J Obstet Gynecol 1979;133:235-41.

24. Dembinski J, Haverkamp F, Maara H, Hansmann M, Eis-Hubinger AM, Bartmann P. Neurodevelopmental outcome after intrauterine red cell transfusion for Parvovirus B19-induced fetal hydrops. BJOG 2002;109:1232-4.

25. Harris SR, Megens AM, Backman CL, Hayes VE. Stability of the Bayley II Scales of Infant Development in a sample of low-risk and high-risk infants. Dev Med Child Neurol 2005;47:820-3.

26. Voigt RG, Brown FR, III, Fraley JK, Llorente AM, Rozelle J, Turcich M, et al. Concurrent and predictive validity of the cognitive adaptive test/clinical linguistic and auditory milestone scale (CAT/CLAMS) and the Mental Developmental Index of the Bayley Scales of Infant Development. Clin Pediatr (Phila) 2003;42:427-32.

27. Harris SH. An evaluation of the Snijders-Oomen Nonverbal Intelligence Scale for Young Children. J Pediatr Psychol 1982;7:239-51.

28. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47:316-23.

29. Touwen BC. Examination of the child with minor neurological dysfunction. Philadelphia (PA): Lippincott Co.;1979.

30. Wolke D, Sohne B, Ohrt B, Riegel K. Follow-up of preterm children: important to document dropouts. Lancet 1995;345:447.

31. Prospective study of human parvovirus (B19) infection in pregnancy. Public Health Laboratory Service Working Party on Fifth Disease. BMJ 1990;300:1166-70.

32. Wang X, Zhang G, Liu F, Han M, Xu D, Zang Y. Prevalence of human parvovirus B19 DNA in cardiac tissues of patients with congenital heart diseases indicated by nested PCR and in situ hybridization. J Clin Virol 2004;31:20-4.

33. Konstantinidou AE, Syridou G, Spanakis N, Tsakris A, Agrogiannis G, Patsouris E. Association of hypospadias and cardiac defect in a Parvovirus B19-infected stillborn: A causality relation? J Infect 2006 May 17 [epub ahead of print].

34. Tiessen RG, van Elsacker-Niele AM, Vermeij-Keers C, Oepkes D, van Roosmalen J, Gorsira MC. A fetus with a parvovirus B19 infection and congenital anomalies. Prenat Diagn 1994;14:173-6.

35. Kilham L, Margolis G. Problems of human concern arising from animal models of intrauterine and neonatal infections due to viruses: a review. I. Introduction and virologic studies. Prog Med Virol 1975;20:113-43.

36. Margolis G, Kilham L. Problems of human concern arising from animal models of intrauterine and neonatal infections due to viruses: a review. II. Pathologic studies. Prog Med Virol 1975;20:144-79.

37. Kerr JR, Barah F, Chiswick ML, McDonnell GV, Smith J, Chapman MD, et al. Evidence for the role of demy-elination, HLA-DR alleles, and cytokines in the pathogenesis of parvovirus B19 meningoencephalitis and its sequelae. J Neurol Neurosurg Psychiatry 2002;73:739-46.

38. de Haan TR, van Wezel-Meijler G, Beersma MFC, von Lindern JS, van Duinen SG, Walther FJ. Fetal stroke and congenital parvovirus B19 infection complicated by activated protein C resistance. Acta Paediatrica 2006;95:863-7.