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Intrauterine management of fetal parvovirus B_{19} infection

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ABSTRACT

Objectives *The aim of our study was to determine the outcome of pregnancies after intrauterine management of fetal parvovirus B_{19} infection.*

Design *Retrospective study.*

Subjects *A total of 37 cases of maternofetal parvovirus B_{19} infection, 35 of which were associated with hydrops fetalis, were referred to our tertiary level center between 1989 and 1996. With regard to fetal hydrops, no apparent cause other than parvovirus B_{19} infection was found in any patient.*

Methods *In all patients, cordocentesis was performed to assess the degree of fetal anemia. When anemia was present, cordocentesis was followed by intrauterine transfusion with packed red cells into the umbilical vein. Further management depended on the degree of fetal anemia and gestational age and included follow-up fetal blood sampling/transfusion as well as ultrasound examinations as deemed appropriate.*

Results *Packed red cell transfusion was performed in 30 patients with significant fetal anemia (Z-score 1.6–7.8 below the mean for gestational age). The fetal hemoglobin values ranged from 2.1 to 9.6 g/dl. Serum levels of platelets in the transfusion group were 9–228 $\times$ 10^9/l with Z-scores in the range of < 1 to 3.8 below the mean. During treatment and follow-up, there were five intrauterine deaths (13.5%), one neonatal death (2.7%) and 31 live births (83.8%).*

Conclusions *Fetal parvovirus infection can lead to marked anemia and hydrops formation. Cordocentesis allows precise assessment of fetal anemia which can then be corrected by intravenous transfusion. Under this regimen, the outcome proved favorable in the majority of fetuses, even those that were severely anemic.*

INTRODUCTION

Human parvovirus B_{19} is a single-stranded, spherical DNA virus. It is a small virus of 20–25 nm in diameter[1]. Its discovery dates back to 1975 when it was found in the serum of asymptomatic blood donors[2]. Since 1984, parvovirus infection has been known to cause fetal infection, with marked fetal hydrops and intrauterine demise[3].

Parvovirus mainly attacks erythroid progenitor cells, leading to anemia and its sequelae. It may, however, also affect progenitor cells of other cell systems, leading to thrombocytopenia and/or neutropenia[1]. The virus is unusually dependent on the infected host cell, owing to a limited genetic capacity[4]. Infection with B_{19} becomes symptomatic predominantly in patients with a shortened life span of red cells, which includes immunocompromised patients as well as fetuses and young children. The majority (50–75%) of women of reproductive age possess antibodies against B_{19}, rendering them immune[5]. It is only an acute infection in pregnancy that puts the fetus at risk of severe anemia and hydrops formation. As it is a self-limiting viral infection, however, there is still some controversy as to the best management of fetal B_{19} infection despite the life-saving potential of intrauterine transfusions in severely anemic cases. It is in this context that we report our experience in the management of fetal parvovirus infections.

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Table 1 Summary of results of study of 37 cases of maternofetal parvovirus B_{19} infection

Patient number	*Year*	*GA* (weeks)	*IUT* (*n*)	*Grading of ascites*	*Fetal hemoglobin*		*Platelets*		*Outcome*
					g/dl	*Z-score*	$\times 10^9$/*l*	*Z-score*	
1	1989	23+	4	severe	3.9	–5.20	66	–3.1	LB
2	1989	24+	5	severe	2.7	–5.94	22	–3.8	LB
3	1990	25+	7	severe	5.2	–5.59	228	< 1.0	LB
4	1991	35+	0	none	12.4	< 1.0	161	< 1.0	LB
5	1992	23+	3	severe	2.2	–6.25	41	–3.5	LB
6	1992	26+	0	moderate	9.3	–2.11	195	< 1.0	LB
7	1992	22+	0	mild	11.6	< 1.0	131	–2.0	LB
8	1993	25+	3	severe	6.9	–4.36	41	–2.9	LB
9	1993	26+	4	severe	2.5	–6.06	76	–2.4	LB
10	1993	20+	3	mild	6.2	–4.32	178	< 1.0	LB
11	1993	26+	2	severe	8.2	–3.41	125	–1.7	LB
12	1993	24+	3	severe	3.3	–5.56	39	–3.5	LB
13	1993	29+	0	moderate	12.4	< 1.0	220	< 1.0	LB
14	1993	21+	3	mild	3.7	–5.31	177	< 1.0	IUD
15	1993	26+	4	severe	2.1	–7.83	51	–2.8	LB
16	1993	24+	2	moderate	9.6	–1.63	130	–2.0	LB
17	1993	22+	2	severe	5.4	–4.25	66	–3.1	LB
18	1993	21+	1	severe	4.9	–4.56	83	–2.8	IUD
19	1993	27+	4	severe	3.4	–6.88	55	–2.7	IUD
20	1994	29+	5	severe	3.6	–4.54	186	< 1.0	LB
21	1994	29+	2	severe	5.9	–3.50	23	–2.4	NND
22	1994	19+	2	severe	2.8	–7.00	123	–2.0	LB
23	1994	22+	1	mild	9.4	–1.69	159	–1.5	LB
24	1994	27+	5	severe	2.8	–7.33	53	–2.7	LB
25	1994	25+	3	severe	3.4	–6.89	48	–2.8	LB
26	1994	21+	1	moderate	2.4	–6.13	29	–3.7	IUD
27	1994	24+	7	severe	2.7	–5.94	37	–3.6	LB
28	1994	20+	4	severe	2.7	–7.09	66	–2.9	LB
29	1995	21+	3	severe	2.4	–6.13	60	–3.2	IUD
30	1995	17+	1	moderate	6.0	–4.48	26	–3.6	LB
31	1995	20+	1	moderate	8.5	–2.51	164	–1.2	LB
32	1995	22+	0	none	10.5	–1.06	223	< 1.0	LB
33	1995	22+	0	severe	9.9	–1.44	249	< 1.0	LB
34	1996	24+	4	severe	2.4	–6.13	108	–2.4	LB
35	1996	22+	4	severe	2.5	–6.06	23	–3.8	LB
36	1996	20+	0	moderate	12.5	< 1.0	178	< 1.0	LB
37	1996	19+	2	severe	3.5	–6.45	9	–3.95	LB

GA, gestational age at first diagnosis; IUT, intrauterine transfusion; *Z*-score, number of standard deviations from the mean for gestational age; LB, live birth; IUD, intrauterine death; NND, neonatal death

PATIENTS AND METHODS

Between 1989 and 1996, 37 cases of maternofetal parvovirus B_{19} infection, 35 of which were associated with hydrops fetalis, were seen at our department for further management. During the same time, a total of 485 cases of fetal hydrops were diagnosed and treated in our center, with parvovirus B_{19} being prevalent in 7.2% of cases (35/485). Two patients were referred after prior clinical B_{19} infection and three patients after seroconversion to the B_{19} virus. In the remaining 32 patients, the reason for referral was the presence of fetal hydrops. The majority of patients were first referred in the second trimester (31 cases); the remainder were seen in the third trimester. The earliest referral was at 17+ weeks' gestation, the latest at 35+ weeks. First, the patients' histories were taken with special emphasis on potential infectious causes. Then, for each patient, a detailed fetal sonography was performed and the degree of ascites was graded according to Fairley and coworkers[6]. Maternal blood tests included a full blood count, Coombs' test and Kleihauer–Betke stain to rule out a fetomaternal hemorrhage. Subsequently, fetal full blood count and karyotype were determined by cordocentesis. Normal ranges for fetal hemoglobin count and platelet levels were used as described by Forrestier[7]. Fetal and maternal infections other than parvovirus B_{19} (TORCH) were excluded by appropriate tests. Maternal parvovirus infection was diagnosed by determining parvovirus-specific IgG and IgM antibodies using enzyme immunoassay (EIA), immunofluorescence testing (IFT) or radioimmunoassay (RIA). Fetal infection was diagnosed by detection of parvovirus-specific IgM in fetal blood by EIA, IFT or RIA and by detection of viral DNA in fetal blood by the polymerase chain reaction (PCR) technique. Reticulocyte counts were not obtained routinely during the study period. Likewise, slides from cord blood were not assessed for B_{19}-infected erythroblasts. Fetal hemoglobin levels were measured on site with an automatic red cell counter while the needle was left in the umbilical vein. Results were obtained within 1 min and transfusion of packed red cells (blood group 0 rhesus negative, hematocrit 65–70%) into the umbilical vein was immediately started in cases of significant fetal anemia (Table 1). The volume of transfusion depended mainly on the severity of anemia and gestational age at occurrence

and ranged from 5 to 39 ml. Perfusion time was kept to a minimum and generally did not exceed 5 min. All invasive procedures were performed by authors R.B., M.H. and H.P. All patients were extensively counselled about B_{19}-associated anemia, its consequences for the fetus and further management options, the latter depending on the severity of fetal anemia. For the first few days after establishing the diagnosis of fetal hydrops, patients were monitored by daily ultrasound examination and cardiotocography when appropriate. The former examination included biophysical activity of the fetus, Doppler sonography of the umbilical and middle cerebral arteries and, in latter years, Doppler flow in the ductus venosus. Furthermore, the presence and extent of tricuspid valve regurgitation were noted. After the initial hospitalization period, patients were examined by ultrasound on a regular weekly basis until no further decline in fetal hemoglobin levels was noted on fetal blood sampling. Further follow-up was at the discretion of the referring obstetrician.

RESULTS

All mothers-to-be had serological evidence of parvovirus B_{19} infection (37 and 27 patients with positive titers of parvovirus B_{19} IgG and IgM, respectively) verified by one or more of the following assays: IFT, EIA and RIA. Ultrasound examination revealed hydrops in 35 fetuses. The severity of hydrops was assessed by the degree of ascites[6]. Severe, moderate and mild ascites were diagnosed in 24, seven and four cases, respectively. Severe versus moderate or mild ascites showed a positive, albeit non-significant, correlation with the degree of anemia. Fetuses with severe, moderate and mild forms of ascites had a mean hemoglobin content of 4.0 g/dl (range 2.1–8.2 g/dl), 8.7 g/dl (range 5.7–12.4 g/dl) and 7.7 g/dl (range 3.7–11.6 g/dl), respectively (Table 1). Equally, we found only a weak correlation between fetal hemoglobin counts and platelet levels as determined by cordocentesis ($r = 0.67$).

In two affected pregnancies (Cases 4 and 32), there was no evidence of fetal hydrops on presentation. In both patients, seroconversion for B_{19} had occurred after a previous flu-like viral infection with generalized exanthema suggestive of parvovirus B_{19} infection. In both cases, fetal hemoglobin was found to be only moderately lowered to a level of 10.5 g/dl and 12.4 g/dl, respectively. No intravascular transfusion was therefore deemed necessary.

The number of referred patients per year was highest in 1993, when 12 cases associated with B_{19} infection were seen at our center. The time between exposure and referral with fetal hydrops was known in 15 patients and ranged from 2 to 8 weeks, with a mean of 5.2 weeks.

Values of α-fetoprotein in the amniotic fluid were measured in 15 patients and were found to be within normal limits (< 2.0 multiples of the median for gestational age). Chromosomal analyses were normal in all but one case, in which the fetus showed a balanced translocation between chromosomes 14 and 15, like her father-to-be.

Twelve of the 37 affected fetuses had positive IgM titers against B_{19}, as assessed by cordocentesis. In the remainder, cord blood IgM titers were found to be negative or equivocal. In 32 fetuses, cord blood was tested by the PCR technique for the presence of parvovirus B_{19}, yielding positive results in 30 cases. In five fetuses, all serological tests for B_{19} remained negative, with the PCR technique being performed in two of these cases only. The remaining three cases occurred at the beginning of the study period when the PCR technique was not yet routinely used. In this group, fetal hemoglobin values ranged from 2.5 to 5.2 g/dl and ascites was deemed severe in every case. No further cause for fetal hydrops other than B_{19} infection was found in the affected fetuses. On first presentation, cordocentesis in seven pregnancies found hemoglobin counts between 9.3 and 12.5 g/dl and no transfusion was instituted. Follow-up of these cases included weekly ultrasound examinations and up to two further cordocenteses. No downward trend in hemoglobin levels was noted. In contrast, 30 fetuses were diagnosed to be moderately to severely anemic on first admission, with hemoglobin levels between 2.1 and 9.6 g/dl. Of these, a total of 26 fetuses had a hemoglobin count of less than 7 g/dl, and 12 fetuses had hemoglobin levels of less than 3 g/dl. Platelet and white blood cell counts ranged from 9 to 228×10^9/l and 1.9 to 72.3×10^9/l, respectively. These cases were treated with a total of 95 intravenous transfusions of packed red cells into the umbilical vein (mean 3.17, range 1–7 transfusions per patient). The initial transfusion was performed between 17+ weeks and 29+ weeks (Table 1). In addition, four intrauterine transfusions of platelets into the umbilical vein, four intracardiac transfusions and one intraperitoneal transfusion were also given. The daily decline in hemoglobin levels between the first intravenous transfusion and the second fetal blood sampling had a mean of 0.25 g/dl (range between a decline of 1.1 g/dl and a rise of 0.5 g/dl).

Follow-up of affected pregnancies has been outlined above. Ultrasound and Doppler examinations were used serially and non-invasively to assess fetal well-being after the initial invasive procedure. The results of these tests, however, served only as an adjunct and further management depended mainly on the degree of fetal anemia, as assessed by cordocentesis. There were five B_{19}-related intrauterine deaths (13.5%) in the study period. Two intrauterine deaths (Cases 14 and 19) occurred several days after the last of three and four intravenous transfusions, respectively, and were therefore not considered to have been a direct consequence of the transfusion. There was one neonatal death (2.7%) (Case 21) due to multiple organ failure, 6 days after a spontaneous vaginal delivery at 30 + 2 weeks' gestation. The vast majority of pregnancies in our series (31 of the 37 patients; 83.8%), however, had a successful outcome with a live birth.

DISCUSSION

To the best of our knowledge, this is the largest series of fetal parvovirus infections managed at a single center. At reproductive age, most women possess antibodies against

B_{19} and are therefore not susceptible to the virus. Nevertheless, maternal parvovirus infection in pregnancy continues to pose problems in that it either goes unrecognized or is misdiagnosed as a flu-like viral illness[5]. Those patients who acquire an acute infection in pregnancy run an approximately 10% risk of fetal demise, which can occur up to 12 weeks after maternal infection[8,9]. It is our experience that fetal B_{19} infection is often not suspected until fetal hydrops becomes evident on routine mid-trimester sonography. Only five of the patients described here were referred to our center following documented seroconversion or clinical disease. While the exact percentage of B_{19} infections in cases of non-immune hydrops fetalis remains unknown, a recent report put the figure at 18%[10]. By contrast, in our series only 7.2% of cases with hydrops fetalis were associated with parvovirus B_{19}. The reason for this difference remains speculative.

The second-trimester fetus is particularly vulnerable to B_{19} infections, since fetal red blood cells have a shortened life span of 45–70 days and since the red cell mass increases approximately three- to four-fold during gestational months 3–6[4].

In our series all maternal sera gave evidence of B_{19} infection. Equally, with the PCR technique, fetal infection could be reliably found in 30 of the 32 tested cord blood samples. In contrast, analysis of cord blood B_{19} IgM titers showed positive results in only 12 of the 37 cases, questioning the value of determining fetal IgM levels. The literature describes similar cases of negative cord blood results in infected fetuses. Explanations of these findings may be sought in the immaturity of the fetal immune system or in the prolonged latency between exposure to the virus and development of hydrops[11].

The value of serum α-fetoprotein levels in the diagnosis and prognosis of fetal parvovirus infections remains controversial. Whereas some reports have described a direct correlation between raised α-fetoprotein levels and poor fetal prognosis[12,13], others have failed to find any such association[14,15]. Komischke and co-workers[16] recently reported that neither serum α-fetoprotein nor serum human chorionic gonadotropin (hCG) can be used to predict the outcome of parvovirus B_{19}-affected pregnancies. In our series, maternal serum α-fetoprotein values were not routinely assessed. Amniotic α-fetoprotein levels were measured in 15 patients and found to be within the normal range in all cases tested.

Parvovirus B_{19} has been associated with central nervous system defects in cats and hamsters[4]. B_{19} is also thought to play a causative role in the pathogenesis of some abnormalities in humans but only a few cases have been reported and most of these have occurred in aborted fetuses. Anomalies described include ocular anomalies[17], inflammatory changes in the myocardium, endocardial fibroelastosis[11], myocardial infarction, splenic calcifications, hydrocephalus[18], prenatal stroke[19] and meconium peritonitis[20,21]. With the exception of the last two, none of these anomalies have been found in liveborn infants. Equally, no abnormality other than one case of meconium peritonitis[20,21] was diagnosed in our series of live births. This lends credence to the fact that the majority of infected fetuses make a full recovery once they survive the marked depression of their hematopoietic cell system.

In our opinion, management of maternal exposure to the parvovirus in pregnancy should be based on the initial serological status of the patient. If there is evidence of a past infection (IgG positive, IgM negative) no further tests will be necessary, as the patient is considered to be immune. In an IgG- and IgM-negative pregnant woman, it is important to exclude seroconversion through a repeat test within 2–3 weeks after exposure. In all patients with strong suspicion of an acute infection in pregnancy (IgG- and IgM-positive), weekly ultrasound examinations for up to 12 weeks after maternal exposure should be performed, preferably in a prenatal center with a dedicated ultrasound service. In cases of early or overt fetal hydrops, fetal blood sampling to assess the degree of anemia is warranted. Further management of intrauterine B_{19} infection then mainly depends on the severity of anemia and gestational age at first occurrence. Generally, the more severe the anemia and the younger the fetus, the more urgent intrauterine transfusion will become; but the more severe the hydrops the less well transfusion will be tolerated by the fetus[22]. Three treatment options have been described: the 'wait and see' policy; delivery of the fetus within a short period of time; and intrauterine transfusion. Expectant management involves regular assessment of the fetal condition and appears to be a safe alternative in cases of mild anemia. All such reported cases have been characterized by either marginally lowered fetal hemoglobin levels or by management without invasive testing[23–25]. Immediate delivery of an infected fetus becomes feasible in the third trimester but is certainly not an option for the majority of cases seen in the mid-trimester before viability[26]. Schwarz and co-workers[27] and Hansmann and co-workers[28] were the first to describe intrauterine transfusion as a new therapy regimen in B_{19}-infected hydropic fetuses. Preceding these initial reports, however, B_{19}-associated fetal anemia was very likely to have been treated in the same manner, although without serological confirmation. Still, the case of intrauterine transfusion rests against the spontaneous resolution of fetal hydrops. If the fetal hemoglobin count is above the hydropic range, expectant management appears feasible. Assessing erythropoietic recovery by means of the reticulocyte count may help in deciding on the fetus that would probably not need transfusion. In practice, estimation of the reticulocyte level is too time-consuming to have any influence on immediate management decisions. Awaiting the result would mean a two-step procedure with a higher rate of complications[25]. Intrauterine transfusion is predominantly performed as transfusion of packed red cells into the umbilical vein, with intraperitoneal transfusion and intracardiac transfusion generally reserved for technically difficult cases or as life-saving procedures. Immediate measurement of fetal hemoglobin values allows transfusion to proceed without undue delay while the needle is left in the umbilical vein. With this policy it is essential to have packed red cells available for transfusion. The volume of transfusion in our series ranged from 5 to 39 ml, depending

on fetal condition and gestational age. From the third trimester, the fetus has a more developed immune system and may thus mount a more efficient immune response against parvovirus[3]. This, in part, may also explain the lower rate of affected late-trimester fetuses seen at our center. Four out of five intrauterine deaths occurred at 21+ weeks' gestation, when cordocentesis and intrauterine transfusion are technically more demanding. The combination of severe fetal anemia and accompanying technical difficulties may have had a detrimental effect on the survival chances of these fetuses.

Since ours was a retrospective study on fetal B_{19} infection, we had no control or non-invasively managed group for direct comparison. Our results nevertheless compare favorably with already published findings. In an observational study, Fairley and colleagues[6] reported on 66 cases of fetal hydrops arising from B_{19} infection throughout England and Wales between June 1992 and September 1994. Twelve of the 38 fetuses alive at the first abnormal scan received intrauterine transfusions and three of the 12 died. Twenty-six did not receive transfusions and 13 died. After adjustment for the severity of the hydrops and for gestational age, the odds of death in the transfusion group was significantly less (odds ratio 0.14, 95% CI 0.02–0.96), suggesting that intrauterine transfusion will benefit some fetuses with hydrops arising from parvovirus B_{19} infection[6]. Cameron and co-workers[29] performed a retrospective study on 17 pregnancies with non-immune hydrops fetalis due to parvovirus B_{19} infection referred to their center over a period of 10 years. If left untreated, an affected fetus had a poor prognosis. Out of the total 17 pregnancies, three fetuses received intrauterine transfusions with only one live birth in the whole series[29]. Smoleniec and Pillai[25] described management and outcome of eight fetuses with parvovirus B_{19}-associated hydrops. In two out of these eight fetuses, no fetal blood sampling was performed, since one had an isolated pericardial effusion and the other had ultrasound evidence of resolving hydrops. In both cases, the neonatal outcome was normal. One patient requested termination of pregnancy, and the remaining five fetuses underwent intrauterine transfusions for severe anemia (hemoglobin range 1.7–5.0 g/dl), resulting in one intrauterine death, one neonatal death and three live births[25].

It has also been our center's established practice to treat fetal anemia by intrauterine transfusion[30]. In hindsight, some of our cases were treated quite aggressively and more transfusions than necessary may have been given during the course of treatment. This, in turn, may have led to bone marrow suppression by overtransfusion in some cases. We have since then changed our policy to rely more on initial reticulocyte counts and to defer further invasive procedures whenever feasible. It is, however, our firm belief that marked fetal anemia, as in the vast majority of fetuses in our series, should preferably be treated by transfusion rather than by awaiting spontaneous resolution of hydrops.

A prospective randomized trial of the different management options in fetal parvovirus infections may be necessary to shed more light on the optimal form of treatment. The successful outcome in 83.8% of affected pregnancies at our center, however, demonstrates that intravenous transfusion of packed red cells, although still not universally accepted as the treatment of choice in marked fetal parvovirus B_{19} infection, plays an essential role in the management of hydrops fetalis associated with significant anemia.

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