Fetal parvovirus B19 infection

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ABSTRACT

Parvovirus B19 infection during pregnancy causes up to 27% cases of non-immune hydrops in anatomically normal fetuses. The virus is believed to cause arrest of maturation of red blood cell precursors at the late normoblast stage and also causes a decrease in the number of platelets. Fetal anemia is presently thought to be responsible for the development of skin edema and effusions. Myocarditis leading to heart failure may contribute to the development of fetal hydrops. We reviewed the literature regarding prevalence, transmission rates, clinical presentation, diagnostic techniques, current invasive vs. conservative management options, outcome and postmortem findings in a total of 82 studies involving 230 invasively and 435 conservatively managed pregnancies. In this non-selected population, the proportion of seronegative susceptible mothers ranged from 19 to 65%, seroconversion with an incubation time of up to 20 days occurred in 5.7– 12.1%, and 188/230 (82%) who were transfused infected fetuses had a normal outcome as opposed to only 239/435 (55%) in the conservatively managed group. The average time from diagnosis to resolution in both groups was 6 weeks (range, 3–12 and 2–12 weeks, respectively). The most promising diagnostic techniques were PCR of amniotic fluid or fetal blood and electron microscopy. There are some reports of fetal abnormalities occurring (probably coincidentally) in cases of parvovirus, but the majority of postmortem findings were infection-related, in particular myocarditis and hepatic abnormalities. Although management guidelines cannot be derived from this study due to the variable degree of hydrops in the analyzed studies, the present data suggest a benefit of transfusion therapy over conservative management in infected fetuses. The only study which was corrected for severity of hydrops using ultrasound criteria showed a clear benefit of intrauterine transfusion.

INTRODUCTION

The name parvovirus B19 was introduced to avoid possible confusion with the human papilloma virus (HPV) family. Parvoviruses B1–18 do not exist[1]. Symptoms in infected mothers include mild fever, headache, 'slapped cheek' appearance, erythematous rash, arthralgia and arthritis[2]. Parvovirus B19 accounts for up to 27% of cases of non-immune hydrops fetalis (NIHF) in anatomically normal fetuses[3]. Infection of fetuses is especially damaging between 10 and 20 weeks of gestation. During this time, the major development of the erythroid precursors takes place, and parvovirus B19 infections lead to arrest of maturation of these cells at the late normoblast stage and extremely low hemoglobin levels have been reported[4]. Disrupted red blood cell development and a rapidly expanding blood volume are the underlying causes for the fetal vulnerability but neutropenia or thrombocytopenia may also contribute to this. The virus may also affect the myocardium, culminating in myocarditis; the resulting high output cardiac failure can lead to tissue hypoxemia, fetal hydrops and effusions.

Sonographically detectable markers of fetal compromise include increased (> 95th centile) cardiac biventricular outer diameter[5], pericardial or pleural effusions, ascites, abdominal wall edema, bilateral hydroceles, amniotic fluid volume disorders, hydrocephalus, microcephaly, intracranial and hepatic calcification and sporadic cases of contractures[6]. Laboratory diagnosis can be achieved through specific IgM antibodies or the detection of viral DNA by polymerase chain reaction (PCR) or electron microscopy (EM). Virus culture usually fails. Increased maternal serum alpha-fetoprotein (AFP) has also been used as a prognostic factor for poor outcome[7].

Although abnormalities have been reported in infected fetuses, there are no reports presenting evidence of fetal malformation as a result of parvovirus B19 infection. The use of intrauterine transfusion can lead to resolution of the fetal hydrops. Direct fetal digitalization has also been used and in postnatal immunodeficient patients with chronic aplastic anemia, immunoglobulins have been successfully administered[2,3]. There is one report of terminal cardiac heart failure in a 34-week fetus, which had a successful transplant postnatally[8]. In view of these therapeutic options, termination of pregnancy is rarely indicated.

REVIEW

INCIDENCE/TRANSMISSION

Maternal infection with parvovirus B19 is estimated to occur in 0.25–6% of susceptible pregnancies (Table 1). It has been estimated that fetal death occurs in 9% of these cases, which suggests that parvovirus B19 may cause more than 150 fetal deaths in England and Wales each year[9].

After exposure, there is a minimal or no risk of transmission if the mother has positive IgG titers for parvovirus B19 and maternal IgM is negative indicating maternal re-infection. For the majority of pregnancies in which maternal seroconversion occurs, transmission of infection to the fetus will not take place. If transmission occurs, there may be spontaneous abortion, fetal hydrops or isolated fetal myocarditis with cardiomegaly and heart failure. There are several factors which determine a fetus at risk. Adverse prognostic factors are high maternal age, maternal immunity and seroconversion, raised maternal AFP and ultrasound findings.

Maternal infection results in increased miscarriage and stillbirth even in the absence of transplacental transmission, which occurs in approximately one third of infected mothers. The overall risk of fetal loss following maternal exposure is much less than previously thought, and may be less than 3% in the first 20 weeks of gestation or approximately 10% if the mother is actually infected[10]. In the study by Enders and Biber[11], 2279 pregnant women were screened for antiparvovirus B19 IgG and IgM antibodies. Of these, 41% were seronegative and 54% had specific IgG but no IgM antibodies, indicating an infection in earlier life. Acute infection was demonstrated by IgM antibody detection in 114 pregnant women (32% in the first, 54% in the second and 14% in the third trimesters)[11]. Serum remaining from specimens submitted for diagnosis from 6864 people of all ages to seven public health laboratories in England was tested for antibody to parvovirus B19. The antibody prevalence rose with age to 45% at 10 years and 60% to 70% in adults. The age-specific risk of infection was highest in children aged less than 10 years and was lowest in adults.

Data from studies of outbreaks of parvovirus B19-associated erythema infectiosum and aplastic crisis suggest that the risk of infection among susceptible adults following household exposure to a parvovirus B19-infected person is approximately 50% and following school exposures during outbreaks of erythema infectiosum is 20–30%. All susceptible school staff members appear to be at risk of infection during outbreaks. Based on these and other data we can estimate that pregnant women whose serological status is unknown have a less than 2.5% chance of suffering fetal loss after household exposure and less than 1.5% chance after school exposure[12]. The relative risk of maternal parvovirus B19 infection was 2.8 if the source was a related child living in the household (95% confidence interval, 1.7–4.6; $P < 0.001$). No significant differences were found for maternal parvovirus B19 infection in eight categories of maternal occupation.

Maternal symptoms of polyarthralgia (46%), fever (19%), and non-specific rash (38%) were significantly more common ($P < 0.001$) in IgM-positive patients than in non-infected women (4.1%, 2.8%, and 5.7%, respectively). Only 17 (33%) of the IgM-positive women were entirely asymptomatic[13].

A prospective study during a non-epidemic period included 457 women admitted to an antenatal care center. Serum samples were collected at 7–13, 21, and 33 weeks of gestation, and 7–9 weeks after delivery. Parvovirus-specific antibodies were present in 81% of the women in the first sample. Six women (6/88 susceptible, 6.8%) underwent seroconversion and 28 women (28/369, 7.6%) boosted their antibody response during or after pregnancy. All gave birth to healthy infants. One woman free of symptoms experienced an intrauterine fetal death at 37 weeks of gestation. She had no rise in parvovirus B19 antibodies during pregnancy, but parvoviral DNA was found in maternal serum samples and in the placenta[14]. One thousand six hundred and ten women who were < 28 weeks' pregnant at enrolment were screened for parvovirus infection. The prevalence of IgG positivity was 35.03% (564/1610). The incidence of acute infection during pregnancy was 5.7% (60/1046). There were five miscarriages among the parvovirus B19-infected women but only one was caused by parvovirus, as assessed by histological examination and PCR. The incidence of fetal loss caused by parvovirus was therefore 1.66% (1/60). The remaining 55 pregnancies were uneventful and at 1 year of age, none of the infants had serious abnormalities. The incidence of vertical transmission of infection was estimated to be 25%. This study provides evidence that although acute parvovirus infection may occur relatively commonly during pregnancy, an adverse fetal outcome is a rare complication[15].

Table 1 Results of studies involving more than 11 210 pregnancies reporting maternal immunity, seroconversion, rate of infected fetuses and outcome

Ref	n	Sero-negative mothers	Seroconversion rate	Transmission rate
12	NM	NM	NM (50%, household exp.) NM (20–30%, school exp.)	
11	2279	934/2279(41%) 32% 1st trimester 54% 2nd trimester 14% 3rd trimester	114/934 (5%)	10/114 (8.7%)
9	6864	55% (10 years) 30–40% (adults)	About 1 : 400	NM
15	1610	1046/1610 (65%)	60/1046 (5.7%)	1/60 (1.66%)
14	457	88/457 (19%)	6/88 (6.8%)	1/6 (16.6%)
Total	11 210	(range, 19–65%)	(range, 0.25–6.8%)	(range, 1.66–16.6%)

Ref, reference; NM, not mentioned; exp, exposure.

A recent study, investigating 30 946 serum samples, found that the risk of maternal infection is highest in epidemics and is directly proportional to the number of children at home. Nursery school teachers have a three-fold increased risk of seroconversion[16].

PATHOPHYSIOLOGY

Parvovirus B19, the only known human pathogenic parvovirus, is highly tropic to human bone marrow and replicates only in erythroid progenitor cells. The basis of this erythroid tropism is the tissue distribution of the parvovirus B19 cellular receptor, globoside (blood group P antigen)[17]. The tissue distribution of the P antigen is consistent and helps explain the extreme tropism of parvovirus B19 for erythroid cells. Cells in the S-phase of DNA mitosis are particularly vulnerable to parvovirus B19. Infections may be cytolytic to selected cell groups, resulting in specific developmental defects, or may produce more generalized effects such as anemia, pancytopenia, or hemorrhage. The fetus is at particular risk because of the vast number of cells in active mitosis. The P antigen is also found on fetal cardiac myocytes[18], consistent with evidence that the fetus infected with parvovirus B19 can develop myocarditis. In individuals with underlying hemolytic disorders, infection with parvovirus B19 is the primary cause of transient aplastic crisis. In immunocompromised patients, persistent parvovirus B19 infection may develop that manifests as pure red cell aplasia and chronic anemia[19].

CLINICAL PRESENTATION

Parvovirus B19 is a widespread virus with the primary infection generally occurring in childhood through family and community outbreaks. Its most typical manifestation is transient erythroblastopenia with aplastic crisis. This is often profound, mostly affecting patients with chronic hemolytic anemia or those with defective erythropoiesis (chronic hypoplastic anemia, iron deficiency anemia). In normal individuals the primary parvovirus B19 infection is usually asymptomatic but may give transient hematological signs for a few days: moderate reticulocytopenia, thrombopenia and neutropenia.

Clinically, two phases of the infection are described: a first phase of viremia of 2–3 days which may be accompanied by fever and myalgia, and a second phase which may last for several weeks, with dermatological signs (the most typical one being erythema infectiosum), vasculitis, arthralgias or arthritis. Long-term persistence of the virus in the organism may be responsible for chronic manifestation, essentially but not exclusively in immunodeficient patients: prolonged erythroblastopenia and chronic rheumatological manifestations. It may also be responsible for cases of juvenile arthritis, thrombocytopenic purpura and chronic neutropenia of childhood.

In pregnant women, the primary infection with parvovirus B19 may lead to fetal anemia and hydrops fetalis with variable outcomes: fetal death, hydrops fetalis, congenital anemia or spontaneous resolution[20]. Although the incidence of fetal parvovirus B19 infection in non-immunized pregnant women is still unknown, the question is raised of the recognition and protection of non-immunized pregnant women at high risk of exposure to infected subjects[21].

During the first trimester, fetuses with parvovirus B19 infection can present with increased nuchal translucency[22], myocarditis and intrauterine growth restriction (IUGR)[23]. Transmission to the fetus in the second trimester can lead to pleural effusions, ascites, cardiomegaly, hydrops[4] and meconium peritonitis[24,25]. In the third trimester or postpartum, parvovirus B19 infection can appear as bone marrow failure with prolonged aplastic periods[26].

DIAGNOSTIC TECHNIQUES

Diagnostic techniques aim at detecting maternal antibodies or either viral particles or DNA in maternal serum, amniotic fluid or fetal blood (Table 2). Parvovirus B19 may individually affect one of two fetuses in a dichorionic diamniotic twin pregnancy[27]. Zerbini *et al.*[28] analyzed the diagnostic value of virological and serological techniques on maternal serum, fetal cord blood, and amniotic fluid specimens obtained at

Table 2 Diagnostic techniques and samples used for diagnosing congenital parvovirus B19 infections

Ref	Sample	Technique
36	Maternal serum	IgG/IgM, ELISA, Western blot, immunofluorescence
24	Maternal serum	*In situ* hybridization
32	Maternal serum	AFP (elevated prior to detection of hydrops)
59	Maternal serum	AFP (elevated)
29	Maternal serum	PCR
33	Maternal serum	IgG antibodies against viral non-structural protein NS1
60,61	Amniotic fluid	PCR
30	Amniotic fluid	PCR, Southern blot, chemiluminescence
31	Amniotic fluid	Enzymatic amplification of parvovirus B19 (segment)
24	Fetal blood	PCR, dot-blot hybridization, *in situ* hybridization
31	Fetal blood	Enzymatic amplification of parvovirus B19 (segment)
29	Fetal serum	PCR
34	Fetal heart tissue	Microscopy: VP1 and VP2 viral particles
35	Fetal tissues	Microscopy: histology was found to be as sensitive as PCR

Ref, reference; Ig, immunoglobulin; ELISA, enzyme-linked immunosorbent assay; AFP, alpha-fetoprotein; PCR, polymerase chain reaction (DNA test).

the time of clinical diagnosis of parvovirus B19 fetal hydrops. Parvoviral B19 DNA was detected by nested PCR, dot blot hybridization and *in situ* hybridization. Anti-parvovirus B19 IgM and IgG antibodies were detected by immunoassays using recombinant parvovirus B19 antigens. They found that for maternal sera, virological and serological methods have a complementary role in diagnosis, while for fetal specimens the *in situ* detection of parvoviral B19 DNA in fetal cord blood is the most sensitive diagnostic system. Dieck *et al.*[29] concluded that, at least in doubtful cases, the sensitive PCR for DNA detection is indicated and may be the best indicator of infection not only in fetal but also in maternal blood. Wattre *et al.*[30] concluded that amniotic fluid was the most common and reliable sample for use with PCR, electrophoresis and Southern blot hybridization following chemiluminescence detection. Kovacs *et al.*[31] used amniotic fluid and fetal blood for an assay based on enzymatic amplification of a segment of the human parvovirus B19 genome. Carrington *et al.*[32] analyzed maternal serum of five affected fetuses and 11 unaffected cases with parvovirus B19 infection during pregnancy and found a correlation between raised maternal serum AFP level and poor prognosis for the affected pregnancies, with the subsequent development of hydrops fetalis. Hemauer *et al.*[33] used IgG antibodies against the viral non-structural protein NS1 and found that, in persistent or prolonged parvovirus B19 infections, the prevalence of NS1-specific antibodies was as high as 80% and therefore may be an indicator of chronic or more severe courses of parvovirus B19 infection. Respondek *et al.*[34] and Mark *et al.*[35] investigated techniques in fetal tissues and found that microscopy techniques (to identify intranuclear inclusions such as electron-dense marginated chromatin and virus particle clusters or crystalline arrays) are as sensitive as PCR. Although some data are available regarding the sensitivity or specificity of commercially available tests[36], there has been little comparison of the sensitivities and specificities of the various tests.

There is one recent publication on Doppler velocimetry for the management of pregnancies with proven seroconversion for parvovirus B19[37]. The results appear encouraging especially as three of the nine anemic fetuses had hydrops and one had ascites. Further studies are required since increased fetal cardiac output with parvovirus B19 could be masked by both severe myocarditis and cardiac dilatation. It is, however, known from rhesus disease that fetal hydrops develops if hemoglobin concentration deficit exceeds 6 g/dL[38]. This development may be the result of several mechanisms including extensive infiltration of the liver by erythropoietic tissue leading to portal hypertension as the result of compression of portal vessels, and hypoproteinemia[39], and at this very low level of hemoglobin, the oxygen content may decrease below a critical level of 2 mmol/L[40]. There are several reports on rhesus immunization describing increased fetal cardiac output, most likely to maintain adequate oxygen delivery to tissues in anemia[41]. Based on this observation, several investigators found increased blood flow velocities in such fetuses[42]. A recent multicenter study involving 111 rhesus-immunized fetuses found increased peak velocity in the middle cerebral artery in all fetuses with moderate or severe anemia, whereas none of the fetuses with a peak velocity below the mean was

anemic[43]. Although the mechanism of the development of fetal anemia with parvovirus B19 is different from rhesus disease and antibodies are of limited diagnostic use, it could be speculated that anemia may be detected by increased peak systolic velocity prior to the appearance of sonographically detectable markers of hydrops. This hypothesis, however, awaits confirmation. The observation of reversed flow in the ductus venosus could be explained by both end-stage heart failure[8] and regurgitation due to valve insufficiency.

MANAGEMENT

At the present time, the finding of parvovirus B19 infection is usually serendipitous based on the finding of fetal hydrops on a routine scan. If significant progress is to be made in the management of this condition, I would recommend routine screening for B19 antibodies in all women and the monitoring of all seronegative women for 6 weeks after exposure to detect seroconversion, although the incubation time may be only 3 weeks. Key monitoring parameters would be MCA Doppler, cardiomegaly and ductus venosus blood flow.

Treatment options for confirmed cases of fetal parvovirus B19 infection include:

1 expectant management using close ultrasound surveillance and intrauterine transfusion, if required;
2 cordocentesis in all fetuses and transfusions in those with anemia;
3 immediate delivery after 33 weeks;
4 termination of pregnancy of non-viable fetuses with severe hydrops (not recommended, see options 1 and 2)[44].

The first option could be extended using fetal arterial peak systolic velocimetry. In the absence of increased peak blood flow velocity, without cardiomegaly, expectant management and close ultrasound surveillance seems justified in all cases of seroconversion. If cordocentesis is performed, however, anemia could be detected before a critical decrease of hemoglobin of > 6 g/dL from the normal and before the development of severe hydrops; in parvovirus B19 there is no boost for the maternal development of antibodies known for rhesus isoimmunization which could justify a more invasive approach. Once sonographic signs of hydrops are present, transfusion is indicated using erythrocytes and platelets.

Adverse prognostic parameters are maternal seroconversion at an early gestation, early gestational age at detection of non-immune hydrops, the number and results of fetal blood samples and prolonged duration from intrauterine transfusion to resolution of hydrops. In postpartum patients, treatment for parvovirus B19-associated neutropenia was attempted using rhesus G-CSF in a patient with malignancy[45] and with low doses of gammaglobulin in a family with acute red cell aplasia[46]. The results of studies investigating transfusion and conservatively managed cases of confirmed fetal parvovirus B19 infection are shown in Tables 3 and 4. In the transfused group, there were 705 cases and in the non-transfused group there were 731 cases. The survival rate in the transfused group was 188/230 (82%) as opposed to 239/435 (55%) in the non-transfused group. These data suggest a significant advantage of transfusion vs. conservative treatment regardless of procedure-related complications.

Table 3 Summary of the results of 14 studies involving a total of 705 confirmed cases of fetal parvovirus B19 infection, in 230 of which the fetus received intrauterine transfusion

Ref	n*	GA at cordocentesis (weeks)	Transfusion	GA at and time to resolution	Outcome
11	10	24–28	5 transfused	NM	5/5 (100%) transfused, survival (1 ongoing) 3 IUFD hydropic fetuses second trimester 2 TOP (1 hydropic, 1 for other reasons) Total fetal death: 9 (7.8%)
4	2	21, 22 26, 27, 28	IVT IVT	25 weeks (3 weeks to resolution) 30 weeks (4 weeks to resolution)	2/2 (100%) transfused, survival
62	1	26	IVT	5 weeks to resolution	1/1 (100%) transfused, survival
63	1	21	IVT	27 weeks (6 weeks to resolution)	1/1 (100%) transfused, survival
60	11		1 IVT attempted	15–28 weeks (4 weeks to resolution)	0/1 (0%) transfused, survival (IUFD after IVT) 7/10 (70%) survival, 3 IUFD
64	1	25	IVT	29 weeks (4 weeks to resolution)	0/1 (0%) survival, placental detachment
65	8	18–27	5 transfused	Average time to resolution 4 weeks	3/5 (60%) transfused, survival 2/5 (40%) transfused, IUFD 2/3 (66%) not transfused, survival 1/3 (33%) TOP
66	1	17	IVT	7 weeks to resolution	1/1 (100%) transfused, survival
67	38		12 transfused	NM	9/12 (75%) transfused, survival, 3 IUFD 13/26 (50%) not transfused, survival 13/26 (50%) not transfused, IUFD (data corrected for severity of hydrops)
68	17	32, 33 23 24	IVT	Hydropic at 34 weeks (delivery) IUFD 24 h after transfusion 29 weeks (5 weeks to resolution), IUFD 32 weeks	1/3 (33%) transfused, normal, 1 IUFD 14/14 (100%) not transfused, IUFD
69	1	22	IVT	27 weeks (5 weeks to resolution)	1/1 (100%) transfused, survival
70	38	26 23 19	IVT IVT IPT	35 weeks (9 weeks to resolution) 35 weeks (12 weeks to resolution) 23 weeks (4 weeks to resolution)	3/3 (100%) transfused, survival 35/35 (100%) not transfused, survival
44	539		164 IVT	6 weeks to resolution in 94%	137/164 (83.5%) transfused, survival 27/164 (16%) transfused, IUFD 158/303 (52%) spontaneous resolution, survival 138/303 (46%) not transfused, IUFD 7/303 (2%) not transfused, TOP 72 missing outcome and/or transfusion information
71	37		30 IVT	NM	24/30 (80%) transfused, survival 5/30 (16.6%) transfused, IUFD 1/30 (3.3%) transfused, neonatal death
Total	705		230 IVT	Average 6 weeks to resolution (range 3–12 weeks)	188/230 (82%) transfused, survival

*Total of confirmed cases of fetal parvovirus B19 infection (hydrops, fetal IgM, PCR or EM-positive). Ref, reference; GA, gestational age; IVT, intravascular transfusion; IPT, intraperitoneal transfusion, NM, not mentioned; IUFD, intrauterine fetal death; TOP, termination of pregnancy.

POSTMORTEM

Postmortem evaluation of infected fetuses (Table 5) has demonstrated that in the majority of cases there are abnormalities in either the erythroblasts or the hepatic cells which are believed to be infection-related. The findings of hepatic siderosis with fibrosis and bile duct proliferation have been proposed for the histological identification of cases of fetal parvovirus B19 infection[47]. Others have reported a pronounced leukoerythroblastic reaction, hepatitis and eosinophilic changes in the hematopoietic cell nuclei[48] or intranuclear inclusions in erythroid cells[49,50]. Histological examinations of fetal tissues demonstrated leukoerythroblastic reaction in the liver and spleen, granular hemosiderin deposition in hepatocytes and Kupffer cells, and bilirubin deposition in the intercellular space in the liver. This evidence indicates that, in some fetuses with intrauterine human parvovirus B19 infection, hydropic changes may be induced by the sudden decrease in oxygen-carrying capacity of the blood due to severe anemia caused by the infection[51]. In 16/16 mid-trimester spontaneous abortions with confirmed parvovirus infection, erythroblasts with intranuclear inclusions (lantern cells) were found with no other structural malformations. The authors postulated that parvovirus B19 infection may be a particular threat to the fetus during this stage of gestation, because lantern cells were found in all of the fetuses[52].

Some authors have reported abnormalities of the fetal heart or brain. Infection of fetal organs and vascular inflammation have both been held responsible for the observed pathology in prenatal parvovirus B19 infection. There is one report with myocardial infarction, splenic calcifications and mild hydrocephalus, and another with moderate hydrocephalus with central nervous system scarring[53] perhaps due

to hemorrhage as a result of thrombocytopenia. In a series of 673 fetal and neonatal autopsies, there were five of 32 (16%) hydropic fetuses with confirmed parvovirus B19 infection and one with a ventricular septal defect (VSD)[54]. The incidence of this cardiac anomaly in the general population is about 1 : 500 and it is therefore unlikely that the observed VSD can be attributed to parvovirus B19. In addition, if there had been a fetal parvovirus B19 infection at the time of fetal cardiac development, this fetus would most likely have spontaneously aborted. In a series of 15 cases of cardiac involvement, 10 of the cases were collected from fetuses during the second trimester of maternal–fetal infection. *In situ* hybridization detected viral DNA sequences in the nucleus of infected myoblasts with myocarditis as the most frequent histological damage. Therefore, cardiac failure, secondary to myocarditis, may occur in the absence of fetal anemia. In cases of severe anemia, as usually occurs in cases of hydrops, damage to the cardiac tissues might hamper the reactive increase of cardiac output due to the anemia. This might account for the poor prognosis of parvovirus B19 fetal hydrops in the second trimester of pregnancy, despite transfusion therapy attempts in the third trimester[55].

Evidence of viral DNA in lung tissue has also been reported. In a series of 13 cases of unexplained non-immune hydrops fetalis, there were four specimens containing parvovirus DNA in cells in the blood vessel lumina and alveoli confirmed by *in situ* hybridization[56]. There is one report with multiple structural defects at prenatal ultrasound examination. After termination of the pregnancy, a bilateral cleft lip, alveolus and palate, micrognathia and webbed joints were seen. Fetal tissues showed indications of infection, intranuclear inclusion bodies, chronic stress, hemolysis, arterial wall damage, and profuse hemorrhage[57]. Other reports include anencephaly or multiple ocular abnormalities[58]. Histological changes in erythrocytes, liver, spleen, lung and heart are most likely due to the congenital parvovirus B19 infection, whereas fetal malformations such as cleft lip and palate, ocular abnormalities, webbed joints, myocardial infarction or VSDs, anencephaly and even hydrocephaly or central nervous system scarring are either sporadic in parvovirus B19 or, most likely, coincidental. Alternatively, some fetal abnormalities may render the fetus more prone to congenital parvovirus B19 infection and therefore the incidence in such fetuses may be higher than in a general population.

Table 4 Summary of the results of 23 studies involving a total of 435 confirmed fetal parvovirus B19 infections which were conservatively managed

Ref	n*	Diagnosis to resolution of hydrops	Outcome
11	10	NM	0/5 (0%) survival 2/5 (40%) TOP (1 hydropic, 1 for other reasons)
72	1	18 weeks	0/1 (0%) survival, IUFD (26 weeks)
51	2	21 weeks, IUFD at 26 weeks, still hydropic at 22, 24 weeks PPROM and neonatal death	0/2 (0%) survival, IUFD (24, 26 weeks)
58	11	11 hydropic	2/11 (18%) survival 2/11 (18%) TOP
73	1	14 weeks	0/1 (0%) survival
74	2	Both 27 weeks (5 weeks to resolution)	2/2 (100%) survival
75	1	26 weeks (6 weeks to resolution)	1/1 (100%) survival
76	1	21 weeks (2 weeks to resolution)	1/1 (100%) survival
77	2	22 weeks, week of resolution NM 27 weeks (3 weeks to resolution)	2/2 (100%) survival
5	2	30 weeks (6 weeks to resolution) 24 weeks (2 weeks to resolution)	2/2 (100%) survival
60	11	15–28 weeks (4 weeks to resolution)	7/10 (70%) survival, 3 IUFD, 1 attempted transfusion (Table 4)
78	2	23 weeks	2/2 (100%) survival, monochorionic, diamniotic twins
79	1	40 weeks	0/1 (0%) survival
27	2	18 weeks	0/1 (0%) survival (twin pregnancy with one affected)
65	8	18–27 weeks (4 weeks to resolution)	2/3 (66%) survival 1/3 (33%) TOP
67	38	NM	13/26 (50%) survival (data corrected for severity of hydrops)
80	1	NM (4 weeks to resolution)	1/1 (100%) survival
81	3	12 weeks (10 weeks to resolution) 12 weeks (6 weeks to resolution) 12 weeks (10 weeks to resolution)	3/3 (100%) survival
68	17	11–35 weeks	0/14 (0%) survival
82	1	21 weeks (6 weeks to resolution)	1/1 (100%) survival
70	38	19, 23, 26 weeks (4, 9, 12 weeks to resolution)	35/35 (100%) survival
44	539	weeks to resolution: < 5 : 66%; 5–8: 20%; > 8: 14%	158/303 (52%) survival 7/303 (2%) TOP 72 missing outcome and/or transfusion information
71	37	7 weeks	7/7 (100%) survival
Total	731	Average 6 weeks (range 2–12 weeks)	239/435 (55%) survival

*Total of confirmed cases of fetal parvovirus B19 infection (hydrops, fetal IgM, PCR or EM-positive). Ref, reference; NM, not mentioned; IUFD, intrauterine fetal death; PPROM, preterm premature rupture of membranes; TOP, termination of pregnancy.

Table 5 Postmortem findings in a total of 66 cases in association with parvovirus B19 infection of fetuses

Ref	Organ	n	Histology
53	Brain	1	Mild hydrocephalus
53		1	Moderate hydrocephalus
53		1	Central nervous system scarring
58		1	Anencephaly
58		1	Ocular (microphthalmia, absent lens and iris)
57	Face	1	Bilateral cleft lip and palate, micrognathia
83	Heart	1	Postpartum lethal myocarditis
53		1	Myocardial infarction
54		1	Ventricular septal defect
55		15	Myocarditis
51	Liver	2	Leukoerythroblastic reaction
51			Hemosiderin deposition (hepatocytes, Kupffer cells)
51			Bilirubin deposition in intercellular space
47		1	Siderosis with fibrosis and bile duct proliferation
48		2	Leukoerythroblastic reaction
48			Eosinophilic changes in the hematopoietic cell nuclei
48			Hepatitis, excessive iron pigment
49		1	Intranuclear inclusions in erythroid cells
50	Red Cells	16	Abnormal erythroblasts with typical nuclear inclusions
52		16	Erythroblasts with intranuclear inclusions (lantern cells)
57	Skeleton	1	Webbed joints
51	Spleen	2	Leukoerythroblastic reaction
53		1	Calcifications

Ref, reference.

CONCLUSION

We have reviewed the literature regarding prevalence, transmission rates, clinical presentation, diagnostic techniques, invasive vs. conservative management options, outcome and postmortem findings in a total of 82 studies involving 230 invasive and 435 conservatively managed pregnancies. Seronegative susceptible mothers ranged from 19 to 65%, seroconversion occurred in 0.25–6.8%, 188/230 (82%) transfused infected fetuses were normal as opposed to only 239/435 (55%) in the conservatively managed group. The average time from diagnosis to resolution in both groups was 6 weeks. The most promising diagnostic techniques were PCR of amniotic fluid or fetal blood and electron microscopy. There are some reports on fetal abnormalities being associated with parvovirus, but the majority of postmortem findings were infection-related, in particular myocarditis and hepatic abnormalities, and it is most likely that the findings of fetal malformations are coincidental. Although management guidelines cannot be definitively derived from this review due to the variable degree of hydrops in the studies analyzed, there is evidence of a benefit of transfusion therapy in infected fetuses.

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