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Review

Parvovirus B19 in pregnancy

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Abstract

Parvovirus B19 is a widespread infection that may affects 1–5% of pregnant women, mainly with normal pregnancy outcome. The prevalence of infection is higher during epidemics – between 3 and 20% with sero-conversion rate of 3–34%. Infection during pregnancy can cause a variety of other signs of fetal damage. The risk of adverse fetal outcome is increased if maternal infection occurs during the first two trimesters of pregnancy but may also happen during the third trimester. It is a significant cause of fetal loss throughout pregnancy, but has a higher impact in the second half of pregnancy when spontaneous fetal loss from other causes is relatively rare. Parvovirus infection can cause severe fetal anemia as a result of fetal erythroid progenitor cells infection with shortened half life of erythrocytes, causing high output cardiac failure and therefore nonimmune hydrops fetalis (NIHF). The P antigen expressed on fetal cardiac myocytes enables the Parvovirus B19 to infect myocardial cells and produce myocarditis that aggravates the cardiac failure. Although there are several reports of major congenital anomalies among offspring of mothers infected by Parvovirus, the virus does not seem to be a significant teratogen. Since Parvovirus B19 infection can cause severe morbidity and mortality, it should be part of the routine work up of complicated pregnancies. Risk assessment for maternal infection during pregnancy is especially important during epidemics when sero-conversion rates are high.

Keywords: Parvovirus B19; Pregnancy; Nonimmune fetal hydrops; Anemia

Contents

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1. Introduction

Parvovirus B19 particles were first described in 1975 by Cossart, an Australian virologist working in London [1]. While checking normal blood donor's serum in an assay for hepatitis B she noticed an anomalous reaction in position 19 plate B. The virus discovered in human blood was called Parvovirus from the Latin word parvum meaning small. She described the particles in the sera of nine healthy blood donors and two patients, and found that 30% of adults possessed specific antibodies to this virus.

A disease was linked to Parvovirus B19 first by Pattison et al. who found either virus specific antibodies, or the virus itself in samples from children suffering from sickle cell anemia that developed transient aplastic crisis [2].

The more common disease caused by this virus was described by Anderson et al. [3], who found that this virus caused erythema infectiosus occurring mainly among children. An outbreak of the disease took place in a primary school in London. Among each of 36 cases investigated virologically the illness was associated with Parvovirus B19 infection. Pre-existing antibodies to Parvovirus B19 were correlated with protection from erythema infectiosum in 16 of 17 close family contacts of the patients. Other common diseases associated with this virus are: arthropathy in normal adults; transient aplastic cri-

sis in patients with increased erythropoesis; persistent anemia in immuno-deficient and immuno-compromised patients and in the fetus, hydrops fetalis and congenital anemia [4].

2. Parvovirus B19

2.1. Taxonomy

This group of viruses includes many pathogenic animal viruses [5].

Parvovirinae (viruses from vertebrates)	Densovirinae (viruses from insects)
Parvovirus	
Minute virus of mice (MVM)	
Rat autonomous Parvovirus H1	
Aleutian mink disease virus	
Dependovirus	
Adeno associated virus (AAV)	
Erythrovirus	
Parvovirus B19	
Parvovirus V9	
Parvovirus from rhesus and piglet macaques	

The Parvoviridae family is divided into two sub-groups: the Parvovirinae infecting vertebrate cells, and the Densoviridae infecting invertebrate cells. The Parvovirinae are further sub-divided into three groups: (1) genus *Parvovirus* that replicate autonomously, (2) genus *Dependovirus* that need helper viruses to replicate, and (3) genus *Erythrovirus* that need erythroid cells to replicate.

Parvovirus B19 belongs to the genus *Erythrovirus*.

2.2. Morphology

The virion has a structure composed of two proteins and a single strand DNA molecule. It is composed of 60 copies of capsomer, and both negative and positive strands of DNA are packaged [6]. The limited DNA content and the absence of a lipid envelope makes this virus resistant to heat (56 °C for 60 min) and lipid solvents [7]. The inactivation is achieved by beta propiolactone, gamma irradiation and formaldehyde [8].

2.3. Genetics

The Parvovirus B19 genome has two open reading frames; with the single Nonstructural Protein 1 (NS1) encoded by genes on the left side of the genome, and Viral Protein 1 (VP1) and Viral Protein 2 (VP2), the two capsid proteins, by genes on the right side. Transcription produces at least nine overlapping mRNA transcripts, all initiating from the single P6 promotor at the left side of the genome [9].

A large number of isolates have been sequenced, but they all show only 6% divergence among themselves. The NS1 is well conserved while the VP1 and VP2 show some variability of 2–3% [10]. Lately few new variants were identified whose sequence diverged more than the divergence found within the B19 group Nguyen et al. detected an erythrovirus (V9) markedly different 11–14% divergence from Parvovirus B19 [11]. The same group found later the A6 virus who diverged 12% from B19 and 8% from V9 [12]. Hokynar found the K71 variant that differed within the protein-coding region from the B19 reference sequences by 10.8% and from the V9 variant by 8.6% and within the noncoding region [13]. In these cases serological tests may fail to demonstrate a response characteristic of acute B19 infection. A recent publication reported the development of a recombinant VP1 antigen (VP1u and VP2 regions) from prototype genotype strain V9 from blood donors in Ghana. All 10 Parvovirus B19 antigen-reactive samples and 10 of 26 nonreactive samples (38.5%) were reactive with the V9 virus antigen-derived enzyme immunoassays. However, a significantly lower level of reactivity was observed for the samples reactive with V9 antigen only for those also reactive with Parvovirus B19 antigen. Parvovirus B19 based antibody assays that failed to detect the Ghanaian samples containing antibodies to V9 did not fail to detect cases of persistent infection. This study indicates a potential African origin of V9 and considerable shortcomings in the tools currently used to diagnose erythrovirus infection [14].

There is no correlation between special sequences and specific disease symptoms [15].

2.4. Proteins

The capsid proteins VP1 and VP2 are encoded by overlapping reading frames. Each capsid consist of an icosahedral structure with a total of 60 capsomeres, the major one being VP2 accounting for 96% of the total capsid proteins. VP1 and VP2 can be expressed in bacterial, mammalian and insect cells. In mammalian and insect cells expression of VP2 can self-assemble in the absence of viral DNA to produce virus like particles that are physically, antigenically and immunogenically similar to native virions [9,16,17].

NS1 is the main nonstructural protein in Parvovirus B19. Its cytotoxicity was explained by possessing site-specific-DNA-binding, DNA nicking, ATPase, transcriptional and helical activities. Moffatt et al. [18] indicated that NS1 of Parvovirus B19 induces cell death by apoptosis in at least erythroid-lineage cells by a pathway that involves caspase 3, whose activation may be a key event during NS1-induced cell death. Other open reading frames have been discovered but the roles of the derived proteins are not known.

2.5. Viral life cycle

Like other nonenveloped DNA viruses the Parvovirus B19 life cycle includes the following stages: binding to host cell receptor, internalization, translocation of the genome to the host nucleus, DNA replication, RNA transcription, assembly of capsid, packing the genome and cell lysis with release of the mature virion [4].

The P antigen on the red blood cell is a cellular receptor of the Parvovirus B19. It is a globoside that contains two common antigens: P1 and P and one less common Pk. Only 1 in 100,000 humans is P negative and those persons are resistant to Parvovirus B19 infection [19].

Parvovirus B19 is a potent inhibitor of the erythroid cell differentiation and is cytotoxic for erythroid precursor cells. Direct toxic cell injury or cytolytic effect of Parvovirus B19 as well as Parvovirus B19 – induced apoptosis may be involved in the pathogenesis of erythroid aplasia in high risk patients. The Parvovirus B19 induces a cell cycle arrest at either Gap 1 (G1) or Gap 2 (G2) phase. Chisaka et al. [20] found that NS1 protein of Parvovirus B19 plays a critical role in the G1 arrest and apoptosis induction, while the G2 arrest is induced even in the absence of Parvovirus B19 gene expression, suggesting the possible involvement of Parvovirus B19 viral DNA in the G2 arrest.

The cytopathic effect of the Parvovirus B19 infection on the erythroid progenitor cells is manifested as giant pronormoblasts. Transmission electron microscopy of the cells reveals cytotoxic ultrastructural changes that include pseudopod formation, marginated chromatin and virus particles in the nucleus [21]. Boctor and Schreiber described a 32 years old AIDS patient with severe anemia where the giant pronormoblasts had diameter five times that of the neighboring lymphocytes, and a lacy nuclear pattern suggestive of megaloblastic or dysplastic development [22].

2.6. Culture

Parvovirus B19 can be grown in culture with difficulty, and there is no good animal model for it. Chisaka et al. developed transgenic mouse lines that may provide an animal model for human nonimmune hydrops fetalis [23]. Gallinella et al. showed that the Parvovirus B19 can be replicated in cynomolgus monkey bone marrow and offered it as a suitable model for pathogenesis studies of the virus [24].

3. Clinical findings and immune response

Following infection, specific immunoglobulins IgM, IgG and IgA are produced. The clinical course is biphasic in correlation with the immune response. One week after the infection, a mild illness appears during virus excretion from the respiratory tract, presenting with pyrexia, malaise, myalgia and itchiness. The predominant immune response in healthy individuals at this stage is humoral and consists of IgM against VP2. The IgM rises at 10–12 days post-infection and peaks when viral level is highest, it lasts for about 3 months from the primary illness. A second phase of symptoms commence about 17–18 days from infection, characterized by rash, itchiness, or arthralgia. About 2 weeks from inoculation IgG against VP1 is detected and presumably lasts for life [25]. IgA is detected in about 90% of infected individuals and may play a role in protection against infection by the nasopharyngeal route [26].

Bluth et al. demonstrated in an 8 years old boy IgE anti-Parvovirus antibodies and presumed that IgE may play a role in anti-viral immunity perhaps in conjunction with CD23+ cells [27].

A cellular immune response must be present to illicit the humoral response.

Corcoran et al. showed that B cell memory is established and maintained against conformational epitopes of VP2 and against linear epitopes of VP1 but not against linear epitopes of VP2 [28]. T lymphocyte response against NS1 protein in human Parvovirus was elicited by Klenerman et al. [29].

3.1. Epidemiology

Parvovirus B19 infection is global. It is common in childhood, continues at a low rate throughout adult life, and by the time they are elderly, most people are sero-positive [30]. Koch and Adler found an annual sero-conversion of 1.5% among women at childbearing age unrelated to their occupation [31].

The peak incidence of erythema infectiosum is in late winter and early spring. Small epidemics at intervals of a few years are typical. The virus is spread by respiratory droplets [32], by blood products especially pooled factor XIII and IX concentrates [33] and trans-placentally during pregnancy.

3.2. Laboratory tests

3.2.1. Cytopathology

Giant pronormoblasts in either bone marrow or peripheral blood is suggestive but not diagnostic of Parvovirus B19 [22].

3.2.2. Virus detection

Parvovirus B19 can be detected by isolation of viral DNA by direct hybridization or by the polymerase chain reaction (PCR).

The direct hybridization assay detects all known variants of Parvovirus B19 but there is a detection limit of about 10^5 genome copies/ml, or 1 pg of Parvovirus B19 DNA [34]. PCR is more sensitive but possesses a great propensity for contamination. It can detect 1–10 fragments of Parvovirus B19 DNA or 10–100 genome copies of viral particles. PCR is 100–1000 times more sensitive than direct hybridization [35].

The presence of low levels of Parvovirus B19 DNA alone may be detectable for extended period of time in serum, synovial membranes and bone marrow.

3.2.3. Immunological assays

IgM assays are reliable to detect a current or recent infection for about 2–3 months in immunocompetent persons [36]. IgG rises about 10–14 days post-infection and presumably lasts for life [37]. There was a highly significant correlation ($P < 0.001$) between the relative amounts of low avidity B19 specific IgG antibodies and time after onset of illness. This finding allows the detection of IgG to be used for diagnosing acute infection [38].

4. Clinical picture

4.1. Healthy individuals

4.1.1. Asymptomatic infection

Asymptomatic sero-conversion following viremia with Parvovirus B19 is common in both children and adults.

4.1.2. Erythema infectiosum (fifth disease)

Erythema infectiosum is the most common clinical manifestation of Parvovirus B19 during childhood. After a prodromal period of about 2 weeks, many times unnoticed, but sometimes including: fever, coryza, headache and nonspecific gastrointestinal symptoms, a rash erupts. The rash is characterized by red cheeks with circumoral pallor (slapped cheeks). The rash consists of maculae that undergo central fading which extends during the next 1–4 days to the trunk and limbs. It may include vesicles and be itchy and scaly. The rash is likely due to the formation and deposition of immune complexes in the skin and elsewhere [6]. Exposure to sun light, heat [39], emotion and exercise [6] may intensify the rash.

4.1.3. Arthropathy

Arthralgia and arthritis are the most common manifestations of Parvovirus B19 in adults – it affects about 60% of adult females compared to 30% of the adult males [40], and only about 10% of the infected children [41]. The symptoms coincide with the appearance of circulating antibodies. The acute polyartheritis involves the metacarpophalalangeal joints, wrists, knees and ankles. The arthroparhy may last from few weeks to years and may mimic the clinical picture of rheumatoid arthritis but joint destruction does not occur [42].

4.1.4. Hematologic disorders: thrombocytopenia

Parvovirus B19 infection may precede the appearance of idiopathic thrombocytopenic purpura (ITP) in children [43]. Parvovirus B19 can cause in vitro bone marrow suppression by inhibiting the megakaryocytic colony formation [44], or by increased platelet destruction [45].

4.1.5. Neurologic disorders

Meningoencephalitis can be associated with infection with Parvovirus B19. Barah et al. estimated that the incidence of undiagnosed meningoencephalitis that can be attributed to Parvovirus B19 infection during an outbreak year in the United Kingdom is 4.3% [46]. Chronic fatigue syndrome (CFS) may also follow Parvovirus B19 infection [47].

4.1.6. Hepatitis

Transient self-limited elevation of liver aminotransferases may be associated with Parvovirus B19 infection [48]. Detection of human Parvovirus B19 DNA was reported in livers from patients requiring transplantation for acute fulminant liver failure [49] but it is still not clear whether Parvovirus B19 is the cause of the hepatic failure or an incidental finding.

4.1.7. Myocarditis

Parvovirus B19 has been identified as a possible cause of myocarditis and heart failure in both children and adult patients. Parvovirus B19 DNA is present within the myocardium of patients with suspected myocarditis and idiopathic left ventricular dysfunction and can be detected and quantified in endomyocardial specimens via real time PCR [50]. Schowengerdt et al. reported that Parvovirus B19 genome was found through PCR in 0.8% of children suffering from myocarditis, in 3% of children suffering from cardiac transplant rejection, and none in control cases [51]

4.1.8. Vasculitis

Parvovirus B19 has been implicated in various vasculitic syndromes including Henoch Schonlein Purpura (HSP), Wegener's Granulomatosis and microscopic polyarteritis [52]. These are mostly single case reports without corresponding case control studies.

5. Immunocompromized host

5.1. Aplastic crisis

5.1.1. Transient

Transient aplastic crisis in Parvovirus B19 infection is involved in short life span of red blood cells. There is an abrupt cessation of erythroid progenitors in the bone marrow with the disappearance of reticulocytes in the circulatory blood with normal granulopoesis and megakaryopoesis [20]. Any person suffering from decreased red blood cell production or increased destruction or loss, may be in danger of developing aplastic crisis following Parvovirus B19 infection [4]. Acute red cell aplasia was described in patients suffering from a variety of syndromes accompanied by short RBC survival, like those with iron deficiency anemia [53], congenital dyserythropoetic anemia [54], thalassemia [55], GSPD [56,57], hemoglobinopathies [55], sickle cell anemia [58,59] and many other conditions. Concurrent thrombocytopenia, neutropenia and rarely pancytopenia can accompany the red blood cell aplasia. Reticulocytes in normal individuals can fall to zero but hemoglobin levels usually remain stable because the erythrocyte has a long life span, compared

to individuals with short life span of the red blood cells that depend on normal reticulocytosis. The aplastic crisis happens during the viremia and disappears after anti-viral antibodies clear the infection. After the aplastic crisis the patient gets a life long immunity to Parvovirus B19. The aplastic crisis can be fatal and may be accompanied by congestive heart failure, cerebrovascular accidents, acute splenic sequestration, weakness and lerhargy [60].

5.1.2. Chronic red blood cell aplasia

In the absence of anti-viral immunity pure red blood cell aplasia can persist. Predisposing conditions include immune deficiency syndromes, acute and chronic leukemia [61], lymphomas [62], neoplastic disorders, HIV infection [63]. Severe combined immune deficiency (SCID) [64], bone marrow, organ transplantation and immunosuppressive therapy [61]. Parvovirus B19 infection can mimic a leukemic relapse or therapy induced cytopenia when anemia and thrombocytopenia develops. There is severe anemia without reticulocytes in the peripheral blood and in the bone marrow. The finding of giant pronormoblasts is typical [65]. The antibodies to Parvovirus B19 are low or absent and the viral load is high [66].

5.1.3. Virus associated hemophagocytic syndrome (VAHS)

This is usually a benign self-limited condition accompanying viral, bacterial, rickettsial, fungal and parasitic infections. Parvovirus B19 was found in bone marrow of some of the patients suffering from the syndrome [67], in many of them an underlying immune-suppression condition exists. It is characterized by histiocytic hyperplasia, hemophagocytosis, and cytopenia.

6. Pregnancy

Parvovirus B19 infection during pregnancy can cause severe anemia, nonimmune hydrops fetalis (NIHF), a variety of symptoms of fetal damage and fetal death. These manifestations, however, seem to be rare and in several of the reported cases a causal relationship between infection with Parvovirus B19 and the fetal damage has not been definitely established. The risk assessment for maternal infection during pregnancy is especially important during epidemics.

6.1. Epidemiological studies

Numerous investigations among pregnant women either in normal or at risk populations showed low incidence of trans-placental transmission. The infectivity rate was evaluated either by IgM tested in the mother or offspring, or by DNA analysis, histopathology and immunohistochemistry. The prenatal diagnosis by IgM in fetal cord blood was found to have low sensitivity [68] (Table 1).

Most women are already immune to Parvovirus B19 before pregnancy, as seen here by the high rate of IgG levels in maternal serums evaluated, between 24% as described by Di Domenico et al. [69] to 84% in the series described by Barros De Freitas et al. [70]. Since Parvovirus B19 infection can cause severe morbidity and mortality, the virus is part of the routine work up of complicated pregnancies. During pregnancy the risk of acquiring Parvovirus B19 infection, is quite low, ranging from 0 [71,72] to 16.5% [73] mainly with normal outcome [69,70,74,75].

The prevalence of maternal infection is higher during epidemics, with sero-conversion rate between 3% [76] to 34%. [77]. The risk of adverse fetal outcome is increased if maternal infection occurs during the first two trimesters of pregnancy [73,78,79,80] but may also happen during the third trimetster [81]. In a cohort of cases studied by Yahegashi the source of infection as was the mother's older child in six out of 10 cases and children at a kindergarten where the mothers worked in two cases. The interval in this cohort between the onset of infection and the diagnosis of NIHF ranged from 2 to 6 weeks [82].

6.2. Pathogenesis

Transmission of Parvovirus B19 can lead to fetal infection. The virus infects the liver which is the main site of erythrocyte production in the embryo [80]. The fetus is more vulnerable during the second trimester when the liver is the main source of hematopoetic activity and the half life of red blood cells is short, 50–75 days compared with later hematopoetic stages. Yhaegashi et al. established an in vitro infection experimental system of Parvovirus B19 using erythroid lineage cells derived from fetal liver. They demonstrated that the erythroid lineage cells proved to be appropriate targets for Parvovirus B19 virus and that the infection could induce apoptosis of infected cells. To analyze the cytotoxic mechanism they established a stringent regulatory expression system of the NS1 protein encoded by the Parvovirus B19 genome and indicated that the apoptosis induced by B19 was directly caused by the NS1 protein [83]. The severe anemia can lead to congestive heart failure and the development of hydrops fetalis. Hydrops fetalis is defined as the presence of fetal generalized subcutaneous tissue edema accompanied by serous effusion in one or more body cavities. Fetal hydrops was first considered to be primarily the consequence of severe maternal isoimmunization to fetal blood group antigens foreign to the mother, most commonly those in the Rhesus (Rh) family. Later, recognition of factors other than isoimmune hemolytic disease that can cause or be associated with fetal hydrops led to the use of the term nonimmune hydrops fetalis (NIHF) to identify those cases in which the fetal disorder was caused by factors other than isoimmunization. The ultrasonographic signs of general edema include: subcutaneous edema, pleural effusion, pericardial effusion, ascites and placental edema [20]. The P antigen expressed on fetal cardiac myocytes enables the Parvovirus B19 to infect myocardial cells [84] and produce

Table 1
Prevalence of Parvovirus B19 infection among normal and at risk pregnant women

Population	Reference authors	Number of pregnancies studied	Prevalence of women or offspring infected with Parvovirus B19	Method of diagnosis	Outcome of pregnancy
Normal	Baschat et al. (2003) [71] prospective	686 women	0	PCR-amniotic fluid	
	Di Domenico et al. (2002) [69] prospective	647 newborns	IgG-156/647 – 24%, PCR-3/491 – 0.6%	IgG, IgM, PCR-cord blood	Two years follow-up all normal
	Tolfvenstam et al. (2001) [72] prospective	53 women	0	PCR, histopathology, immunohistochemistry in placenta	
	Barros De Freitas et al. (1999) [70] prospective	300 women	IgG-253/300 – 84%, IgM and IgG-5/47 – 10.6%, PCR – 0	IgG, IgM, maternal blood, PCR in serum of IgM pos offspring	All newborns – normal
	Makhseed et al. (1999) [73] prospective	1047 women	IgG – 53.3%, IgM – 2.2%, sero-conversion – 16.5%	IgG, IgM maternal serum	Fetal loss – 15.4%, all during first and second trimester
	Skjoldebrand-Sparre et al. (1996) [123] prospective	457 women	IgG-369/457 – 81%, sero-conversion-6/88 – 6.8%, boosted-28/369 – 7.5%, PCR in placental fetal death-pos	IgG, IgM, PCR in maternal serum. PCR in one placenta-fetal death	One fetal loss – infected embryo
	Gratacos et al. (1995) [74] prospective	1610 women under 28 w	IgG-564/1610 – 35%, IgM-60/1610 – 3.7%, PCR in abortions-1/60 – 1.6%	IgG, IgM maternal serum, PCR-fetal tissues	One fetal loss – infected embryo, 1 year follow-up all newborns – normal
	Schoub et al. (1993) [124] prospective	1967 women	IgM-64/1967 – 3.2%	IgG, IgM maternal serum	
	Friese et al. (1991) [75] prospective	512 women	IgG – 29%, IgM-10/363 – 2.7%	IgG, IgM maternal serum	All newborns – normal
	Enders et al. (1990) [125] prospective	2279 women	Seronegative – 41%, IgG – 54%, IgM-114/2279 – 5%, sero-conversion: Trim I – 32%, Trim II – 54%, Trim III – 14%	IgG, IgM maternal blood	Fetal loss – 9, hydrops fetalis – 3, spontaneous abortion – 6
	Woernle et al. (1987) [77] prospective	19 women	0	IgM maternal and offspring serum	
During epidemics	Jensen et al. (2000) [126] prospective	3147 women out of 3596 pregnancies	IgG before 24 weeks – 66%, sero-conversion – 10.3%	IgG, IgM maternal and cord blood	
	Harger et al. (1998) [127] prospective	618 women	IgG-307/618 – 50%, sero-conversion-52/259 – 20%	IgG, IgM maternal serum	All newborns – normal
	Kerr et al. (1994) [76] retrospective	2400 women 12 w	IgM-8/24000 – 3%	IgM maternal serum	One IUFD – 26 w seven newborns – normal
	Cartter et al. (1991) [128] prospective	796 women	IgG-419/796 – 52%, IgM-23/377 – 6.1%	IgG, IgM maternal serum	
	Woernle et al. (1987) [77] prospective	12 women	IgM-4/12 – 34%	IgM maternal and offspring serum	One infected newborn, fetal loss: hydrops fetalis three normal newborns
Nonimmune hydrops fetalis (NIHF)	Ismail et al. (2001) [129] retrospective	63 cases, nonimmune – 55	8/55 – 14.5%		
	Kailasam et al. (2001) [130] prospective	6 cases during Parvovirus B19 epidemic	IgM mother-6/6 – 100%, IgM-offspring-3/6 – 50%	IgM maternal and fetal blood	Three intrauterine transfusions: two resolved, one fetal loss
	Kaiser et al. (2000) [131] retrospective	15 cases	4/15 – 26.6%	Immunohistochemistry	All fetal loss
	Yaegashi et al. (1999) [132] prospective	168 cases	13/168 – 7.7%, 12/13 cases during two epidemics	IgG IgM in fetal serum	

Table 1 (*Continued*)

Population	Reference authors	Number of pregnancies studied	Prevalence of women or offspring infected with Parvovirus B19	Method of diagnosis	Outcome of pregnancy
	Essary et al. (1998) [133] prospective	29 NIHF	1/29 – 4%	PCR in fetal tissues	All fetal loss
	Lenkiewicz et al. (1998) [134] prospective	29 cases	9/29 – 31%	IgG, IgM, PCR maternal and fetal tissues	All fetal loss
	Wattre et al. (1998) [78] retrospective	79 cases	IgM-3/79 – 3.8%, PCR-11/79 – 13.9%, infection: 17–28 weeks gestation	IgG, IgM maternal blood PCR-amniotic fluid, fetal tissues	2/11 – 18% resolved after intrauterine blood transfusion
	Kyriazopoulou et al. (1997) [135] prospective	9 cases	1/9 – 11%	IgG, IgM, PCR in maternal serum and amniotic fluid	Twin pregnancy: one normal, one NIHF-neonatal death
	Jordan et al. (1996) [136] retrospective	57 NIHF cases	6/34 – 17.6%	PCR placenta and fetal tissues	
	Yaegashi et al. (1994) [79] prospective	42 NIHF cases	4/42 – 9.5%, all during an epidemic between 20 and 23 weeks gestation	IgG, IgM, PCR maternal and fetal serum	
	Porter et al. (1988) [137] retrospective	13 NIHF cases	4/13 – 30.7%	PCR in embryonal lung tissue	
Mortality and or severe morbidity	Satosar et al. (2004) [138] retrospective	60 cases	2/60 – 3.3%	Viral DNA in placenta	Eleven cases fetal or neonatal death 49 cases severe respiratory and neurologic disease
	Genen et al. (2004) [139] prospective	33 cases severe morbidity unknown cause	1/33 – 3%	In situ hybridization/PCR placenta	All poor neonatal outcome
	Norbeck et al. (2002) [98] retrospective	92 fetal loss after 22 weeks gestation	13/92 – 14%, 2/13 NIHF	PCR fetal tissues	All fetal loss
	Nyman et al. (2002) [80] prospective	Abortions: first trimester – 36, second trimester – 64	First-1/36 – 2.7%, second-8/64 – 12.5%, third-0/53 – 0%	PCR in placenta	All fetal loss
	Tolfvenstam et al. (2001) [72] pro	47 IUFD after 22 w, 37 miscarriages. Under 22 w	IUFD-7/47 – 14.8%, miscarriages-2/22 – 9%	PCR in placental and fetal tissues, histopathology, immunohistochemistry	One fetal loss NIHF
	Skjoldebrand-Sparre et al. (2000) [81] prospective	93 fetal losses during third trimester	7/93 – 7.5%	PCR placenta and fetal tissues, immunohistochemistry, maternal serology	All fetal loss
	Xu et al. (1998) [140] prospective–retrospective	116 cases spon abortions	34/116 – 29.3%	PCR in fetal tissues	All fetal loss
	Sifakis et al. (1998) [68] prospective	102 cases missed abortions	IgM-10/102 – 9.8%, PCR-2/102 – 2%	IgM maternal blood PCR fetal tissues	
	Wattre et al. (1998) [78] retrospective	70 cases spontaneous abortions or NIHF	10/70 – 14.2%	PCR, in situ hybridization fetal tissues	Two cases of NIHF resolved after intrauterine blood transfusion
	Wang et al. (1997) [141] prospective–retrospective	105 spontaneous abortions	26/105 – 24.7%, fetal tissues		
	Rogers et al. (1993) [142] retrospective	80 cases spontaneous abortions before 20 weeks gestation	IgM-5/80 – 6.2%, PCR-2/5 – 40% of IgM pos	IGg, IgM maternal serum PCR fetal tissues	All fetal loss
Prematurity	Koga et al. (2001) [143] prospective	76 cases	0	IgG, IgM, PCR in cord blood	
Ultrasound abnormalities	Dieck et al. (1999) [144] prospective	57 women	IgM-7/58 – 12%, PCR-16/58 – 27.5%	IgM, PCR fetal serum	
Hyperechogenic bowel	Yaron et al. (1999) [105] retrospective	79 cases	1/79 – 1.2%		
Liver calcifications	Simchen et al. (2002) [145] prospective	61 pregnancies	1/61 – 1.6%	IgM maternal	Normal newborn

myocarditis [85]. The myocarditis caused by the Parvovirus B19 can worsen the high output cardiac failure [86].

Parvovirus B19 infection may be associated with cases of nonhydropic intrauterine fetal death. The main targets for B19 replication are the erythroid precursor cells that posse's globoside, the cellular receptor necessary for B19 infectivity. Other nonerythroid cells that can express this receptor are megakaryocytes, endothelial cells, cardiac myocytes and placental trophoblast cells [87].

Placentas from 26 pregnancies with documented maternal and/or congenital B19 infection, 14 with poor outcomes and 12 with good outcomes were examined by Jordan et al. [87] for evidence of apoptosis. The results of the immunohistochemical analysis revealed a significant increase in apoptotis among placental villous trophoblast cells from Parvovirus B19-complicated pregnancies with poor outcomes compared to Parvovirus B19-complicated pregnancies with good outcomes. Inflammation-mediated cellular immune responses within placentas from women whose pregnancies were complicated with Parvovirus B19 infection were an increase in CD3-positive T cells and IL2 levels The presence of an inflammatory response was not associated with an increased risk of adverse pregnancy outcome [88].

Parvovirus B19 particles can also be found in different embryonic tissues [89] and lead to a large variety of clinical manifestations without clear association to the viral existence (Table 2).

The risk of fetal complications depends largely upon the gestational age at the time of maternal infection with Parvovirus B19. It seems that the highest risk for fetal loss is if maternal infection occurs during weeks 9–16 of pregnancy, is reduced with infection in the second half of pregnancy, and rare if infection occurs in the last 2 months [90,82,91].

Trans-placental Parvovirus B19 infection occurs in about 30% [92] to 50% of infected, previously sero-negative mothers with most neonates born normal [93]. The interval between maternal Parvovirus B19 infection and diagnosis of hydrops fetalis varies between 1 and 20 weeks [82,90,91,94] the median interval is about 3 weeks. Early pregnancy loss

Table 2
Outcome of Parvovirus B19 infection during pregnancy

References	Number of infected women	Outcome of pregnancy	Diagnosis	Prognosis of offsprings
Enders et al. (2004) [91] prospective	1018 cases	NIHF-40/1018 – 3.9%; intrauterine blood transfusion 16/40 – 40%, fetal loss-64/1018 – 6.3%. All infected before 20 weeks gestation	Serology, DNA	Born alive-954/1018 – 93.7%, NIHF-28/40 – 70% born alive
Nunoue et al. (2002) [94] retrospective	13 cases	NIHF-3/13 – 23%; 23, 21, 26 weeks gestation post-infection at 3, 16, 19 weeks gestation. Spontaneous abortions-2/13 – 15.3%; 5, 16 weeks post-infection	Serology, DNA	Born alive: all normal-8/13 – 61%
Li et al. (2001) [146] prospective	67 cases	Fetal loss-4/67 – 7.4%, anencephaly-1/67 – 1.5%	DNA	
Schild et al. (1999) [100] retrospective	37 cases	NIHF-35/37 – 95% (referral center). Fetal loss-5/37 – 13.5%, 30/35 intrauterine blood transfusions	DNA	Neonatal death-1/37 – 2.7%. Born alive: normal-31/37 – 83.8%
Yaegashi et al. (1999) [132] prospective	48 cases	NIHF-8/48 – 16.6%. Fetal loss-1/48 – 2%. All infected under 16 weeks	Serology, DNA	Fetal loss-7/47 – 14.6%
Koch et al. (1998) [93] prospective	43 cases	22/43 – 51% infected embryo	Serology, DNA	Born alive: normal-43/43 – 100%
Miller et al. (1998) [90] prospective	427 cases	NIHF – 2.9% between 9 and 20 weeks. Fetal loss – 9%	Serology, DNA	Born alive: normal-7 years follow-up-367/427 – 86%
Odibo et al. (1998) [147] retrospective	38 cases	NIHF-3/38 – 7.9%, intrauterine transfusions all 3	Serology	Born alive: normal-38/38 – 100% including three NIHF
Rodis et al. (1998) [148] retrospective	113 cases	NIHF-1/113 – 0.9%, fetal loss-4/113 – 3.5%, ectopic pregnancy-1/113 – 0.9%	Serology	Born alive-107/113 – 95%, developmental delay – 7.3% (no statistical significance)
Bruu et al. (1994) [149] retrospective	19 cases	Fetal loss-2/19 – 10.5%	Serology	Born alive: normal-15/19 – 79%, born alive: hyperactivity-1/19 – 5.3%
Guidozzi et al. (1994) [96] prospective	64 cases	Fetal loss-1/64 – 1.6%	Serology	Born alive: normal-61/64 – 95.3%, born alive: small for gestational age-2/64 – 3.2%
Levy et al. (1990) [97] retrospective	180 cases	Fetal loss-44/180 – 24%, 1–12 weeks post-infection	Serology	
Public Health Laboratory Service Working Party. Bmj 1990 [92] prospective	190 cases	Fetal loss-30/186 – 16%, elective abortion-4/190 – 2.1%, transplacental transmission – 33%	Serology	Born alive: normal-156/186 – 84%
Rodis et al. (1990) [150] prospective	39 cases	Fetal loss-2/39 – 5.1%	Serology	Born alive: normal-37/39 – 94.9%

is rarely accompanied by hydrops fetalis [95] Nonimmune hydrops fetalis was the main complication in 0.9% [32,92] to 23% [93] of pregnancies among proven maternal infections with Parvovirus B19. A maximal risk of 7.1% for hydrops fetalis has been observed for pregnant women who acquire Parvovirus B19 infection during gestational week 13 and 20 [91]. Fetal loss occurs in 1.6% [96] to 24% [97]. Nonhydropic fetal loss in late gestation complicated by Parvovirus B19 was described [72,98] but is controversial [99]. In a prospective study nonhydropic stillbirth was rare among women infected with Parvovirus B19 [91]. Intrauterine packed red blood cells transfusions for cases of hydrops fetalis improves the anemia and may lead to resolution of fetal heart failure and edema [100,101]. The hydrops fetalis may resolve spontaneously while in utero [101]. Children having survived successful intrauterine transfusion for Parvovirus B19-induced fetal anemia and hydrops, have a good neurodevelopmental prognosis [102].

Persistent Parvovirus B19 infection can be the reason for congenital anemia with characteristic findings of Diamond-Blackfan anemia. The blood smear contains normochromic, either normocytic or macrocytic erythrocytes with partial maturation arrest at the level of proerythroblasts, leading to reticulocytopenia. Three children were reported with congenital anemia after intrauterine infection with Parvovirus B19. All the fetuses developed hydrops fetalis that was treated by blood transfusion. In all three, sera lacked Parvovirus B19 but viral DNA was found in bone marrow. One child died and Parvovirus B19 was found in various tissues. In the other two cases, virus could no longer be detected after therapy but the patients remained persistently anemic [103]. It may be that exposure of the fetal immune system to virus early in pregnancy may cause tolerance to the viral proteins and absence of an immune response in spite of persistent viral infection, allowing persistent suppression of red cell production in the bone marrow [20]. The prenatal diagnosis by IgM in fetal cord blood has low sensitivity [68].

7. Fetal morbidity and mortality as observed from case reports

7.1. Neurology

Katz et al. [104] reported two cases of congenital hydrocephalus. One infant also had myocardial infarction and splenic calcifications, while the other suffered from central nervous system scarring.

Post mortem examination of a fetus infected with Parvovirus B19 revealed multinucleated giant cells of macrophage and microglia lineage and many small calcifications around the vessels, predominantly in the cerebral white matter. Parvovirus B19 genome DNA was detected in the nucleus of the multinucleated giant cells and solitary endothelial cells by PCR.

7.2. Gastrointestinal system

7.2.1. Hyperechogenic bowel

Parvovirus B19 infection was diagnosed in a fetus with hyper echogenic bowel by Yaron et al. [105].

7.2.2. Meconium peritonitis

Zerbini et al. [106] reported four cases of meconium peritonitis in hydropic fetuses with laboratory diagnosis of B19 infection. Meconium peritonitis was also found in association with hydrops fetalis in Parvovirus B19 infected fetuses by Schild et al. [107] and Zerbini et al. [108]. Meconium peritonitis in a nonhydropic fetus was reported by Bernard et al. during the second trimester of pregnancy [109].

7.2.3. Fetal liver calcifications

Simchen et al. described a neonate with isolated fetal liver calcifications in association with maternal Parvovirus B19 infection [145].

7.3. Opthalmology

A combination of hydrops fetalis secondary to Parvovirus B19 infection and congenital corneal opacification was seen by Plachouras et al. [110].

Hartwig et al. [111] described aphakic eyes from human embryos infected with Parvovirus B19 during early pregnancy.

Ocular malformations and extensive inflammatory reactions in all fetal and placental tissues were found in an elective abortion of Parvovirus B19 infected embryo [89].

7.4. Cardiac malformations

Fetal Parvovirus B19 infection has been reported in association with myocarditis.

Wang et al. reported the presence of Parvovirus B19 DNA in cardiac tissues at autopsies, 5/29–17.2% of congenital heart specimens were positive while all 30 controls were negative [112]. White et al. [113] described an infected neonate with Ebstein's anomaly who also had portal tract fibrosis with proliferation of bile ducts Rogers et al. noted a case of muscular ventricular septal defect in one of five cases of Parvovirus infection complicated by hydrops fetalis [114].

7.5. Multiple structural defects

Parvovirus B19 DNA was detected in fetal tissues in a fetus with bilateral cleft lip and palate; micrognathia; and arthrogryposis possibly as a consequence of intrauterine infection [115].

7.6. An increased fetal nuchal translucency

Markenson et al. reported a fetus with increased nuchal translucency and a normal karyotype and outcome, in which

Parvovirus B19 was detected by PCR in the amniotic fluid [116].

Fetal abnormalities associated with Parvovirus B19 are rare. Both direct infection of fetal organs and vascular inflammation have been documented in association with Parvovirus B19 [104]. There is no evidence that Parvovirus B19 is a significant teratogen in man but the possible teratogenicity of the Parvovirus B19 needs to be evaluated in more studies.

8. Treatment

Erythema infectiosum and arthropathy are self-limited conditions requiring only symptomatic relief. Acute red cell aplasia is also transient but may need support by repeated blood transfusions to prevent complications of severe anemia. Persistent red cell aplasia usually improves by treatment with intravenous immunoglobulins as source of neutralizing antibodies since most adult population is sero-positive to Parvovirus B19 [117].

During pregnancy intrauterine blood transfusions of red blood cells can improve fetal survival. Cordocentesis allows precise assessment of fetal anemia which can then be corrected by blood transfusion. Under this regimen, the outcome proved favorable in the majority of fetuses, even those that were severely anemic. Packed red cell transfusion was performed in 30 patients with significant fetal anemia. The fetal hemoglobin values ranged from 2.1 to 9.6 g/dl. The survival rate was 83.8% [100]. The observed survival rate among 13 cases with severe hydrops fetalis who received intrauterine transfusion was 11/13–84.6%. All the nontransfused fetuses with severe hydrops fetalis died [91]. Among 12 of 38 cases of hydrops fetalis alive at the first abnormal ultrasound examination, who received intrauterine transfusions only 3/12–25% died, while among 26 that did not receive intrauterine transfusions 13 died – 50% [118].

High-dose intravenous gamma globulin was used in placental exchange transfusion to prevent hydrops fetalis during pregnancy in an infected woman [119].

Human IgG monoclonal antibodies with potent neutralizing activity were generated from two healthy donors and one human immunodeficiency virus type 1-seropositive individual with high serum titers against Parvovirus. These IgG monoclonal antibodies could be suggested as immunotherapy of chronically Parvovirus B19 virus-infected individuals and acutely infected pregnant women [120].

9. Vaccine

A specific vaccine is important in order to prevent aplastic crises in patients with underlying disorders, and pregnancy complications in sero-negative women at child-bearing age. Effective vaccines are already available for animal parvoviruses [121]. A recombinant human Parvovirus B19 vaccine composed of the VP1 and VP2 capsid proteins was already proven safe and immunogenic in Phase 1 trial on 24 sero-negative adults [122].

10. Conclusions

Human Parvovirus B19 is a small single stranded DNA virus transmitted via the respiratory tract, by blood products or trans-placentally during maternal infection. The wide variety of disease manifestations depends on the immunologic and hematologic state of the host.

Most studies find the sero-conversion rate among pregnant women to be 1–5% mainly with normal outcome. The prevalence of the maternal infection is higher during epidemics – between 3 and 20%. Even though trans-placental Parvovirus B19 infection occurs in about 30–50% of acutely infected pregnant women most neonates are born normal. Diagnosis is based on IgM in the maternal and fetal blood and PCR or in situ hybridization analysis in maternal blood, amniotic fluid, cord blood or fetal tissues. Fetal infection with Parvovirus B19 can cause severe anemia, hydrops fetalis, myocarditis and death. Fetal abnormalities associated with Parvovirus B19 are rare and there is no evidence that Parvovirus B19 is a significant teratogen. Repeated red blood cell transfusion during pregnancy improves fetal survival. The children having survived successful intrauterine transfusion for Parvovirus B19-induced fetal anemia and hydrops fetalis have a good neurodevelopmental prognosis.

Since most pregnancies infected with Parvovirus B19 have a favorable outcome' it seems that the indications for invasive prenatal diagnosis should be only if there are definite signs of fetal anemia or hydrops fetalis.

A specific vaccine is important in order to prevent aplastic crises in patients with underlying disorders, and fetal morbidity and mortality among sero-negative women in child-bearing age. Effective vaccines are already under trial.

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