

Human Parvovirus B19 Infection in Pregnancy

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Abstract:

Background: It was found that incidence of acute human parvovirus B19 (HPV B19) infection in pregnancy is approximately 1-2%. In pregnant women who are immunocompromised or suffering from pre-existing hematological conditions, or infected fetuses where there is widespread tissue and red cell destruction, mortality and morbidity may occur. Fetal hydrops develops in cases 0-12.5% of infected fetuses with a peak between 17 and 24 weeks' gestation, while fetal demise is estimated to occur at a rate of 5–10%, with or without the diagnosis of fetal hydrops in cases of unclear pathophysiology.

Objective: To assess the frequency of parvovirus B19 infection in cases of unexplained intrauterine fetal death, non-immune hydrops, and abortion.

Patients and methods: The present study was a cross-sectional study that included female patients who suffered from unexplained intra-uterine fetal death, abortion or, non-immune hydrops. All patients fulfilling the inclusion criteria were recruited from Obstetrics and Gynaecology Department of Zagazig University hospitals and Suez Health Insurance Hospital. We are expecting cases during 6 months study period. Ten (10) cases are expected per month so during 6 months study period, a comprehensive sample of at least 60 patients was determined to be included in the study. A non-probability, consecutive, sampling technique was utilized.

Results: Thirty (50%) cases had intrauterine fetal death, 26 (43.3%) cases had abortion, and 4 (6.6%) cases had non-immune hydrops. Seropositivity for HPV B19 was 53.3% in IUFD cases, 42.3% in cases abortions and 50% in cases of non-immune hydrops. Seven cases had abortions in the first trimester and 4 cases in the second trimester. Three cases of them were IgM positive. The patients were diagnosed as missed abortion at 10, 12 and 15 weeks.

Conclusion: The presence of parvovirus B19 seropositivity in cases of unexplained IUFD was 16 cases (53.3%). The presence of parvovirus B19 seropositivity in cases of unexplained abortion was 11 cases (42.3%).

Keywords: Human parvovirus B19, Pregnancy, Fetal hydrops.

Introduction:

Parvovirus B19 infection has a seasonal variation being most prevalent in the winter, spring, and early summer months. The virus causes a lytic infection of erythroid progenitor cells leading to a suppression of erythropoiesis. In pregnant women, the virus can be vertically transmitted to the fetus, with an infection rate of about 30% resulting in fetal anaemia, fetal hydrops, miscarriage, or intrauterine fetal death ⁽¹⁾.

Previous reports have shown that parvovirus B19 infection can cause fetal death mainly in combination with hydrops fetalis. The frequency of parvovirus B19 infection, especially in non-hydrotic cases of intrauterine fetal death, is an important consideration ⁽²⁾.

Increased nuchal translucency and/or the presence of fetal hydrops during first-trimester ultrasound examination has been reported as a sign of congenital infection with parvovirus. Reports on parvovirus infection in pregnancy have described altered fetal hemodynamics resulting from mild cardiomegaly, progressive augmentation of peak systolic velocity in the middle cerebral artery, reversed flow in ductus venosus during atrial contraction and development of hydrops ⁽³⁾.

Maternal parvoviral seroconversion rates vary between 3% and 34% and the risk of vertical transmission is approximately 30%. Fetal hydrops develops in cases 0-12.5% of infected fetuses with a peak between 17 and 24 weeks' gestation, while fetal demise is estimated to occur at a rate of 5–10%, with or without the diagnosis of fetal hydrops in cases of unclear pathophysiology ⁽⁴⁾.

There are three hypothetical causes of fetal demise in first-trimester parvovirus fetal infection: 1) primary viral infection of the myocardial cells initially causes myocarditis, leading to hydropic cardiac failure and demise; 2) bone marrow transient aplastic crisis occurs as the *primum movens* for anemia, leading to the sequence of congestive heart failure/hydrops/death; 3) placentitis without fetal infection causes placental dysfunction and ultimately fetal demise ⁽⁵⁾.

Investigation for parvovirus B19 infection was recommended apart from the standard workup for fetal hydrops or intrauterine fetal death ⁽⁶⁾.

Results of IgM testing are particularly difficult to interpret. Standardization between laboratories is lacking. High-level viremia in acutely infected persons may cause virus-antibody complexes, which will result in a false-negative IgM test result. In this setting, polymerase chain reaction (PCR) may be a better diagnostic modality ⁽⁷⁾.

The aim of the study was to assess the frequency of parvovirus B19 infection in cases of unexplained intrauterine fetal death, non-immune hydrops, and abortion.

Patients and methods:

The present study was a cross-sectional study that included female patients who suffered from unexplained intra-uterine fetal death, abortion or, non-immune hydrops. All patients fulfilling the inclusion criteria were recruited from Obstetrics and Gynaecology Department of Zagazig University hospitals and Suez Health Insurance Hospital. We studied the cases from May 2019 to April 2020.

Ten (10) cases are expected per month so during 6 months study period, a comprehensive sample of at least 60 patients was determined to be included in the study. A non-probability, consecutive, sampling technique was utilized.

Inclusion criteria:

- Adults female aged > 18 years old and <35 years old.
- Female patients with unexplained intra-uterine fetal death, first and second trimester missed abortions, or non-immune hydrops.
- All patients must be +ve Rh.

Exclusion criteria:

- Patients with medical disorders as hypertensive disorders with pregnancy or diabetes.
- Patients with previous diagnosis of TORCH infection, lupus anti-coagulant or anti-cardiolipin antibodies.
- Patients with diagnosis or history of chromosomal abnormalities or fetal anomalies (other than hydrops fetalis).

Ethical Statement:

The present study runs in concordance with international ethical standards and applicable local

regulatory guidelines. A written informed consent was obtained from every eligible patient. Patients were informed about the study objectives, methodology, risk, and benefit. The study's protocol was reviewed and approved by IRB, ethics committee or audit department of Zagazig University Hospital.

For all cases, the following were performed:

1- History taking.

- Demographic characteristics including age, residency, and education level.
- Obstetric history (previous sibling death, previous admission to NICU, etc.).
- Prenatal history (history of exposure to a patient infected with parvovirus or history of rash, arthralgia or anaemia).
- History of comorbidities.

2- Thorough clinical, obstetric and neurological examination:

- Weight, length, BMI.

3- Ultrasound examination:

- To confirm: IUFD, abortion or hydrops and other findings as gestational age.
- To exclude other fetal anomalies not included in our study.

4- Laboratory investigations:

- Complete Blood Count (CBC), FBS.
- Liver function tests.
- Kidney function tests.
- Immunological (if suspected).
- Urine analysis
- Venous blood sample:
 1. Filling tubes to the stated draw volume to ensure the proper blood-to-additive ratio. Allowing the tubes to fill until the vacuum is exhausted and blood flow ceases.
 2. Mixing all gel barrier and additive tubes by gentle inversion 5 to 10 times immediately after the draw.
 3. Tubes stored at 4-25°C (39-77°F).

5- Detection of human parvovirus B19 antibody IgM in the serum samples:

By using a third generation qualitative capture enzyme immunoassay (Diasorin-Biotrin; catalog no. V619IM) that detect IgM antibody against human parvovirus B19 structural proteins. The kit contained 3 standard controls S1, S2 and S3 that were used in interpretation of the results as recommended by manufacturer briefly; samples with HBV B19 IgM index value of $\leq$ S1 (negative standard control) were considered negative, samples with HBV B19 IgM index value of $\geq$ S3 (low positive standard control) were considered positive and samples with HBV B19 IgM index value of equal S2 (cut-off standard control) were considered equivocal samples and were retested 10 to 14 days and if the results were equivocal again they were considered as negative samples as recommended by the manufacturer.

• Detection of human parvovirus B19 antibody IgG in the serum samples:

It was done using a third generation qualitative indirect enzyme immunoassay (Diasorin-Biotrin catalog no. V619IG) that detect IgG antibody against human parvovirus B19 structural proteins VP1 and VP2. The interpretation of the results was done according to manufacturer recommendations and it was on the same rules as that of IgM.

Statistical Analysis:

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. The analyses were carried with SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). Numerical data were described as mean $\pm$ SD if normally distributed; or median and interquartile range [IQR] if not normally distributed. Frequency tables with percentages were used for categorical variables. Independent Student t-test and paired t-test were used to compare parametric quantitative variables. Chi-square tests were used to analyze categorical variables. A p-value < 0.05 is considered statistically significant.

Results:

Table (1) shows the demographic characteristics of the studied patients. The age of the included patients have a range(18-35)years; while the majority of them were from rural areas (61.7%). In addition, 33.3%of patients were categorizedashigh socialclassand66.6% were categorized as low.

Table (1): The demographic characteristics of the studied patients.

Variables	Patients (N =60)
BMI in Kg/m ²	
• Mean $\pm$ SD	26.9 $\pm$ 4
• Range	21 - 32
Age in years	
• Mean $\pm$ SD	27 $\pm$ 3.92
• Range	18 - 35
Residency, No. (%)	
• Urban	23 (38.3%)
• Rural	37 (61.7%)
Social class, No. (%)	
• Low	30 (50%)
• mid	20 (33.3%)
• High	10 (16.7%)

* Data are presented as mean $\pm$ SD, median (Range), or number (%).

Table (2) clearsthe obstetric history for the participants.In term of obstetric history, the majority of the womenwerein their second trimester during abortions or non-immune hydrops occurrence. Most of the cases had one parity.

Table (2): The obstetric history for the participants.

Variables	Weeks
Gestational age inweeksattimeofinclusion,(Mean $\pm$ SD):	
Unexplained abortion:	
• First trimester (N=15)	9 $\pm$ 1.1
• Second trimester (N=11)	20 $\pm$ 2.05
Unexplained hydrops	25 $\pm$ 2.16
Unexplained IUFD	30 $\pm$ 2.4
	Patients (N =60)

Parity, No. (%)	
1	24 (40%)
2	20 (33.3%)
3	13 (21.7%)
4	3 (5%)
History of previous abortion, No. (%)	
Yes	9 (15%)
No	51 (85%)
History of previous nonimmune hydrops, No. (%)	
Yes	4 (6.7%)
No	56 (93.3%)
History of previous IUFD, No. (%)	
Yes	17 (28.3%)
No	43 (71.7%)

* Data are presented as mean $\pm$ SD, median (Range), or number (%).

Table (3) demonstrates the IgG and IgM seropositivity for parvovirus B19 in the studied cases. The presence of seropositive parvovirus B19 IgG was 43.3% and the presence of parvovirus B19 IgM was 5%.

Table (3): IgG and IgM seropositivity for parvovirus B19 in the studied cases.

Variables	Patients (N =60) N. & %
Seropositivity for parvovirus B19	29 (48.3%)
IgG	26 (43.3%)
IgM	3 (5%)
Seronegative for parvovirus B19	31 (51.7%)

* Data are presented as number and percentage.

Table (4) reveals the association between seropositivity for parvovirus B19 and demographic data in the studied cases. The obtained results showed that there was statistically significant association between patients' age and seropositivity for parvovirus B19 ($p=0.002$); patients with seropositive results were older than patients with negative results. On the other hand, there were no statistically significant associations between seropositivity for parvovirus B19 and residency ($p=0.96$) or education level ($p=0.94$). The obtained results showed that there was statistically significant association between patients' BMI and seropositivity for parvovirus B19.

Table (4): Association between seropositivity for parvovirus B19 and demographic data in the studied cases.

Variables	Positive (N=9)	Negative (N=31)	P value
Age in years			
Mean $\pm$ SD	27 $\pm$ 4.26	22.98 $\pm$ 3.58	0.002
Range	23 - 35	18 - 31	
Residency, No. (%)			
Urban	11 (37.9%)	12 (38.7%)	0.96
Rural	18 (62.1%)	19 (61.3%)	

Social class, No. (%)			
Low	16 (55.2%)	14 (45.2%)	0.94
mid	9 (31%)	11 (35.5%)	
High	4 (13.8%)	6 (19.4%)	
BMI in Kg/m ²			
Mean $\pm$ SD	29 $\pm$ 4.2	55 $\pm$ 3.9	0.005
Range	26 - 32	21 - 27	

*Data are presented as mean $\pm$ SD, median (Range), or number (%).

Table (5) clearsthe association between seropositivity for parvovirus B19 and obstetric history. There were no statistically significant associations between seropositivity for parvovirus B19 and gestational age (p=0.07) or parity (p =0.61).

Table (5): The association between seropositivity for parvovirus B19 and obstetric history.

Variables	Positive (N =29)	Negative (N =31)	P- value
Gestational age in weeks at time of inclusion, (Mean $\pm$ SD):			
Unexplained abortion:			0.07
First trimester	7	8	
Second trimester	4	7	
Unexplained hydrops	2	2	
Unexplained IUFD	16	14	
Parity, No. (%)			0.61
1	14 (48.3%)	10 (32.3%)	
2	9 (31%)	11 (35.5%)	
3	5 (17.2%)	8 (25.8%)	
4	1 (3.4%)	2 (6.4%)	

*Data are presented as mean $\pm$ SD, median (Range), or number (%). A p-value < 0.05 is considered statistically significant.

Table (6) shows the association between seropositivity for parvovirus B19 and CBC findings. The obtained results showed that there were no statistically significant associations between seropositivity for parvovirus B19 and hemoglobin levels (p =0.38), WBCs (p=0.33), or platelet count (p =0.42).

Table (6): Association between seropositivity for parvovirus B19 and CBC findings.

Variables	Negative (N =31)	Positive (N =29)	P- value
Hemoglobin (g/dL)			
Mean $\pm$ SD	11.2 $\pm$ 2.2	11.7 $\pm$ 2.2	0.38
Range	8 - 14	8 - 14	
WBCs x103 (cell/mm ³)			
Mean $\pm$ SD	6.9 $\pm$ 1.2	7.2 $\pm$ 1.2	0.33
Range	4 - 9.5	4 - 9.5	

Platelet (cell/mm ³)			
Mean $\pm$ SD	139214.2 $\pm$ 4138.8	119214.2 $\pm$ 4138.8	0.42
Range	100000 - 190000	100000 - 190000	

*Data are presented as mean $\pm$ SD, median (Range). A p-value < 0.05 is considered statistically significant.

Table (7) reveals the seropositivity for parvovirus B19 in the studied cases. There was no statistically significant difference between negative and positive groups (P=0.61). Seropositivity for HPV B19 was 53.3% in IUFD cases, 42.3% in cases abortions and 50% in cases of non-immune hydrops. Seven cases had abortions in the first trimester and 4 cases in the second trimester. Three cases of abortions were IgM positive. The patients were diagnosed as missed abortion at 10, 12 and 15 weeks.

Table (7): Seropositivity for parvovirus B19 in the studied cases.

Variables	Positive(N =29)	Negative (N=31)	P-value
Diagnosis, No.(%) Unexplained;			
• IUFD (N=30)	16/30(53.3%)	14(45.2%)	0.61
• Abortion (N=26)	11/26(42.3%)	15(48.8%)	
First trimester	7	8	
Second trimester	4	7	
• Non-immune hydrops (N=4)	2/4(50%)	2/4(50%)	

*Data are presented as mean $\pm$ SD, median (Range). A p-value < 0.05 is considered statistically significant.

Discussion:

The present study included 60 female patients who suffered unexplained; intrauterine fetal death, abortion, or non-immune hydrops. Thirty (50%) cases had intrauterine fetal death, 26 (43.3%) cases had abortion, and 4 (6.6%) cases had non-immune hydrops. Regarding the primary outcomes of the present study, we found that the seropositivity for parvovirus B19 IgG was 43.3% and for parvovirus B19 IgM was 5%.

The mean age of the included patients was 27 $\pm$ 3.92 years and the majority of the women were in their third trimester during fetal death. The majority of the residency of the included patients was rural and the majority of them (66.6%) were categorized as low social class. Forty percent of the women had had one previous pregnancy, while only 5% had previous 4 pregnancies. The mean hemoglobin of the included patients was 11.7 $\pm$ 2.2 g/dL and the average WBCs was 7.2 $\pm$ 1.2 x 1000 cell/mm². The patients had normal liver and kidney functions.

In this study, we found 16 cases (53.3%) positive for HPV B19 IgG which had IUFD in the third trimester with ages ranging between 23 and 35 years. **Tolfvenstam et al.**⁽²⁾ investigated the frequency of parvovirus B19 infection in unselected cases of intrauterine fetal death and to assess the sensitivity of different diagnostic procedures of 14147 deliveries in three hospitals in the major Stockholm area of Sweden, all cases of intrauterine fetal death that occurred between January, 1998, and May, 1999 (n=47) were included. The frequency of parvovirus B19 infection during pregnancy was 15%.

Similarly, **Sarfraz et al.**⁽⁸⁾ performed a case-control study to assess the association between maternal parvovirus B19 infection and fetal death, birth weight and length of gestation. Cases were all 281 women with fetal death within a cohort of 35,940 pregnant women in Norway. Two of 281 (0.7%) of the women who experienced fetal death and nine of 957 (0.9%) of the controls had presence of IgM antibodies. In our study IgG was more associated with fetal deaths than IgM (all positive cases were IgG positive not IgM).

Syridou et al.⁽⁹⁾ performed a prospective case-control study to examine the incidence of parvovirus B19 in intrauterine fetal death and their association with fetal and placenta pathological findings. Molecular assays were performed on placenta tissue extracts of 62 fetal deaths and 35 controls for the detection of HPV B19 genomes. Thirty-four percent (34%) of placental specimens taken from intrauterine fetal deaths were positive for HPV B19, whereas only 6% of those taken from full term newborns were positive ($P=0.0017$).

In our studied cases ($N=60$), there were 26 cases of abortion, 11 cases were positive for HPV B19, 7 of them were in the first trimester and 4 cases were in the second trimester. Eight cases (30.7%) were positive HPV B19 IgG and 3 cases were IgM positive (11.5%). The cases with positive HPV B19 IgM had missed abortions at the 10, 12 and 15 weeks of gestation, so acute infection is high risky to the fetus. The rest of the cases were HPV B19 IgG positive which indicated infection more than 3 months when pathological process starts ending in abortion, IUFD or non-immune hydrops. Moreover, **Sorour et al.**⁽¹⁰⁾ aimed at assessment of the relation between maternal human parvovirus B19 infection and recurrent spontaneous abortion and comparing the serological diagnostic methods and PCR for diagnosis of HPV B19 infection in this type of patients. Sera were collected from 50 patients with RSA (patients group) and 25 pregnant females without history of abortion (control group) and all sera were tested by nested PCR to detect HPV B19 DNA and by EIA to detect HPV B19 IgM and IgG. Parvovirus B19 IgM was positive in 6% of the patients group and HPV B19 IgG was positive in 62 % of the patients.

Goa et al.⁽¹¹⁾ investigated the infection of HPV B19 in first trimester spontaneous abortions and the corresponding immune response. One hundred abortion patients aged from 17 to 47 years were included in the study. By serology, 30.0% of patients were positive for HPV B19 IgG, while 2% for HPV B19 IgM.

Notably, the frequency of parvovirus B19 infection during pregnancy was lower in studies from developed countries. For example, **Lassen et al.**⁽¹²⁾ conducted a case-control study in 3 regions in Denmark from 1992 to 1994. Cases of women with fetal loss were identified in the National Patient Register ($n=2,918$), First trimester serum samples were tested for parvovirus B19 immunoglobulin M positivity. It was found 0.8% of the cases.

Additional report from Finland showed similar findings. **Riipinen et al.**⁽¹³⁾ conducted a retrospective study to investigate the prevalence of parvovirus B19 DNA among fetuses from miscarriages and fetal death. The authors retrospectively studied 535 unborn fetuses, including 120 fetuses from miscarriages and 169 from fetal death. Parvovirus B19 DNA was detected in 5 fetuses with gestational ages of 14, 22, 23, 30, and 39 weeks; these included fetuses from 4 (2.4%) of the 169 fetal death and 1 (0.8%) of the 120 miscarriages.

In this study, 4 cases had non immune hydrops were included. We found 2 of them (50%) positive for HPV B19 IgG. **De haan et al.**⁽¹⁴⁾ conducted a retrospective study in The Leiden University Medical Centre in The Netherlands on the prospectively collected clinical and laboratory data from severely hydropic and anaemic fetuses, with a proven HPV B19 infection during gestation from January 1997 until August 2007. Fetal blood samples were evaluated for quantitative HPV B19 viral load. All cases included had positive fetal blood samples for HPV B19 antibodies with 100% congenital HPV B19 infection.

Kaiser et al.⁽¹⁵⁾ conducted a retrospective study and examined the occurrence of hydrops in fetal and neonatal cases in a five-year period. During this time, the clinical and pathologic diagnosis of hydrops was established in 28 cases. In three cases, the hydrops was caused by Rh incompatibility, and in 25 cases non-immune hydrops was discovered by clinical and pathologic examination. Infection was the cause of non immune hydrops in 7 cases (28%).

Conclusion:

In conclusion, The study shows that 48.3% of the women with unexplained, intrauterine fetal death, abortion, or non-immune hydrops were seropositive for HPV B19, 43.3% of them were IgG positive and 5% were IgM positive.

The presence of parvovirus B19 seropositivity in cases of unexplained IUFD was 16 cases (53.3%). The presence of parvovirus B19 seropositivity in cases of unexplained abortion was 11 cases (42.3%). The presence of parvovirus B19 seropositivity in cases of unexplained non immune hydrops was 2 positive cases (50%).

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