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Human Parvovirus (B19) Infection in Pregnancy: A Retrospective Study

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Abstract:
Objective: *To highlight the clinical findings and rates of fetal outcome among women exposed to human parvovirus B19 infection in pregnancy, from a district general hospital in United Kingdom.*
Materials and Methods: *Retrospective study of pregnant women referred to district general hospital in United Kingdom, for possible parvovirus B19 exposure between January 2007 and April 2013. All patients with suspected exposure to parvovirus B19 infection had serological investigations and were followed up with hospital protocol. For women with documented maternal infection, the fetus underwent serial ultrasound evaluations. When ultrasound demonstrated evidence of fetal hydrops women were referred to tertiary fetal medicine unit.*
Results: *A total of 335 pregnant women were exposed to parvovirus B19 infection between January 2007 and April 2013. Of these, 213(63.5%) had IgG antibodies and were immune. In 122 women, no IgG antibodies were detected giving the nonimmune incidence of 36.5 % for parvovirus B19 infection. Of the 122 nonimmune women, there were 24 cases of serologically documented parvovirus B19 infection and this represented a rate of infection of 18.8% following exposure to B19 infection.*
Of the 24 women,18 tested positive for IgM on their first visit and 6 were seroconverted between blood samples. Among these 24 infected women four had poor obstetric outcome in the form of intrauterine fetal death (IUD) at 16, 19, 26 and 30 weeks respectively. This gave a frequency of 16% for inutero fetal demise.
Conclusions: *Most women with B19 infection in pregnancy had satisfactory outcome, but there was substantial risk of fetal loss. Therefore there is need for enhanced surveillance of maternal parvovirus B19 infection. Local hospital policies should be developed for maternal screening of B19 infection and to correctly manage pregnancies at risk.*
Key words: *Parvovirus B19, pregnancy, nonimmune fetal hydrops, fetal anemia*

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I. Introduction:

Human parvovirus B19 is a small single-stranded DNA virus.[1,2] It is the only member of the Parvoviridae family, known to be pathogenous to humans.[1,3]. Human parvovirus B19 infection is the most common viral infection associated with rashes in school aged children. Parvovirus infection occurs worldwide but seroprevalence rates vary according to age and geography. Approximately 15% of preschool children, 50% of adults and 85% of the elderly are seropositive.[4,5,6] The prevalence may be higher in developing countries [4,7]. Parvovirus B19 infection follow a seasonal variation with higher prevalence in temperate climates around late winter to early spring. Epidemics occur and tend to follow a 3-6 year cycle Parvovirus B19 infection may

manifest as erythema infectiosum or fifth disease or slapped cheek syndrome. The slapped cheek syndrome describes a characteristic facial rash. [4] The transmission of parvovirus B19 may be by respiratory droplets, transfusion of blood and blood products or to the fetus by transplacental passage.[4,10,11]

About 35-45% of women of childbearing age do not possess protective Ig G antibodies against parvovirus B19 infection. In case of maternal infection, vertical transmission occurs in 33-51% of cases, the risk of adverse fetal outcome is approximately 10%. [1, 12,13] .Fetal infection with parvovirus B19 is associated with intrauterine fetal death, non-immune hydrops fetalis and neurological manifestations. Fetal infection may be asymptomatic. We describe a more recent series of women exposed to human parvovirus B19 infection in pregnancy, from a district general hospital in United Kingdom, to highlight clinical findings and rates of fetal outcome, emphasising the need for continued surveillance of this potentially devastating infectious disease in pregnancy.

II. Materials And Methods:

This is a retrospective analysis of pregnant women referred to a district general hospital in the northeast of England, with possible parvovirus B19 exposure between January 2007 and April 2013. The study was approved by the hospital audit department and received local caldicott approval.

Patients' age, parity, gestation at exposure, obstetric history, reason for B19 testing, contact history, description of symptoms and adverse outcome of pregnancy were obtained from a computerised database maintained at the hospital and from patients records. The date of delivery or miscarriage or fetal death was also obtained. In case of live birth, the birth weight, gestational age at delivery, mode of delivery and details of any neonatal problems were also retrieved. Results of serological screening were obtained from parvovirus antibody screening log from hospital microbiology database.

All patients with suspected exposure to parvovirus B19 infection had serological investigations and were followed up with the protocol outlined in Figures 1&2. Serological investigations were performed in the department of microbiology at the district general hospital. Maternal serum samples were analyzed for B19 IgG and IgM antibodies using enzyme-linked immune sorbent assays according to manufacturer's instructions. Women screening positive for B19 IgM were further tested for B19 DNA using a validated quantitative real-time PCR assay. Antenatal booking bloods retained in line with national standards (UK National Screening Committee, 2010) were retrieved, where possible, when a B19 infection was confirmed in pregnancy, in line with laboratory policy. This was performed to check for evidence of infection at the time of booking or for subsequent seroconversion. Parvovirus B19 infection during pregnancy was accepted as confirmed when both B19 IgM and DNA were detected in maternal blood and when maternal B19 IgM seroconversion was confirmed.

For women with documented maternal infection (positive for IgM or seroconversion to IgM), the fetus underwent serial ultrasound evaluations weekly. When ultrasound demonstrated evidence of fetal hydrops or if the middle cerebral artery peak systolic velocity values suggested severe anemia (peak systolic velocity > 1.50 multiples of the median), women were referred to tertiary fetal medicine unit, where intrauterine blood transfusion is offered and carried out as per local fetal medicine unit guidelines. Pregnant women who tested negative for B19 specific IgM and IgG on their first visit following exposure, were offered repeat serological testing performed 4 weeks later to check for seroconversion.

III. Results

A total of 335 pregnant women who were exposed to parvovirus B19 infection attended the district general hospital between January 2007 and April 2013. Of the 335 pregnant women exposed to B19 infection, 213 (63.5%) had IgG antibodies and were immune. In 122 women no IgG antibodies were detected giving the non-immune incidence of 36.5 % for parvovirus B19 infection. Of the 122 pregnant women who were non-immune, 105 (86%) tested negative for B19 specific IgM and IgG antibodies and were susceptible to B19 infection on their first visit to hospital following exposure to parvovirus B19. Of the 122 women, 18 (14 %) tested positive for IgM and were infected with B19 infection on their first visit. Of the 105 who were susceptible to B19 infection, 92 women had repeat serology in 4 weeks and 13 women had no repeat serology. Of the 92 women who had repeat serology, 6 were seroconverted between blood samples, confirming acute B19 infection giving the seroconversion rate of 6.5%. Of the 122 non-immune women, there were 24 cases of serologically documented parvovirus B19 infection and this represents a rate of infection of 18.8% following exposure of non-immune women to B19 infection. Of the 24 women 18 tested positive for IgM on their first visit and 6 were seroconverted between blood samples.

In this series, of the 24 women who were infected with parvovirus B19 infection, the median age of the women was 26 years (range 16-37). The median number of children living at home with the woman was 2 (range, 0-4), and the median gestational age at the time of diagnosis of infection or maternal seroconversion was 21 weeks

(range, 9 -34). Presence or absence of symptoms was available for 12 women (12/24) among whom 2 women had sore throat and 2 women had arthralgia. The source of mothers' infection was stated to be unknown in 11/24 cases. Among the 13 women in whom the source of infection was known, 5 women had acquired the infection from their other children, 4 acquired infection in the work setting, of whom two were teachers and two were child care workers. 4 women acquired infection from friend's child. There were no antenatal complications in all 24 infected women and all had weekly scans as per hospital protocol.

Among the 24 infected women four had poor obstetric outcome in the form of intrauterine fetal death (IUD) at 16, 19, 26 and 30 weeks respectively. This gives a frequency of 16% for in utero fetal demise. Among the four women with adverse outcomes, three were diagnosed with intrauterine fetal death and one woman was diagnosed with fetal hydrops at 19 weeks and was referred to tertiary fetal medicine unit for intrauterine blood transfusion but fetal demise occurred just after the procedure. Fetal tissue from all 4 pregnancies with poor outcome showed B19 infection. However 20 women among the 24 infected women had live births of which 11 women had normal deliveries, 5 had elective caesarean sections, 2 had emergency caesarean sections and 2 women had instrumental deliveries. The median gestational age at birth was 37 weeks (range, 35 - 41 weeks), median birth weight was 3240 grams (range, 2780- 4160 grams) and median apgar scores were 9 and 9 at 1 and 5 minutes respectively.

IV. Discussion

Currently B19 is not offered as part of antenatal screening. In most pregnant women with confirmed parvovirus B19 infection, the pregnancy outcome is favourable. In others, adverse fetal outcome like miscarriages, hydrops fetalis and fetal death may occur. The fetus is most susceptible to parvovirus B19 infection during the first and second trimesters of pregnancy. [15] Parvovirus B19 has a propensity for infecting rapidly dividing cells, particularly erythroblasts. Between the third and sixth months of pregnancy the fetal red blood cell mass increases, with a risk of developing anemia if the fetus is infected with parvovirus B19 [16] By the third trimester, the fetus is able to mount a more effective immune response to the virus , which may account for the decrease in fetal loss at this stage of pregnancy. [15]

Incidence of fetal loss secondary to parvovirus B19 was initially estimated to be as high as 26-38%. [15,17,18,19,20] However recently this loss is thought to be much lower. In a large prospective study in the United Kingdom between 1985-88, where 186 women with serologically confirmed B19 infection were studied, the overall fetal loss rate was 16%.[15] In our study, we report a similar frequency of 16% for inutero fetal demise. Also similar fetal loss rate was reported in a retrospective case series by Beigi in 2008, where the rate of inutero fetal demise was 16% and frequency of hydrops fetalis is 12%.[18] However other larger studies report frequencies that are much lower ranging from 1 - 6 % . [18,21,22] Our series reported non immune incidence of 36.5 % for parvovirus B19 infection and 6 of 92 women who were susceptible to B19 infection and had repeat serology, were seroconverted between blood samples confirming acute B19 infection, giving a seroconversion rate of 6.5 %. In our series we report the rate of infection of 18.8% following exposure of non immune women to B19 infection.

A large cohort of 618 parvovirus exposed pregnant women, described by Harger et al. suggested that the majority of those women (67%) had symptoms attributable to parvovirus B19 infection and thus sought care. Our data suggest that maternal symptoms in the pregnant women exposed to B19 infection are uncommon. Similar observations were reported by Beigi et al. in their case series [18] In our study, women presented either due to a child at home with symptoms of parvovirus B19 infection or exposure to friend's child with symptoms or teachers and child care workers. This highlights the importance of educating women about the risk of exposure to parvovirus infection in the paediatric setting . It is important to have local policies and guidelines to manage women exposed to parvovirus B19 infection. Testing should be offered to any potentially exposed pregnant woman for parvovirus infection even if she is asymptomatic, given the relatively low frequency of symptoms among women who acquired the infection. No woman in our study had any antenatal complications.

In our study, 4 out of 24 pregnant women who were infected with parvovirus B19 infection, had poor obstetric outcome giving a fetal loss rate of 16% as mentioned earlier. Recent data support the association of parvovirus B19 infection in pregnancy with hydrops fetalis and intrauterine fetal death in second and third trimesters of pregnancy. [23] In this study analysis of results were based only on women who had suspected exposure to parvovirus or having symptoms of parvovirus B19 infection. Therefore the reproductive burden of parvovirus B19 infection during pregnancy may be greater than our estimate in this study.

Given the sample size of this study, our findings may not be generalisable to the obstetric population at large and represent a small window into the overall reproductive burden of parvovirus B19 infection. One strategy that may be available in the future for prevention of disease outbreaks is vaccination. A phase 1 study of a recombinant human parvovirus B19 vaccine suggests safety and immunogenicity in 24 women [24] Certainly such an intervention is early in the development phase, but hopefully will provide us with a solution to a

concerning problem. Until the development of such a vaccine, it is important to maintain vigilance for this infection and counsel pregnant women appropriately with respect to both prevention and management of this potentially devastating congenital infectious disease. Information about B19 infection should be added to health education package provided for antenatal women. It should describe possible outcome and interventions following diagnosis and this may help pregnant women exposed to parvovirus B19 infection to seek consultation with obstetrician or general practitioner and make a decision regarding investigation and further management.

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