British Journal of Obstetrics and Gynaecology
February 1998, Vol. 105, pp. 174–178

Immediate and long term outcome of human parvovirus B19 infection in pregnancy

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Objective To estimate more precisely the risk of fetal loss and congenital abnormalities after maternal parvovirus B19 infection, and to assess the long term outcome for surviving infants.

Design Prospective cohort study of pregnant women with confirmed B19 infection with follow up of the surviving infants. The rate of fetal loss in the study cohort was compared with that in pregnant women with varicella.

Setting Cases reported by laboratories in England and Wales between 1985–1988 and 1992–1995.

Sample Four hundred and twenty-seven pregnant women with B19 infection and 367 surviving infants of whom 129 were followed up at 7–10 years of age.

Methods Questionnaires to obstetricians and general practitioners on outcome of pregnancy and health of surviving infants. Maternal infection confirmed by B19-specific IgM assay and/or IgG seroconversion.

Results The excess rate of fetal loss in women with B19 infection was confined to the first 20 weeks of gestation and averaged 9%. Seven cases of fetal hydrops followed maternal infections between 9 and 20 weeks of gestation (observed risk 2·9%, 95% CI 1·2–5·9). No abnormalities attributable to B19 infection were found at birth in surviving infants (observed risk 0%, upper 95% CI 0·86%). No late effects were found at 7–10 years.

Conclusions Around 1 in 10 women infected before 20 weeks of gestation will suffer a fetal loss due to B19. The risk of an adverse outcome of pregnancy after this stage is remote. Infected women can be reassured that the maximum possible risk of a congenital abnormality due to B19 is under 1% and that long term development will be normal.

INTRODUCTION

Parvovirus B19 was identified as a fetal pathogen in 1984 when the first case of hydrops fetalis associated with confirmed congenital infection was reported[1]. Subsequently, many case reports documented fetal B19 infections presenting one to three months after either symptomatic or asymptomatic maternal infection[2]. A large prospective study of the outcome of 190 cases of confirmed B19 infection in pregnancy, conducted by the Public Health Laboratory Service in England and Wales during 1985–1988, found evidence of an increased risk of spontaneous abortion of around 10%[3]. However, the study was too small to provide gestation-specific risks of fetal loss or to estimate the risk of hydrops fetalis. It was also largely confined to women who presented with symptomatic maternal infection. Other smaller studies have provided a range of estimates of fetal loss, from between 4·1% to 16%[4–6]. Although no consistent pattern of congenital abnormalities has been reported in surviving infants, there is a lack of information on the long term outcome particularly with respect to the more subtle developmental abnormalities that may become apparent later in childhood.

In order to obtain more precise estimates of the risk of fetal loss and hydrops fetalis following maternal B19 infection, a further 255 pregnant women who had a laboratory-confirmed parvovirus B19 infection between 1992 and 1995 were followed up prospectively. As in the earlier Public Health Laboratory Service study, to avoid bias in the risk estimate, the 1992–1995 study cohort excluded women whose B19 infection was diagnosed retrospectively when the fetus presented with symptoms consistent with intrauterine B19 infection[3]. The long term outcome for surviving infants has been assessed by follow up of the children born to the

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women in the 1992–1995 study cohort and those in the 1985–1988 Public Health Laboratory Service study.

METHODS

The study population for assessing the immediate outcome of maternal B19 infection consisted of pregnant women in England and Wales reported to the Public Health Laboratory Service Communicable Disease Surveillance Centre between June 1992 and June 1995 with laboratory confirmed infection; 1993 and 1994 were epidemic years for parvovirus B19 in England and Wales. The method of recruitment and the follow up questionnaires were the same as those employed in the 1985–1988 study[3]. Only women who presented because they had symptoms or reported contact with a suspected case were included in the analysis. Women who presented because of an abnormal ultrasound or symptoms suggesting fetal problems (e.g. decreased fetal movements) and whose B19 infection was diagnosed retrospectively were excluded. Maternal B19 infection was confirmed by the detection of specific IgM and/or IgG seroconversion. On receipt of a report of a confirmed case of B19 infection in pregnancy, questionnaires were sent to the reporting laboratory and then to the woman's obstetrician inquiring about the date of the last menstrual period, reason for B19 testing, test results, symptoms and outcome of pregnancy. Stage of gestation at the time of maternal infection was calculated from the number of completed weeks between the last menstrual period and the date of onset of maternal symptoms or, for asymptomatic women, the date of the first IgG or IgM positive sample. For pregnancies which continued to term, information on any congenital abnormalities or neonatal problems was sought from the general practitioner.

To investigate congenital infection rates at successive stages of pregnancy, saliva samples were requested from the first 120 surviving infants at a year and tested for parvovirus B19 IgG by IgG capture radioimmunoassay as previously described[7]. The results were compared with those obtained in infants in the 1985–1988 cohort tested at a year using serum samples[3]. Detection of specific IgM antibody in cord or neonatal blood was not attempted as it was previously shown to lack sensitivity as a marker of congenital infection when compared with detection of persistent IgG at a year[3].

The study population for assessing the long term consequences of maternal B19 infection consisted of liveborn infants of mothers in the first and second cohorts (1985–1988 and 1992–1995) who were at least one year old by December 1996. The general practitioner was sent a questionnaire inquiring about the child's general health and specifically about anaemia, thrombocytopenia, other blood dyscrasias, cardiac abnormalities, hepatitis, arthritis and suspected developmental delays. These conditions were chosen because they represent clinical manifestations of postnatal infection or have been identified in *ad hoc* reports as associated with congenital B19 infection[2,8,9].

To estimate the excess risk of fetal loss attributable to maternal B19 infection, the outcome of pregnancy in the study cohorts was compared with that in a large group of women who were followed up prospectively after varicella infection in pregnancy[10]. Although varicella can cause the rare congenital varicella syndrome, it is not associated with an increased risk of fetal loss[11]. The method of ascertainment of cases of varicella in pregnancy was similar to that of the women with B19 infection, both groups being recruited to follow up at the time of the maternal infection.

The proportions of women with an adverse outcome of pregnancy in the two parvovirus study cohorts and in the varicella cohort were compared by χ^2 test, or where required, Fisher's exact test.

RESULTS

Between June 1992 and June 1995, 424 pregnant women were reported to the Communicable Disease Surveillance Centre with confirmed B19 infection. Of these, 150 were excluded from the analysis because they were retrospectively tested for B19 infection following the detection of fetal symptoms or abnormalities suggestive of congenital B19 infection. Of the remaining 274 women, 236 were tested because of maternal symptoms (e.g. rash or arthralgia), 25 were tested after contact with a suspected case (19 of these were asymptomatic) and in 13 women the reason for testing was not available.

Risk of fetal loss

Information on stage when infected and outcome of pregnancy was obtained for 255 (98%) of the 261 women tested because of maternal symptoms or contact; of these 11 had a therapeutic abortion. Among the remaining 244 women who elected to continue with their pregnancy, 215 had a live birth and 29 (12%) had a spontaneous abortion or fetal death after 20 weeks of gestation. One liveborn infant had a ventricular septal defect; no other congenital abnormalities were reported. The fetal loss rate in the 1992–1995 cohort according to stage when infected is shown in Table 1 together with the outcome for the 183 women from the 1985–1988 cohort who elected to continue with their pregnancy and whose gestational stage at the time of infection was known. No significant differences were found in fetal loss rate between the two study cohorts at any stage of pregnancy. There was a greater proportion of adverse fetal outcomes among women with B19 infection in

Table 1. Number of pregnancies followed up (FU) and ending in spontaneous abortion (SA) or intrauterine death (IUD) according to stage of gestation when B19 occurred. Values are given as *n* or *n* (%). WLMP = weeks from last menstrual period.

Stage (WLMP)	1992–1995 cohort		1985–1988 cohort		Both cohorts combined	
	FU	SA/IUD	FU	SA/IUD	FU	SA/IUD
0–4	10	2 (20)	23	3 (13)	33	5 (15)
5–8	62	12 (19)	37	5 (14)	99	17 (17)
9–12	58	9 (16)	57	13 (23)	115	22 (19)
13–16	45	5 (11)	34	7 (21)	79	12 (15)
17–20	32	1 (3)	15	0	47	1 (2)
21–24	15	0	6	0	21	0
25–28	10	0	4	0	14	0
29–32	6	0	3	0	9	0
≥33	6	0	4	1 (25)	10	1 (10)
TOTAL	244	29 (12)	183	29 (16)	427	58 (14)

Table 2. Risk of fetal hydrops according to stage of gestation of maternal B19 infection: 1992–1995 and 1985–1988 cohorts combined. Values are given as *n* and *n* (%). WLMP = weeks from last menstrual period.

Stage (WLMP)	Followed up	Fetal hydrops
0–8	132	0
9–12	115	3 (2·6)
13–16	79	3 (3·8)
17–20	47	1 (2·1)
21–28	35	0

pregnancy (both study cohorts combined) than among women with varicella who elected to continue to term and whose fetus escaped varicella damage (Fig. 1). The excess was confined to the first 20 weeks of pregnancy; during this gestational stage 57/373 (15%) of pregnancies in the B19 group ended in fetal death compared with 41/852 (5%) in the varicella group, $P < 0{\cdot}00001$. The average excess fetal death rate during the first 20 weeks of gestation was 9%, although the difference was most marked between 9 and 16 weeks of gestation (Fig. 1). There was no difference in fetal loss rate after 20 weeks of gestation (1/54 *vs* 2/476 respectively, $P = 0{\cdot}28$).

A total of seven women in the B19 study cohorts had a hydropic fetus; maternal infection in these cases occurred between 11 and 18 weeks of gestation (median 14 weeks). The risk of hydrops fetalis according to stage of gestation is shown in Table 2. The overall risk between weeks 9–20 was 2·9% (95% confidence interval 1·2–5·9). The interval between onset of maternal infection and diagnosis of hydrops fetalis ranged from 2 to 17 weeks. Three of the seven hydropic fetuses survived; two of these were given an intrauterine transfusion; none of the four hydropic fetuses who died was transfused.

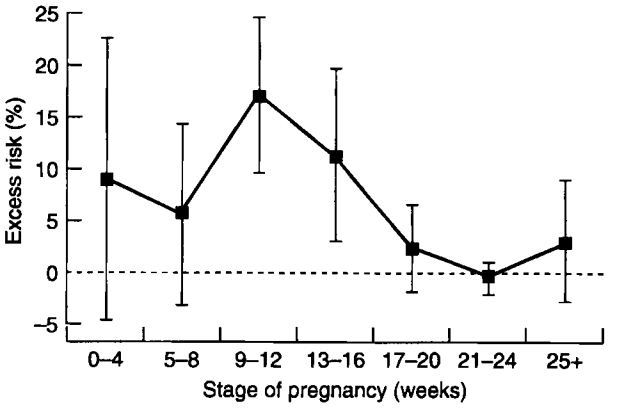

Fig. 1. Excess risk of fetal loss (95% confidence intervals) in women with parvovirus B19 infection compared with women with varicella by gestational stage at maternal infection.

Table 3. Number and percentage of infants positive for parvovirus B19 IgG at a year according to stage of maternal infection: 1992–1995 and 1985–1988 cohorts combined. Values are given as *n* and *n* (%). WLMP = weeks from last menstrual period.

Stage of gestation (WLMP)	Tested	IgG positive
0–4	15	0 (0)
5–8	44	7 (16)
9–12	54	5 (9)
13–16	35	7 (14)
17–20	25	6 (24)
21–24	10	5 (50)
25–28	12	7 (58)
29–32	6	4 (67)
≥33	8	5 (63)
TOTAL	209	46 (22)

A total of 25 women in the B19 study cohorts had an asymptomatic B19 infection; of these, 23 had a live birth and 2 (8%) had a spontaneous abortion. In comparison, 56 of the 402 (14%) women with symptomatic infection had a spontaneous abortion ($P = 0{\cdot}48$)

Congenital infection rate

Of the 215 live births from the 1992–1995 cohort, 214 were at least one year of age by December 1996. Saliva samples were obtained at one year from 101 of the 120 infants (84%) from whom it was requested and B19 specific IgG detected in 20 (20%). This proportion was similar to that in infants in the 1985–1988 study cohort tested at a year for specific IgG antibody in serum; of these 24% (26/108) were B19 IgG positive ($P = 0{\cdot}46$). The results for both study cohorts combined is shown in Table 3 according to stage of gestation of maternal infection. The proportion B19 IgG positive at one year increased progressively towards term.

Long term outcome

One year follow up questionnaires were completed for 182 (85%) of the 214 liveborn infants from the 1992–1995 study cohort. One child had developed mild iron deficiency anaemia at nine months (IgG status not known). No cases of hepatitis, arthritis or blood dyscrasias were reported. Mild development delay such as not walking until 18 months of age was reported in three (1%) children. Both survivors of fetal hydrops from the 1992–5 cohort were developing normally at a year; one was IgG positive and the other IgG negative.

General practitioners of 129 (84%) of the 154 children from the first study cohort born between January 1985 and June 1988 returned questionnaires; at the time of response the children were between 7 and 10·5 years of age. Since birth, two had had iron deficiency anaemia (ages 1·5 and 5 years), one had had transient idiopathic thrombocytopaenic purpura (age 3·5 years) and one had had transient eosinophilia; no other haematological abnormalities were reported. One additional child had had an episode of atrial tachycardia that resolved spontaneously, and another had had a transient episode of torticollis. Three children (2%) were reported to have had some developmental delay. The survivor of fetal hydrops was developing normally with no chronic health problems.

DISCUSSION

This study, together with the earlier cohort, provides the largest group of prospectively followed pregnant women with B19 infection so far reported and confirms the generally favourable outcome for the fetus. Of the 427 B19 infected women who elected to continue with their pregnancies, 369 (86%) had a normal liveborn infant. The only congenital abnormalities reported were a ventricular septal defect in the 1992–1995 cohort and hypospadias in the 1985–1988 cohort[3]. These abnormalities are relatively common and do not suggest a teratogenic effect attributable to parvovirus B19 infection.

An increased risk of fetal loss of 9% during the first 20 weeks of gestation compared with women who had varicella in pregnancy was found, with the largest excess concentrated in the period 9–16 weeks. We chose women with varicella as a control group for two reasons. First, their rate of fetal loss has been shown to be similar to women without varicella in pregnancy[11]. Second, the women with B19 infection were ascertained in a similar fashion to those with varicella infection; in both, the period of observation began at the stage of gestation when the maternal infection occurred. Estimates of gestation-specific fetal loss rates based on cohorts of women recruited prior to conception are not comparable because of the attrition which occurs as a result of the high natural fetal loss rate in early pregnancy.

The seven cases of fetal hydrops detected in the two study cohorts presented 11 to 18 weeks after onset of maternal infection. With the recent evidence that early intrauterine transfusion improves survival in affected fetuses[12], it is important to monitor the women who are at greatest risk of this outcome in order to allow early intervention before fetal death occurs. The normal development of the three survivors of this condition in our study cohorts, two of whom had an intrauterine transfusion, is most reassuring. The risk of acquiring parvovirus B19 during pregnancy, averaged over epidemic and non-epidemic years is around 1 in 400[13]. With a 3% chance of developing fetal hydrops for those infected during weeks 9–20 of gestation, it can be estimated that in the UK there is an annual average of two cases of fetal hydrops due to parvovirus B19 infection per 100,000 pregnancies. In epidemic years, this number would be three- to fourfold higher. Similar estimates applied to the 9% excess of spontaneous abortions and intrauterine deaths observed during the first 20 weeks of gestation, suggest that in the United Kingdom parvovirus B19 is responsible for 12 and 48 spontaneous abortions and intrauterine deaths per 100,000 pregnancies in endemic and epidemic years respectively.

Two small studies have suggested that the risk of fetal loss and hydrops may be greater in women with B19 infection who have no symptoms[14,15]. Since the rash and arthralgia in parvovirus B19 infection are immune mediated, there may be a qualitative or quantitative difference in immune response in women without symptoms; thus viral load and hence risk of fetal infection may be greater. From the small number of women in our study whose parvovirus B19 infection was asymptomatic, there was no evidence that the outcome for the fetus was worse than for those whose maternal infection was symptomatic. These findings need to be confirmed in a larger study. However, the diagnosis of asymptomatic maternal B19 infection is rarely made as the majority of women tested for B19 have presented because of a rash or other symptoms. The true extent of asymptomatic maternal B19 infection is therefore uncertain and could be ascertained only by the serological follow up of a large cohort of pregnant women without IgG antibody to B19 in their booking blood to identify those who seroconvert before delivery.

The normal development of the children in two B19 study cohorts, some of whom were 10 years old at the time of follow up, confirms the absence of late effects of intrauterine exposure to parvovirus B19 infection. No unusual haematological conditions were reported. The three cases of iron deficiency anaemia (one in the second cohort and two in the first) were consistent with the number expected on the basis of a point prevalence study of iron deficiency anaemia in British children[16]. The expected rate of transient idiopathic thrombocytopaenic

purpura is difficult to estimate but post-infection thrombocytopenia is relatively common in childhood, and the self limiting course of the case in our study is consistent with such an aetiology[17]. One case of transient eosinophilia was identified but its causal link with maternal B19 infection is difficult to assess because there are many causes of this condition. The frequency of mild developmental delay (1% at a year, and 2% by 7–10 years) was consistent with that expected in any unselected group of children[18].

Saliva is a satisfactory alternative to serum for the detection of B19 IgG by the radioimmunoassay used in this study[7]. A positive result for salivary or serum B19 IgG at one year, at a time when passively acquired maternal antibody has disappeared, indicates congenital infection because postnatal infection rarely occurs in the first year of life[3]. The results of B19 IgG testing of infants at a year showed that the proportion with evidence of congenital infection increased substantially towards term, even allowing for the 9% fetal loss rate attributable to B19 infection during the first 20 weeks of gestation. An increase in fetal infection rate with stage of maternal infection has also been shown for varicella and toxoplasmosis[10,19]. Over half of the infants exposed to B19 after 20 weeks were infected but no attributable clinical effects were identified. One of the children in our study with parvovirus B19-induced fetal hydrops was B19 IgG negative at a year; similarly some infants with clinical evidence of congenital varicella infection may be negative for varicella-zoster antibody at a year[10]. This suggests that induction of long term humoral immunity may be poor following fetal infection unless there is persistent viral replication, as occurs with congenital rubella.

The number of children followed up in our two study cohorts was sufficient to be confident that the risk of a major congenital or developmental abnormality attributable to maternal B19 infection is less than one in 100 (observed risk 0%, upper 95% confidence interval 0·86%). Our results should therefore enable clinicians to improve the counselling of infected women and the management of pregnancies at greatest risk of fetal hydrops. During epidemics pregnant women need to be warned about the consequences of infection and the importance of avoiding exposure where possible. Exclusion from work may be necessary for those whose occupation brings them into close contact with children, such as teachers and nurses. However, despite such measures, fetal losses due to parvovirus B19 infection will continue to occur and are relatively common during epidemic years; moreover, those associated with fetal hydrops occur relatively late in pregnancy when the consequences for the mother are greatest. The prevention of infection in pregnancy many be one of the possible applications of the parvovirus B19 vaccines now being developed[20].

Acknowledgements

We are grateful to the obstetricians and gynaecologists, general practitioners and microbiologists who provided information on these cases. We would like to thank Mrs J. Vurdien and Mrs T. Gibbs for their help in the follow up of the women and children in the two study cohorts and Ms P. Waight for her help with data analysis. C.K.F. receives a salary from the National Health and Medical Research Council of Australia.

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Received 24 February 1997
Returned for revision 6 August 1997
Accepted 2 September 1997