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1 Crawford JAB. *The involvement of the Royal New Zealand Navy in the British nuclear testing programmes of 1957 and 1958.* Wellington: Ministry of Defence, 1989.
2 Pearce NE, Prior IAM, Methven D, *et al. Mortality and cancer incidence in New Zealand participants in United Kingdom nuclear weapons tests in the Pacific.* Wellington: Department of Community Health, Wellington School of Medicine, 1990.
4 World Health Organisation. *Manual of the international statistical classification of diseases, injuries, and causes of death. 9th Revision, 1975.* Geneva: WHO, 1977.
5 Foster FH. The New Zealand Cancer Registry. *N Z Med J* 1977;**86**:341-3.
6 Coleman M, Douglas A, Hermon C, *et al.* Cohort study analysis with a FORTRAN computer program. *Int J Epidemiol* 1986;**15**:134-7.
7 Rothman KJ. *Modern epidemiology.* Boston: Little, Brown, 1986.
8 Ederer F, Mantel N. Confidence limits on the ratio of two Poisson variables. *Am J Epidemiol* 1974;**100**:165-7.
9 Gardner MJ, Altman DG. *Statistics with confidence.* London: British Medical Journal, 1989.
10 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *JNCI* 1959;**22**:719-48.
11 Darby SC, Kendall GM, Fell TP, *et al.* A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapons tests and experimental programmes. *Br Med J* 1988;**296**:332-8.
12 Checkoway H, Pearce NE, Crawford-Brown DG. *Research methods in occupational epidemiology.* New York: Oxford University Press, 1989.
13 Cardis E. Ionizing radiation and electromagnetic fields. In: Higginson J, Muir CS, Munoz N, Sheridan M, eds. *The epidemiology and causes of human cancer.* Cambridge: Cambridge University Press, 1990.
14 Gardner M. Cancer among participants in tests of British nuclear weapons. *Br Med J* 1988;**296**:309-10.
15 Darby SC, Nakashima E, Kato H. A parallel analysis of cancer mortality among atomic bomb survivors and patients with ankylosing spondylitis given X-ray therapy. *JNCI* 1985;**75**:1-21.
16 Greene MH. Non-Hodgkin's lymphoma and mycosis fungoides. In: Schottenfeld D, Fraumeni JF, eds. *Cancer epidemiology and prevention.* Philadelphia: W B Saunders, 1982.
17 Boice JD, Land CE. Ionizing radiation. In: Schottenfeld D, Fraumeni JF, eds. *Cancer epidemiology and prevention.* Philadelphia: W B Saunders, 1982.
18 Beebe GW. A methodologic assessment of radiation epidemiology studies. *Health Phys* 1984;**46**:745-62.
19 Gulbransen G. New Zealand radiation veterans: Christmas Island 1957-58. *N Z General Practice* 1989;**2**:11-15.
20 Caldwell GG, Kelley D, Zack M, Falk H, Heath CW. Mortality and cancer frequency among military nuclear test (Smoky) participants, 1957 through 1979. *JAMA* 1983;**250**:620-4.
21 Beebe GW. Ionizing radiation and health. *Am Scientist* 1982;**70**:35-44.

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Prospective study of human parvovirus (B19) infection in pregnancy

Public Health Laboratory Service Working Party on Fifth Disease

Abstract

***Objective*—To determine the fetal infection rate and outcome of pregnancy among women who acquire infection with human parvovirus (B19) in the antenatal period.**

***Design*—Prospective study of infected pregnancies till time of delivery or abortion with virological investigation of fetuses, neonates, and 1 year old infants.**

***Setting*—England and Wales during 1985-8.**

***Patients*—190 Pregnant women with serologically confirmed B19 infection in pregnancy, their fetuses, neonates, and 1 year old infants.**

***Results*—Of 186 mothers who elected to go to term, 156 (84%) delivered a normal baby. Follow up of 114 of these infants to the age of 1 year disclosed no appreciable abnormalities, although 27 had serological evidence of intrauterine infection. The overall fetal loss rate (30 cases; 16%) was similar to that in an uninfected antenatal sample (unmatched), but there was a pronounced excess of fetal loss in the second trimester in the B19 infected mothers (11·8%; 95% confidence interval 6·8% to 17·8%). Based on virological findings in the aborted fetuses the risk of fetal death due to B19 in an infected pregnancy was estimated to be 9%. The transplacental transmission rate was estimated to be 33%.**

***Conclusions*—Most women with B19 infection in pregnancy had a satisfactory outcome, but there was nevertheless a substantial risk of fetal loss in the second trimester. In view of the absence to date of any evidence of damage to babies who survive maternal infection therapeutic termination of pregnancy is not indicated.**

Public Health Laboratory Service Working Party on Fifth Disease

Members of the working party and participants in the study are listed at the end of this paper.

Correspondence to: Dr S M Hall, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ.

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Introduction

Human parvovirus (B19), first discovered in 1975 in serum from healthy blood donors,[1] is now known to be the cause of transient aplastic crisis in patients with chronic haemolytic anaemias[2] and of erythema infectiosum (fifth disease).[3] In 1984 the first case reports of B19 having an adverse effect in pregnancy were published.[4,5] At least 20 fetal deaths have been described in which fetal tissues contained B19 DNA.[6] The virus replicates in erythroid progenitor cells,[7] which may cause profound anaemia and congestive cardiac failure in the fetus.

Fifth disease is a common childhood exanthem and the recognition that its causative agent was potentially embryopathic provoked considerable public and professional concern.[8,9] This concern, however, was based either on evidence from small numbers of subjects or on case reports and series in which an adverse outcome of pregnancy had led to the retrospective diagnosis of B19 infection, thus providing a biased estimate of risk.[4,5,10-14] We therefore began a prospective investigation of a larger population of women with B19 infection in pregnancy to determine (*a*) the risk of adverse fetal outcome, (*b*) the transplacental transmission rate, and (*c*) the neonatal and longer term outcome. Long term follow up of the infants is not yet complete, but because of the public health implications we report here our initial results.

Subjects and methods

Study population and recruitment—The study population comprised pregnant women who were investigated prospectively, usually by their general practitioners (for example, because of a rash or contact with erythema infectiosum), and who had B19 infection confirmed by the presence of B19 IgM. Patients with B19 infection who had been investigated because of a fetal death were excluded. Recruitment took place between January 1985 and June 1988. Cases were ascertained when the result for each eligible subject was sent to the study base by one of the five B19 reference laboratories in England.

Data collection and follow up—The patient's age, parity, obstetric history, date of last menstrual period, reason for B19 testing, contact history, and description of symptoms with date of onset were obtained from the general practitioner, who was also asked to inform the investigators of any ensuing adverse outcome of pregnancy. The date of delivery or miscarriage or fetal death and, if a live birth, the birth weight, gestational age, and details of any neonatal problems were provided by the consultant obstetrician. The general practitioners of the liveborn babies were contacted roughly one year later and asked to complete a simple form concerning the infants' physical and neurodevelopmental state.

Specimens collected—In the case of adverse outcomes any available fetal material, regardless of method of preservation, was requested from general practitioners, obstetricians, and local microbiologists. In the case of successful outcomes cord blood, a placental sample, and a throat swab from the neonate were requested. At one year the general practitioner was asked to obtain a thumb prick or ear prick specimen of blood from the baby.

Virological methods—Anti-B19 IgM and IgG were measured by antibody capture radioimmunoassay.[15] B19 DNA was detected by hybridisation assays[16] and parvovirus particles by immune electron microscopy.[16]

Results

Sixty different source laboratories throughout England and Wales sent initial antenatal serum. Of 193 subjects satisfying the case definition, three were lost to follow up leaving 190 women whose outcome of pregnancy was determined. Seventy seven per cent of the subjects were recruited in 1985 and 1986, when B19 virus infection was epidemic in Britain. Cases occurred throughout each year but less frequently in October, November, and December. The last patient was delivered in November 1988.

MATERNAL CHARACTERISTICS

Table I shows the age distribution of the study population. Women over 30 were over represented. Forty (23%) of the 176 women for whom there was information were primigravidas. Of the others, 124 (70%) had had one or more live births and 45 (26%) had had one or more adverse outcomes of pregnancy.

Clinical details of the B19 infection were provided for 184 of the 190 mothers. Of these, 168 (91%) had a rash, of whom just under half also had other symptoms —namely, arthralgia or arthritis, non-specific upper respiratory symptoms, general malaise. Of the 16 mothers with no rash, eight had joint and respiratory symptoms, two had a non-specific illness, and six were asymptomatic.

The reason for the B19 investigation was provided for 186 subjects. In 161 cases (87%) it was because of a rash with negative rubella test findings; in 18 cases (which included the six asymptomatic cases) because of contact either with confirmed erythema infectiosum or with an illness thought to be rubella; and in seven cases because of a flu-like illness, myalgia, or arthropathy.

The source of the mother's infection was stated to be unknown in 146 (77%) cases. Among the 44 subjects for whom it was known, 31 had acquired the infection from their other children. Nine subjects acquired B19 in the work setting, of whom two were teachers, two were doctors working with children, and one a nurse in an obstetric ward ("colleagues" stated to be the source in this case). The type of work setting was not described for the remaining four.

Table II shows the gestational stage at which B19 infection occurred. The distribution was weighted towards the first 20 weeks, which may reflect particular concern among general practitioners about rashes in early pregnancy.

TABLE I—*Age distribution of mothers with B19 infection compared with that of general antenatal population*

Age (years)	No (%) of B19 infected mothers	No (000s) in antenatal population (% of all conceptions†)
15-19	12 (6)	119·3 (15)
20-24	34 (18)	249·2 (31)
25-29	61 (32)	242·6 (30)
30-44	81 (43)	186·2 (23)
Total	188 (100)*	797·3 (100)

*In two cases maternal age was not known.
†Data for 1985. Source: *OPCS Monitor* FMI 87/2.

OUTCOME OF PREGNANCY

Four patients elected to have a therapeutic termination; in none were products of conception available for examination. Among the remaining 186 mothers, 156 (84%) delivered a live baby, 29 had a spontaneous abortion or intrauterine fetal death, and one had a stillbirth. The rate of fetal loss was higher among women infected before 20 weeks of gestation (28/166; 17%) than among those infected later (1/17; 6%) (table II). This difference did not reach significance ($p=0·3$; Fisher's exact test). Nevertheless, the wide 95% confidence interval (0·42 to 19·78) of the relative risk (2·87) suggested that numbers were too small in the late pregnancy group to detect a real difference if it existed.

Although there were no significant differences in age distributions, parity, and previous fetal losses between mothers with adverse and normal outcomes of pregnancy, there was a non-significant tendency for mothers with adverse outcomes to be older (16/30 (53%) mothers with an adverse outcome were aged 30 or over compared with 64/155 (41%) with a normal outcome; χ^2 test with Yates's correction, $p=0·1$) (tables III and IV).

ADVERSE OUTCOMES AND VIROLOGICAL INVESTIGATION OF FETAL TISSUE

Among the 30 adverse outcomes, fetal tissue or products of conception were available in 14. B19 DNA was definitely present in six cases, possibly present in two, and absent in six. Viral particles were detected by immune electron microscopy in four of the six B19

TABLE II—*Outcome of maternal infection with B19 in relation to stage of pregnancy*

Weeks of gestation maternal B19 infection occurred*	No of cases	No of live births	Weeks of gestation spontaneous abortion or fetal death occurred					
			1-12	13-20	21-27	28-40	Not known	Total
1-12	117†	96	7	14	–	–	–	21
13-20	49	42	–	6	1	–	–	7
21-27	10	10	–	–	–	–	–	0
28-40	7	6	–	–	–	1	–	1
Not known	3	2	–	–	–	–	1	1
Total	186†	156	7	20	1	1	1	30

*Occurrence defined as onset of symptoms or first positive blood test result if asymptomatic.
†Excludes four terminations of pregnancy.

TABLE III—*Age distribution of B19 infected mothers with normal and adverse outcome of pregnancy*

Age (years)	No (%) with normal delivery	No (%) with adverse outcome	Total
15-19	11 (7)	1 (3)	12 (6)
20-24	32 (21)	1 (3)	33 (18)
25-29	48 (31)	12 (40)	60 (32)
30-44	64 (41)	16 (53)	80 (43)
Total	155 (100)*	30 (100)	185 (100)

*In one case maternal age was not known.
$\chi^2 = 6{\cdot}247$; $p = 0{\cdot}1$.

TABLE IV—*Previous obstetric histories in B19 infected mothers with normal and adverse outcomes of pregnancy*

Previous history	Outcome of B19 infected pregnancy: No (%) with normal delivery	Outcome of B19 infected pregnancy: No (%) with adverse outcome
1 Or more live births	100/146 (68)	24/30 (80)
1 Or more abortions	33/142 (23)	7/29 (24)
1 Or more stillbirths	2/144 (1)	3/28 (11)*

*p=0·06 (Fisher's exact test).

DNA positive fetuses but not in the others examined. If the proportion (8/14 or 57%) of investigated fetuses with definite or possible B19 DNA is applied to all 30 fetal deaths then 17 (9%) of the 186 conceptuses whose mothers elected to go to term may have died as a result of intrauterine B19 infection.

Table V gives the intervals between maternal illness and fetal death and the relation of these to the virological findings. In 19 (63%) cases this interval was three to five weeks with a mode of four weeks, suggesting a specific incubation period rather than a non-specific effect of a maternal febrile illness. Viral DNA was identified even after some of the longer intervals, including the longest of 11 weeks.

The morphological picture was given in three of the six fetuses with B19 DNA detected: one was hydropic and the other two normal. Hydrops fetalis was not reported in any of the other adverse outcomes, and only one case of a developmental anomaly (anencephaly) was reported. B19 DNA was not detected in the fetus whose mother had acquired the infection at around the time of conception.

NEONATAL FINDINGS

Clinical—Among the 156 liveborn babies there were none with congenital abnormalities apart from two with hypospadias. One neonate who survived hydrops fetalis virologically confirmed as due to intrauterine B19 had been treated by intrauterine blood transfusion.[17] Six (4%) were born before 36 weeks of gestation. Of 142 for whom data were available, 99 (70%) were between the 11th and 90th centiles of birth weight for gestational age; 11 (8%) were under the third centile.

Virological—At least one of the three samples requested (cord blood, throat swab, placenta) was obtained from 134 of the 156 neonates and all three from 86. Among the 128 from whom a cord or neonatal blood sample was examined, eight had B19 IgM (range 1·2-11·5 arbitrary units). None of the premature babies or those under the third centile were in this group. The survivor of hydrops had no detectable B19 IgM in cord blood. B19 DNA was not detected in any of 100 placental specimens or 101 throat swabs or in the cord blood samples.

Follow up at age ≥1 year—Of the 129 infants who were eligible for follow up by the end of June 1989, clinical information was available for 114 (88%) and serological information for 97 (75%). Fifteen (12%) were lost to follow up, including one who had B19 IgM in cord blood. Among the 114, no congenital anomalies had emerged and none had a serious neurodevelopmental problem. Only two (both seronegative) had serious medical problems—namely, recurrent severe respiratory tract infections and cystic fibrosis. None of the 97 infants from whom serum was available had B19 IgM at 1 year, but 21 of the 97 had persistent B19 IgG. This compares with two of 90 infants aged 1-2 years identified in a serological survey of a population in 1982-3 (B Cohen, personal communication). Persistent B19 IgG at 1 year in the absence of B19 IgM implies intrauterine infection as the assay is not sensitive enough to detect maternal antibody at this age. None of the 21 IgG positive infants had been born before 36 weeks of gestation and only one had been under the third centile of weight for gestational age.

Combined serological findings on neonates and infants—A total of 142 (91%) of the 156 liveborn babies had at least one serological investigation either at birth or at 1 year and 82 had both. Table VI shows the relation between the results in these 82 pairs of serum samples.

TABLE V—*Intervals between onset of maternal B19 infection and fetal loss in the 30 cases, and detection of B19 DNA in fetal tissue or products of conception*

B19 DNA test result	Interval (weeks): 1	2	3	4	5	6	7	8	9	10	11	Total
Positive	–	–	1	–	1	–	1	2	–	–	1	6
Equivocal	–	–	–	2	–	–	–	–	–	–	–	2
Negative	–	1	–	2	1	–	1	–	1	–	–	6
Not tested	1	–	2	6	4	–	–	2	–	1	–	16
Total	1	1	3	10	6	0	2	4	1	1	1	30

TABLE VI—*Relation between IgM antibody in cord blood and IgG antibody at age ≥1 year in 82 infants with paired blood samples*

Anti-B19 IgM in cord blood	Anti-B19 IgG at age ≥1 year: Present	Absent	Total
Present	3	2	5
Absent	15	62	77
Total	18	64	82

Sensitivity of cord blood IgM as predictor of persistent IgG at 1 year=3/18 (17%).
Specificity of cord blood IgM as predictor of persistent IgG at 1 year=62/64 (97%).

If we assume that persistent B19 IgG at 1 year of age signifies intrauterine infection the sensitivity and specificity of B19 IgM in cord blood as markers of congenital infection were 17% and 97% respectively.

Transplacental transmission rate—An estimate of the transplacental transmission rate of B19 in the study population was made by assuming that, in addition to the one case with prenatal confirmation of fetal infection, the occurrence of at least one of the following signified intrauterine infection: (*a*) an adverse outcome (regardless of virological findings); (*b*) B19 IgM in cord or neonatal blood; (*c*) persistent B19 IgG in infants aged ≥1 year. The possibly exaggerated effect of these assumptions may be counterbalanced by underascertainment of cases in infants not old enough for the serological examination at 1 year and who may have had a false negative B19 IgM result in cord blood. The transplacental transmission rate was estimated to be 33%, calculated as [30 (adverse outcome)+5 (IgM only available)+21 (IgG with or without IgM)+1 (B19 hydrops survivor)]/[142 (45 cord blood only+82 cord blood and blood at 1 year+15 blood at 1 year only)+30 (adverse outcome)]=57/172 (33%). In 26 of the 27 infants with definite or possible intrauterine infection the mother's gestational stage at infection was known. In 10 (38%) of these cases B19 was acquired after 20 weeks of pregnancy. As only 9% (17/183) of the mothers as a whole were infected after week 20 this suggests that the transplacental transmission rate

increases later in gestation. Alternatively, fetuses infected earlier may be less able to respond immunologically and to produce antibody values that are measurable at birth and during infancy. Nevertheless, we observed one infant whose mother acquired B19 at eight weeks of gestation who had both specific IgM in cord blood and B19 IgG (>100 arbitrary units) at 13 months of age.

Discussion

A favourable outcome of pregnancy despite B19 infection has been documented in case reports[10,11] but this study has provided the first opportunity to estimate the probability of a favourable outcome in a population of B19 infected mothers. Of 186 women who elected to go to term, 156 (84%) had a normal healthy baby, and follow up of 114 of their neonates to the age of 1 year showed no serious problems. Furthermore, among 27 of these infants who were a subset with presumed intrauterine infection (cord blood B19 IgM, persistent B19 IgG at 1 year, or intrauterine fetal diagnosis) no abnormalities were reported. The only neonatal outcome of concern was a slightly higher than expected proportion of babies small for gestational age. The relevance of this cannot be determined in the absence of controls matched for age, parity, ethnic origin, and social class.

A report of an aborted fetus with eye anomalies possibly related to B19 infection[18] together with observations that animal parvoviruses may be teratogenic have caused concern, but none of the neonates or fetuses in this series had eye defects reported. Our study sample, however, was too small to detect a rare teratogenic effect if it existed. If the true severe defect rate is 1% the appropriate sample size with the probability of observing no cases being acceptably small (for example, <1%) would be over 9000 subjects. Furthermore, presumed congenitally infected babies may not have been followed up for long enough to detect possible neurodevelopmental defects or other physical problems.

We do not know whether transplacentally acquired B19 can cause persistent infection. This may occur in immunosuppressed subjects[6] and in young infants[19] and might occur in fetuses, given their immature immune state. Long term follow up of our seropositive infants will be necessary to exclude late sequelae and viral persistence.

The estimated maximum transplacental transmission rate of B19 was similar to that of cytomegalovirus. In contrast with babies with congenital cytomegalovirus infection or with congenital rubella,[20] however, we were not able to find evidence of B19 DNA in the neonates, even those with serological evidence of intrauterine infection. This suggests that these babies do not pose a significant infectious risk to contacts. Measurement of B19 IgM in cord blood is apparently a poor method of detecting intrauterine infection, and diagnosis of this therefore depends on serological follow up of the baby to 1 year. The excess of B19 IgG in 1 year olds in the study compared with the background rate suggests that this is a useful marker of intrauterine infection, but further serological examination of these infants is needed for confirmation.

Although most women infected with B19 had a satisfactory outcome of pregnancy, 30 (16%) did not and we have confirmed the observations of others that B19 may be feticidal.[4-6] Based on virological findings among the fetuses available for examination, the overall risk of fetal death caused by B19 among the total study population was estimated to be 9% (17 of all 186 cases in which the mother elected to go to term). This proportion may be combined with estimates of rates both of susceptibility and of acquisition of infection in order to derive a crude upper limit estimate of risk of fetal death due to B19 in pregnant women of unknown serological state who are exposed in the common settings of the household and the school.[6] In the household this would be 0·09 (risk of fetal death)×0·5 (rate of susceptibility)×0·5 (rate of infection)×100= 2·3%, and in the school 0·09×0·5×0·3×100=1·4%.

The estimated risk of B19 associated fetal death which we have found contrasts with earlier reports which suggested that between one third and three quarters of B19 infected pregnancies had an adverse outcome caused by the virus.[10,13,14] Our findings, however, are supported by the preliminary results of a similar prospective study in the United States.[6] Furthermore, a controlled study of stillbirths and spontaneous abortions has shown that B19 is not responsible for a substantial proportion of fetal deaths in the general population.[21]

Our data suggest (but do not confirm statistically) that the risk of fetal loss might be higher in B19 infections acquired before 20 weeks than in those acquired later.[22] The background rate of spontaneous abortion is also inversely related to duration of gestation and women acquiring B19 in early pregnancy will therefore wish to know the magnitude of any excess risk posed by the infection. Unfortunately, the uncontrolled nature of our study precludes an accurate estimate of this. Published data on background rates of fetal loss may be misleading for comparative purposes because of differences in age, previous reproductive history, ethnic orign, socioeconomic grouping, or gestational stage. Nevertheless, a recent (1986-8) study of women resident in the Cambridge area, who were recruited before conception in order to avoid ascertainment bias and followed up prospectively throughout pregnancy, has provided a useful comparison. A spontaneous overall fetal loss rate of 50/407 (12·3%; 95% confidence interval 9·1% to 15·3%) was found.[23] This compares with 30/186 (16·1%) 95% confidence interval 10·8% to 21·4%) in our B19 infected subjects. In the Cambridge women, however, only 0·6% (2/359; 95% confidence interval 0 to 1·3) of the losses occurred between 12 and 28 weeks of gestation compared with 12·4% (21/169; 95% confidence interval 8·0% to 18·6%) in our mothers. By contrast, 11·8% of the Cambridge women had a first trimester abortion compared with 6·0% of the B19 infected mothers.

The Cambridge study showed that a previous history of one or more abortions was a significant risk factor for spontaneous loss in the current pregnancy. A total of 120 (29%) of 407 subjects in that study had such a history compared with 40 (23%) of 171 subjects in our study for whom there was information. Furthermore, a slightly higher proportion of subjects in the Cambridge study (6·1%) were aged over 38 than in ours (2·7%). Thus among mothers in our study who, by virtue of their age and obstetric history, were apparently no more at risk of an adverse outcome than the Cambridge mothers there was a pronounced excess (12·4% *v* 0·6%) of fetal loss in the second trimester. Comparisons between national and local study samples should be treated with extreme caution for the reasons given above, but it is unlikely that this large difference can completely be explained by differences between the two study groups in other confounding variables for an adverse outcome of pregnancy. That we did not find an excess risk in the first trimester in the B19 infected group compared with the Cambridge sample may reflect under ascertainment. Unlike our sample, the Cambridge women were followed up from conception.

Conclusion and recommendations

Eighty four per cent of mothers with B19 infection in our study had a normal outcome of pregnancy. Never-

theless, we estimate that roughly 9% of them may have had a fetal death caused by this virus, and we suggest that the infection imposes a substantial excess risk of second trimester abortion. Our data do not allow us to reach a conclusion about loss in the first trimester.

Health care workers are expected to provide accurate and informed advice to antenatal patients who are or who may be exposed to an embryopathic agent, but published advice concerning exposure to B19 is conflicting, ranging from the proposal that pregnant women should be excused from working in schools or nurseries for the duration of an outbreak of erythema infectiosum[12] to a suggestion that routine exclusion is unjustified.[6] Certainly epidemics of B19 infection lead to an increased risk of infection and therefore of fetal loss in susceptible pregnant women, but blanket decisions on exclusion from work or transfer to a lower risk area are inappropriate. Instead, decisions should be made on an individual basis after serological determination of susceptibility. They will be influenced by estimates of likelihood, intensity, and duration of exposure, as well as by such personal considerations as loss of income and the value attached to the pregnancy. Pregnant teachers and day care staff, health care personnel who work with children and young adults,[24] and mothers of young children are especially at risk. Most women in our study, however, were unaware of the source of the infection, and among those who did know it was most often their own children. It is usually impracticable to prevent exposure in the patient's own home.

There is no role for a routine antenatal screening programme for B19, and infection in pregnancy is not an indication for therapeutic termination. Recommendations to monitor infected women with frequent ultrasound examinations or serum α fetoprotein determinations, or both, in order to detect fetal hydrops and correct it by intrauterine transfusion should be treated with caution. A small number of B19 infected fetuses have been saved by this means and it presents an attractive therapeutic intervention,[13 17] but it will be necessary to monitor the health of all survivors for a long period as they are likely to have been severely affected in utero. With one exception we do not know whether any of the "presumed infected" liveborn infants in our series went through a transient hydropic phase in utero that would have led to their being unnecessarily subjected to intrauterine transfusion with its associated risks. If intrauterine transfusion were used on a wide scale more fetuses might be lost than saved.

Information about B19 virus should be added to that about other infections in pregnancy in the health education package provided for expectant parents. It should describe the possible outcomes and interventions which would follow serological confirmation of the diagnosis. This will help mothers with symptoms or those exposed to B19 virus to reach, in consultation with their general practitioner or obstetrician, an informed decision about further investigation and management.

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PHLS Working Party on Fifth Disease

MEMBERS OF WORKING PARTY AND PARTICIPANTS IN STUDY—*Public Health Laboratory Service:* Dr S M Hall (study coordinator and compiler of report; PHLS Communicable Disease Surveillance Centre), Dr B J Cohen and Dr P P Mortimer (Virus Reference Laboratory, Central Public Health Laboratory), Dr E O Caul (PHL Bristol), Dr J Cradock-Watson (PHL Manchester). *University College and Middlesex School of Medicine, University College London:* Dr M J Anderson, Professor J R Pattison. *Regional Virus Laboratory, East Birmingham Hospital:* Mrs J A Shirley. *John Radcliffe Hospital, Oxford:* Dr T E A Peto.

1 Cossart YE, Field AM, Cant B, Widdows D. Parvovirus-like particles in human sera. *Lancet* 1975;i:72-3.
2 Pattison JR, Jones SE, Hodgson J, *et al.* Parvovirus infections and hypoplastic crisis in sickle cell anaemia. *Lancet* 1981;i:664-5.
3 Anderson MJ, Lewis E, Kidd IM, Hall SM, Cohen BJ. An outbreak of erythema infectiosum associated with human parvovirus infection. *Journal of Hygiene (London)* 1984;**92**:85-93.
4 Knott PD, Welply GAC, Anderson MJ. Serologically proved intrauterine infection with parvovirus. *Br Med J* 1984;**289**:1660.
5 Brown T, Anand A, Ritchie LD, Clewley JP, Reid TMS. Intrauterine parvovirus infection associated with hydrops fetalis. *Lancet* 1984;ii:1033-4.
6 Centres for Disease Control. Risks associated with human parvovirus B19 infections. *Morbidity and Mortality Weekly Report* 1989;**38**:81-7.
7 Caul EO, Usher MJ, Burton PA. Intrauterine infection with human parvovirus B19: a light and electronmicroscopy study. *J Med Virol* 1988;**24**:55-66.
8 Greer IA. Complications of erythema infectiosum in pregnancy. *Br Med J* 1988;**296**:862-3.
9 Holme C. Concern over report on disease that kills babies. *Glasgow Herald* 1987 Sep 25:4(col 6).
10 Mortimer PP, Cohen BJ, Buckley MM, *et al.* Human parvovirus and the fetus. *Lancet* 1985;ii:1012.
11 Woernle CH, Anderson LJ, Tattersall P, Davison JM. Human parvovirus B19 during pregnancy. *J Infect Dis* 1987;**156**:17-20.
12 Rodis JF, Hovick TJ, Quinn DL, Rosengren S, Tattersall P. Human parvovirus in pregnancy. *Obstet Gynecol* 1988;**72**:733-8.
13 Schwarz TF, Roggendorf M, Hottentrager B, *et al.* Human parvovirus B19 in pregnancy. *Lancet* 1988;ii:566-7.
14 Anand A, Gray ES, Brown T, Clewley JP, Cohen BJ. Human parvovirus infection in pregnancy and hydrops fetalis. *N Engl J Med* 1987;**316**:183-7.
15 Cohen BJ, Mortimer PP, Pereira MS. Diagnostic assays with monoclonal antibodies for the human serum parvovirus-like virus (SPLV). *Journal of Hygiene (London)* 1983;**91**:113-30.
16 Clewley JP, Cohen BJ, Field AM. Detection of parvovirus B19 DNA, antigen and particles in the human fetus. *J Med Virol* 1987;**23**:367-76.
17 Peters M, Nicolaides KH. Prenatal diagnosis and treatment of parvovirus infection. *Obstet Gynecol* (in press).
18 Weiland HT, Vermey-Keers C, Salimans MMM, Fleuren GJ, Verwey RA, Anderson MJ. Parvovirus B19 associated with fetal abnormality. *Lancet* 1987;i:682-3.
19 Belloy M, Morinet F, Blondin G, Courouce AM, Peyrol Y, Vilmer E. Erythroid hypoplasia due to chronic infection with parvovirus B19. *N Engl J Med* 1990;**322**:633-4.
20 Cradock-Watson JE, Miller E, Ridehalgh MKS, Terry GM, Ho-Terry L. Detection of rubella virus in fetal and placental tissues and in the throats of neonates after serologically confirmed rubella in pregnancy. *Prenat Diagn* 1989;**9**:91-6.
21 Kinney JS, Anderson LJ, Farrar J, *et al.* Risk of adverse outcomes of pregnancy after human parvovirus B19 infection. *J Infect Dis* 1988;**157**:663-7.
22 Dylewski J, Khoday S. Erythema infectiosum during pregnancy. *J Infect Dis* 1988;**158**:659.
23 Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. *Br Med J* 1989;**299**:541-5.
24 Bell LM, Naides SJ, Stoffman P, Hodinka RL, Plotkin SA. Human parvovirus B19 infection among hospital staff members after contact with infected patients. *N Engl J Med* 1989;**321**:485-91.

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Correction

Contrasting effects of enalapril and metoprolol on proteinuria in diabetic nephropathy

An editorial error occurred in this article by Dr Staffan Björck and others (7 April, pp 904-7). The wrong figure was printed as figure 1. The correct figure is given below.

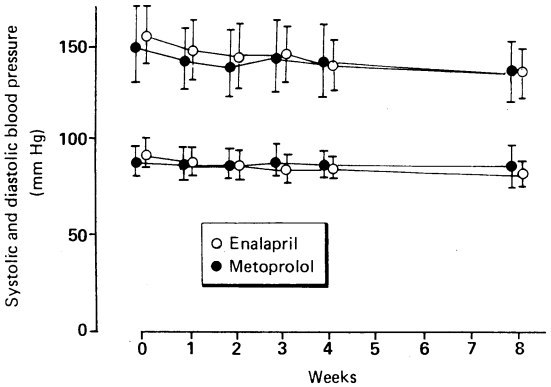

FIG 1—*Blood pressure in 40 patients with diabetic nephropathy treated with enalapril or metoprolol. Values are means (SD) and are the mean of supine and standing blood pressure*