Parvovirus B19 infection in pregnancy and subsequent morbidity and mortality in offspring

Jonathan Lassen,1* Peter Bager,1 Jan Wohlfahrt,1 Blenda Böttiger2 and Mads Melbye1

1Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark and 2Department of Virology, Statens Serum Institut, Copenhagen, Denmark

*Corresponding author. Department of Epidemiology Research, Statens Serum Institut, 5 Orestads Boulevard, DK-2300 Copenhagen S, Denmark. E-mail: jonathan_lassen@hotmail.com

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Background Because parvovirus B19 infection in pregnancy has been associated with infant morbidity and mortality in case reports and after intrauterine transfusion, we tested the population-based association using serum and hospital data of high quality.

Methods We established a cohort of 113,228 children born to women tested for parvovirus B19 infection during pregnancy in a major diagnostic laboratory in Denmark, from 1994 to 2009. Information on 20 selected morbidity diagnoses and on mortality was obtained from the Danish National Patient Register, the Danish Cancer Register and the Danish Civil Registration System. Incidence rate ratios (IRR) were estimated by log-linear Poisson regression with adjustment for age and sex of the child, maternal age and year of maternal parvovirus B19 test.

Results A total of 1095 (1.0%) children were born to mothers who were infected with parvovirus B19 during pregnancy. During 1 million person-years of follow-up, 10,856 children experienced morbidity and 590 children died. Overall, maternal infection status was neither associated with morbidity during infancy (IRR 0.64; 95% CI: 0.40 to 1.02) or childhood (IRR 0.93; 95% CI: 0.77 to 1.14), nor with infant mortality (IRR 0.98; 95% CI: 0.44 to 2.20). Specifically, there was no association with 19 of 20 morbidities. An excess risk of cancer in the central nervous system was observed (IRR 5.88; 95% CI: 1.41 to 24.6); however, the number of exposed cases was very small (n = 2).

Conclusions Parvovirus B19 infection during pregnancy was not associated with overall morbidity or mortality in infancy and childhood.

Keywords Infectious diseases, epidemiology, parvovirus, congenital abnormalities, morbidity, mortality

Introduction

Human parvovirus B19 (B19) infection primarily takes place during childhood, where it causes erythema infectiosum, also known as the fifth disease.1 Infection in pregnancy may cause hydrops foetalis or foetal death through infection of foetal erythroid progenitor cells leading to anaemia and
cardiac failure. Infection may also be associated with foetal myocarditis, which can cause arrhythmias and cardiac arrest without presence of anaemia. Larger epidemiological studies confirm an increased risk of foetal loss, even after maternal B19 serology where up to 50% of mothers may have had asymptomatic infection. Symptomatic treatment is possible, e.g. with intravascular/intrauterine transfusion (IUT) for B19-associated hydrops foetalis. The perinatal survival nowadays ranges from 67% to 85%, although long-term neurodevelopmental impairment in this high-risk group of children has been suggested in some studies but not all.

Maternal and public health concern about an association between B19 infection during pregnancy and morbidity after birth is affected by the risk of foetal loss, asymptomatic infections and morbidities reported in case and animal studies. For example, case studies reported congenital anaemia, thrombocytopenia, heart failure and myocarditis, meningitis and anomalies of the heart, brain and eyes. In addition, one report associated B19-induced hydrops foetalis with death shortly after birth. Animal studies have shown that intrauterine parvovirus infection caused malformations in rodents, cats and dogs.

In general, viral infections in pregnancy have been hypothesized to be associated with auto-immune diseases (e.g. type 1 diabetes, juvenile arthritis), neurobehavioural diseases (e.g. attention deficit hyperactivity disorder (ADHD)), asthma and some malignant diseases (acute leukemia and cancer in the central nervous system). Given the systemic effects of B19 infection in foetal and infant cases (e.g. anaemia) and the small size of previous studies, there is a need for an in-depth long-term follow-up for adverse outcome of the potential concern for pregnant mothers testing positive for B19 infection in routine checkups.

We took advantage of the high number of tests for B19 infection performed in Denmark and the high quality of Danish national registers, and determined morbidity and mortality in infancy and childhood in 113228 children after in utero exposure to a maternal B19 infection measured by IgM seropositivity.

Materials and Methods

Study cohort

Statens Serum Institut, Copenhagen, Denmark, is an institution under the Danish Ministry of Interior and Health with the aim to prevent and control infectious diseases. The diagnostic laboratory at Statens Serum Institut receives blood samples from general practitioners, specialist clinics (e.g. gynaecology), and hospitals all over the country. Since 1994, all test-related personal information, e.g. sex, type of test, date of sampling, and test results have been registered electronically and kept under the unique 10-digit Danish Civil Registration System (CRS) number. The CRS number has since 1968 been assigned at birth or immigration to all Danish residents, and provides identity-secure linkage with personal records in all national registers. Furthermore, the CRS registry is a continually updated demographic database with individual-level information about, for example, date of birth, vital status, and identity of parents and offspring.

We identified all women tested for B19 infection at Statens Serum Institut (n = 161286) from 1994 to 2009. Using complete information about offspring, extracted from the CRS on 31 December 2009, we identified 148248 women with live-born offspring. To identify those women tested for B19 serology during pregnancy, we included women who had given birth less than 280 days (40 weeks) after the date of blood sampling. Accordingly, 114809 women had blood drawn for B19 serology during one or more pregnancies. Their offspring constituted the study cohort (n = 125997). For 12769 children in the study cohort, the maternal B19 IgM result was unregistered or inconclusive, thus leaving 113228 children in the study.

Parvovirus B19 testing

Serum samples were tested for B19 IgM antibodies using enzyme-linked immunosorbent assays, initially IDEIA™ B19 IgM (Dako A/S, Copenhagen, Denmark) and from 2001 EIA™ (Biotrin, Dublin, Ireland). The tests were performed in accordance with the manufacturer’s instructions. The IDEIA™ has been reported to have a sensitivity of 84–97% and a specificity of 95–97% for B19 infection. In pregnant women, the EIA™ test has a reported sensitivity of 100% during acute infection and 64% when the sera of pregnant women were collected 8 to 12 weeks after the infection. The specificity was reported to be 92%. In the study we defined women as having acute B19 infection if they tested positive for B19 IgM antibodies. Thus, cohort children with a maternal record of a positive B19 IgM result during pregnancy were defined as children exposed to maternal B19 infection during foetal life.

The Danish National Patient Register

Information on morbidity (except cancer) was identified in the National Patient Register which contains information about all non-psychiatric hospital admissions in Denmark since January 1977. Outpatient hospital contacts and psychiatric hospital admissions have been included since 1995. Information concerning, for example, dates of admission and discharge, hospital department and diagnoses is kept for every hospital contact linked to the patient’s CRS number. Since 1 January 1994, diagnoses have been coded according to the 10th revision of the International Classification of Diseases (ICD-10).
The Danish Cancer Register
Cancer cases were identified in the Danish Cancer Register. This register contains information on persons diagnosed with cancer since 1943. Since March 1987 reporting has been mandatory for all medical doctors. Information including date of cancer diagnosis as well as method of verification, clinical stage and initial treatment given is kept for every cancer diagnosis linked to the patient’s CRS number. Diagnoses are coded according to the 10th revision of the International Classification of Diseases (ICD-10) since 1 January 2004. Before 2004, diagnoses were coded according to the 7th revision (ICD-7). Subsequently, cancer diagnoses registered between 1978 and 2003 have been converted to ICD-10 codes in the register.

Definition of morbidity
Morbidities included in the studies cited in the introduction section were selected for further studies. For each morbidity, in- and outpatient cases were identified using ICD-7 and/or ICD-10 codes: congenital anaemia (ICD-10: P614), thrombocytopenia (ICD-10: P610, D69), cardiac disease (ICD-10: I40, I420, I424, I429, I509), septal heart defects (ICD-10: Q21), central nervous system (CNS) anomalies (ICD-10: Q02, Q03), mental retardation (ICD-10: F70, F71, F72, F73, F78, F79), delayed psychomotor development (ICD-10: R620), ocular malformations (ICD-10: Q11, Q12, Q13, Q14, Q15), meningitis (ICD-10: G00, G01, G02, G03, A87) including viral meningitis (G020, A87), diabetes type 1 (ICD-10: E10), juvenile arthritis (ICD-10: M082, M083, M084, M088, M089), asthma (ICD-10: J45, J46) and ADHD (termed ‘hyperkinetic disorders’ in the ICD) (ICD-10: F90), eye cancer (ICD-7: 192 equal to ICD-10: C69), CNS cancer (ICD-7: 193 equal to ICD-10: C70-72, D32-33, D42-43), Hodgkin lymphoma (ICD-7: 201 equal to ICD-10: C81), non-Hodgkin lymphoma (ICD-7: 200, 202 equal to ICD-10: C82-85, C96) and leukemia (ICD-7: 204 equal to ICD-10: C91-95) including acute lymphoblastic leukemia (ICD-7: 204.3 equal to ICD-10: C91.0, C92.0, C93.0, C94.0, C95.0).

Statistical analysis
The possible effect of B19 infection in pregnancy on morbidity and mortality in the offspring was analysed by survival analyses. For morbidity, children were followed from date of birth until date of diagnosis of the relevant morbidity, death, emigration or 31 December 2010, whichever came first. For mortality, children were followed from date of birth until death, emigration or 31 December 2010, whichever came first. Incidence rate ratios (IRR) with 95% confidence intervals (95% CI) were estimated in a log-linear Poisson regression model adjusted for sex, maternal age (<20, 20–24, 25–29, 30–34, ≥35 years), year of B19 test (1994–97, 1998–2001, 2002–05, 2006–09) and age of the child (1-year categories; due to a lack of cases in the upper age categories, we combined the upper age categories where needed). IRRs of morbidity and mortality were estimated for both infancy (the 1st year of life) and childhood (from date of birth and maximally up to 16 years of age). For adjustment of IRRs of infant morbidity and infant mortality, age was further categorized as 0–5 months and 6–11 months. For morbidity, effect modification by aforementioned categories of maternal age, sex, and year of B19 test was evaluated by including interaction terms in the model.

Data management and analyses were performed with SAS software (version 9.1, SAS Institute, Cary, NC, USA). Maximum likelihood estimation of IRRs and 95% CIs were performed using the GENMOD procedure in SAS. Two-sided P-values were based on likelihood ratio tests, and 95% CIs were based on Wald’s approximation.

Ethical aspects
The study was approved by the Danish Data Protection Agency (file no. 2008-54-0472). Because subjects were not contacted as part of the study, written informed consent was not required in accordance with Danish law.

Results
Our cohort consisted of 113,228 children born to women tested for B19 infection during pregnancy between 1994 and 2009. Table 1 presents characteristics of the children with regards to sex, maternal age and the year of B19 test. The mean age of the mothers in the cohort at time of birth was 30.7 years (range 14.5 to 48.9 years). Overall, 1095 (0.97%) children were exposed to maternal B19 infection during foetal life. The proportion of exposed children increased with increasing age of the mother (P < 0.001), and varied by year of B19 test (P < 0.001) in accordance with reported epidemics. A total of 10,856 children experienced morbidity according to exposure to maternal parvovirus B19 infection during foetal life. A total of 590 children died during 1,029,618 person-years of follow-up (110,304 person-years in infancy and 919,314 later on). Exposure to maternal B19 infection during foetal life was neither associated with mortality in infancy (IRR 0.98; 95% CI: 0.44 to 2.20) nor during childhood (IRR 0.99; 95% CI: 0.44 to 2.21). A total of 10,856 children experienced morbidity during 965,792 person-years of follow-up. The median duration of follow-up for morbidity in childhood was 9.2 years. Among children who experienced morbidity, 103 were exposed to maternal B19 infection during foetal life (Table 2). Overall, exposure during foetal life was not associated with morbidity in childhood (IRR 0.93; 95% CI: 0.77 to 1.14) (Table 2). The corresponding IRR for morbidity in
infancy (children aged 0–12 months) was 0.64 (95% CI: 0.40 to 1.02). In analyses of effect modifications, the potential association between exposure to maternal B19 infection during foetal life and morbidity in childhood was not modified by sex ($P = 0.26$), maternal age ($P = 0.58$) or year of B19 testing ($P = 0.08$).

In a supplementary analysis of morbidity, we excluded asthma cases because asthma was much more prevalent than other studied morbidities and thus, theoretically, could either weaken or represent a morbidity after B19 infection. However, we found no association between B19 infection and overall morbidity excluding asthma (Table 2).

Table 3 shows the IRRs for each of the 20 specific morbidities. Exposure to maternal B19 infection during foetal life was not associated with the risk of 19 of the 20 specific morbidities (Table 3). B19 exposure was associated with an excess risk of cancers in the CNS (IRR 5.88; 95% CI: 1.41 to 24.6) based on two exposed cases. These two B19-exposed cases of CNS cancer were diagnosed at ages 1 and 4 years, respectively, were not part of multiple pregnancies and experienced no other of the selected morbidities during the study period.

In a supplementary analysis of overall morbidity, we included in the study cohort children born to mothers with an unregistered or inconclusive record of B19 IgM test result (12,769 children), and this did not change the results materially, i.e. regardless of whether the IgM records were interpreted as negative or positive. Finally, analyses of overall morbidity were performed after restricting the study cohort into samples performed in the first, second or third trimester of pregnancy, respectively. These restrictions did not change the results materially.

**Discussion**

This large cohort study demonstrated no overall association between B19 infection in pregnancy and the offspring’s risk of morbidity and mortality in infancy and childhood. The important message is that the detrimental effects (e.g. anaemia, cardiac failure, myocarditis) that B19 may inflict on the foetus are not carried forward as a morbidity into childhood. Extra precautions during the pregnancy are recommended due to the risk of hydrops foetalis and the risk of foetal death; however, this population-based study shows that a live-born child does not carry on an excess risk of serious morbidity or mortality after a maternal B19 infection.

**Table 1** Prevalence of exposure to maternal parvovirus B19 (B19) infection during foetal life according to characteristics among 113,228 children born to women tested during pregnancy for parvovirus B19 IgM, Denmark, 1994–2009

<table>
<thead>
<tr>
<th>Maternal B19 infection during foetal life</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children</td>
<td>1095 (1.0%)</td>
<td>112,133</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>553 (1.0%)</td>
<td>57,495</td>
</tr>
<tr>
<td>Female</td>
<td>542 (1.0%)</td>
<td>54,638</td>
</tr>
<tr>
<td>Maternal age at B19 test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>5 (0.4%)</td>
<td>1,302</td>
</tr>
<tr>
<td>20–24 years</td>
<td>90 (0.7%)</td>
<td>12,147</td>
</tr>
<tr>
<td>25–29 years</td>
<td>359 (0.9%)</td>
<td>42,673</td>
</tr>
<tr>
<td>30–34 years</td>
<td>457 (1.1%)</td>
<td>41,292</td>
</tr>
<tr>
<td>$\geq$ 35 years</td>
<td>184 (1.2%)</td>
<td>15,719</td>
</tr>
<tr>
<td>Year of maternal B19 test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994–97a</td>
<td>315 (1.6%)</td>
<td>19,259</td>
</tr>
<tr>
<td>1998–01</td>
<td>433 (0.9%)</td>
<td>45,758</td>
</tr>
<tr>
<td>2002–05</td>
<td>277 (0.7%)</td>
<td>38,971</td>
</tr>
<tr>
<td>2006–09</td>
<td>70 (0.9%)</td>
<td>8,145</td>
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<table>
<thead>
<tr>
<th>Maternal B19 infection during foetal life</th>
<th>Yes</th>
<th>No</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infancy</td>
<td>18</td>
<td>2877</td>
<td>0.64 (0.40, 1.02)</td>
</tr>
<tr>
<td>Childhood</td>
<td>103</td>
<td>10,753</td>
<td>0.93 (0.77, 1.14)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infancy</td>
<td>5</td>
<td>493</td>
<td>0.98 (0.44, 2.20)</td>
</tr>
<tr>
<td>Childhood</td>
<td>6</td>
<td>584</td>
<td>0.99 (0.44, 2.21)</td>
</tr>
</tbody>
</table>

*Children are followed from date of birth and maximally up to 16 years of age (median follow-up of 9.2 years).

The IRRs are adjusted for age, sex, maternal age and year of maternal B19 test.

Excluding asthma: 32 B19 exposed cases, 3,623 unexposed and an IRR of 0.85 (0.60, 1.21).

Person-years of follow-up were 10,605 in the exposed group and 955,186 in the unexposed group.

Person-years of follow-up were 11,228 in the exposed group and 1,018,390 in the unexposed group.
The concern that B19 infection during pregnancy might cause long-term detrimental effects primarily comes from animal studies where intrauterine B19 infection has been documented to cause malformations in a variety of animal species. In humans, the evidence has primarily been based on case reports suggesting an association between B19 infection during pregnancy and infant morbidities such as anomalies of, for example, the heart, brain and eyes. The literature is very sparse with respect to more systematic evaluations of a possible association. One study identified 182 exposed children and sought information on similar rare morbidities by questionnaires to general practitioners. Results were inconclusive partly because very few cases were identified, and partly because the exposure was incompletely recorded as only mothers with symptomatic B19 infection or reported contact with suspected cases of B19 infection were included in the study. In fact, it has been reported that up to 50% of B19-infected pregnant women are asymptomatic. The few morbidities observed in the study (six cases of mild developmental delay, three cases of iron deficiency anaemia and single cases of thrombocytopenia, eosinophilia, atrial tachycardia and torticollis) could not be causally related to the maternal B19 infection when the authors considered aetiology and expected prevalence.

Our study had several strengths. The incidence rate ratios presented were based on a large cohort of more than 110,000 children born to mothers serologically tested for B19 infection during pregnancy. With a median follow-up time of 9.2 years and more than one million person-years, the present study is, to our knowledge, by far the largest follow-up study on this subject to date. The data provided a unique opportunity to study morbidities that were either congenital or occurred very early in life or later in childhood long after the exposure. Information on the exposure during pregnancy and outcomes in the offspring was obtained independently of each other by taking advantage of the high quality of the national registers in Denmark. The study included pregnant women from all over Denmark who attended a general practitioner or hospital that chose to request a B19 test. In general, B19 IgG and IgM testing is often requested as part of a screening for a range of diseases and thus without a specific clinical suspicion of acute B19 infection. By way of example, all pregnant women are offered serological screening for HIV and hepatitis B infection, and since doctors are aware of the risk of foetal death associated with B19, they often in addition request a B19 test routinely. Finally, the prevalence of B19 infection in our cohort (0.97%) was compatible with population-based seroconversion rates observed in pregnant women (0.84%) during an epidemic in 1994 (2.9% vs 4.5%).

We used hospital diagnoses as outcomes. Most diagnoses have been reported to have a high validity and completeness (e.g. type 1 diabetes and malignant diseases) whereas others have a less complete registration, e.g. far from all cases of ADHD, delayed psychomotor development or asthma are admitted to hospitals.

Theoretically, a low specificity (i.e. many false positives) of the studied diagnoses, as we suspected for pre-school asthma, could cause non-differential misclassification and thereby lead to a deviation towards

<table>
<thead>
<tr>
<th>Maternal B19 infection during foetal life</th>
<th>Yes</th>
<th>No</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital anaemia</td>
<td>1</td>
<td>43</td>
<td>1.92 (0.26, 14.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>514</td>
<td>0.37 (0.09, 1.48)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>0</td>
<td>61</td>
<td>-</td>
</tr>
<tr>
<td>Septal heart defects</td>
<td>4</td>
<td>837</td>
<td>0.47 (0.18, 1.27)</td>
</tr>
<tr>
<td>Viral meningitis</td>
<td>2</td>
<td>78</td>
<td>2.57 (0.63, 10.5)</td>
</tr>
<tr>
<td>Meningitis (incl. viral)</td>
<td>4</td>
<td>299</td>
<td>1.29 (0.48, 3.47)</td>
</tr>
<tr>
<td>Ocular malformations</td>
<td>4</td>
<td>173</td>
<td>2.25 (0.83, 6.07)</td>
</tr>
<tr>
<td>CNS anomalies</td>
<td>0</td>
<td>140</td>
<td>-</td>
</tr>
<tr>
<td>Delayed psycho-motor development</td>
<td>6</td>
<td>1047</td>
<td>0.57 (0.25, 1.27)</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>4</td>
<td>245</td>
<td>1.47 (0.55, 3.96)</td>
</tr>
<tr>
<td>ADHD</td>
<td>4</td>
<td>198</td>
<td>1.87 (0.69, 5.05)</td>
</tr>
<tr>
<td>Asthma</td>
<td>72</td>
<td>7552</td>
<td>0.94 (0.75, 1.19)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>3</td>
<td>180</td>
<td>1.40 (0.45, 4.40)</td>
</tr>
<tr>
<td>Juvenile arthritis</td>
<td>1</td>
<td>194</td>
<td>0.47 (0.07, 3.35)</td>
</tr>
<tr>
<td>CNS cancer</td>
<td>2</td>
<td>35</td>
<td>5.88 (1.41, 24.6)</td>
</tr>
<tr>
<td>Eye cancer</td>
<td>0</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>0</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>0</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Leukemia (incl. ALL)</td>
<td>2</td>
<td>68</td>
<td>2.90 (0.71, 11.9)</td>
</tr>
<tr>
<td>ALL</td>
<td>2</td>
<td>64</td>
<td>3.03 (0.74, 12.4)</td>
</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; ALL, acute lymphoblastic leukemia.

*Children are followed from date of birth and maximally up to 16 years of age (median follow-up of 9.2 years).

IRRs for morbidities and mortality were adjusted for maternal age, sex and age of the child and year of B19 test.
a relative risk of 1. However, excluding morbidity from asthma did not change the overall result.

We observed an association between exposure to maternal B19 infection and an increased risk of rare CNS cancers, based on two exposed cases. We believe this finding should be interpreted with due caution. The very small number of exposed cases and the broad range of association (confidence intervals), as well as the fact that no previous case report implicated B19 in the aetiology of CNS cancers, argue against a strong causal association. Rather, the result reflects the fact that many outcomes were scrutinized in this study.

**Conclusion**

This large population-based study found that B19 infection during pregnancy, as measured by IgM test at routine checkups, is unlikely to be associated with increased risk of offspring morbidity or mortality in infancy and childhood. The finding is reassuring and useful in guidance of B19-infected pregnant women. It should be noted, however, that there is a known risk for foetal complications and a suspicion of rare neurodevelopmental impairment, which in some cases (e.g. immune deficiency, fertility problems) might be an argument for avoiding environmental exposure to the extent possible or for B19 vaccination when it might become available.

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**Conflict of interest:** None declared.

**KEY MESSAGES**

- Parvovirus B19 (B19) infection during pregnancy is known to increase the risk of foetal loss and complications, but animal and case reports have also raised suspicion about infant morbidity and mortality.
- In a large population-based follow-up of children with B19-tested mothers, neither mortality nor 19 of 20 serious morbidities were associated with foetal exposure to the virus.
- The finding is reassuring and may help guidance of B19-infected pregnant women.

**References**


