

Parvovirus B19 Infection in Pregnancy: Implications for Childhood Outcomes?

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Abstract: *Background:* Maternal parvovirus B19 infection can lead to serious consequences in the fetus including fetal death, non-immune hydrops fetalis and possibly long-term adverse neurodevelopmental outcome. To date, there has been no systematic review of the literature regarding long-term outcomes of these infants and children.

Objective: To systematically review the literature on the long-term neurodevelopmental outcomes of infants and children born to mothers with acute parvovirus B19 infection in pregnancy.

Methods: Electronic databases MEDLINE, EMBASE, CINAHL, PsychInfo, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CCRT) were searched to identify studies that reported on long-term neurodevelopmental outcome of infants and children born following maternal parvovirus B19 infection in pregnancy. No language restrictions were applied. Data synthesis was performed using qualitative description and was categorized based on 1) outcome of infants and children with clinical presentation of non-immune hydrops fetalis and 2) outcomes of infants and children born to mothers with serologic evidence of acute infection.

Results: Eleven studies were included. Five studies reported on outcomes in infants and children with non-immune hydrops fetalis while six studies reported on outcomes in infants and children born to mothers with serologic evidence of acute infection. There is a suggestion that the incidence of adverse neurodevelopmental outcome is higher in those who present with non-immune hydrops fetalis [18% (7/39), range from individual studies 0-31.3%] compared to asymptomatic infants and children born to mothers with acute parvovirus B19 infection in pregnancy [2.4% (12/494) range from individual studies 0-7.4%].

Conclusion: Even though the outcome of parvovirus B19 in pregnancy in most cases is favorable, there is some supportive data that fetal parvovirus B19 infection can cause central nervous system damage. Future prospective studies needs to be conducted to address this issue.

BACKGROUND

Parvovirus B19, named from Latin “Parvum” meaning small, is a single-stranded DNA virus responsible for erythema infectiosum, also known as “slapped cheek disease” or “fifth disease” common in young children [1]. The virus was discovered in 1975 by Cossart *et al.* [2] during routine screening of serum for hepatitis B and identified as the cause of erythema infectiosum in 1983 [3]. Since then the link between maternal parvovirus B19 infection and non-immune hydrops and fetal death has been well established [4-7].

The virus attaches to the “P” antigen that is linked to intracellular lytic and/or apoptotic pathways leading to cellular destruction and permitting viral replication [8]. The “P” antigen has been identified on erythroid progenitor cells, megakaryocytes, endothelial cells, placental cells and fetal liver and myocardial cells which are involved in the complex of symptoms that characterize the infection. Parvovirus tend

to be species specific and animal strains are not associated with disease in the humans [1].

Seroprevalent studies have documented that approximately 35-50% of woman of reproductive age are susceptible to parvovirus B19 infection and at risk of vertically transmitting the infection to the fetus [9, 10]. Approximately 1-3% of susceptible pregnant women without a known history of exposure to parvovirus B19 will seroconvert during pregnancy [10-13]. Up to 50% of susceptible pregnant women exposed to parvovirus B19 through household contacts will develop seropositivity while the rate of seroconversion is 20-30% when the exposure occurs in day care centres or school [11-13].

The risk of transmission to the fetus has been reported in the range of 17-33% [14-16] but infection remains asymptomatic in most cases [1]. However, a wide range of adverse outcomes have been reported in association with intrauterine parvovirus B19 infection including: spontaneous abortions (rate of 14.8% if infected prior to 20 weeks gestation and 2.3% if the infection occurs after 20 weeks gestation) [17-19]; occurrence of non-immune hydrops fetalis (NIHF) [11,14-18]; congenital anomalies including central nervous system, craniofacial and eye anomalies [1, 20]. The presenting features on ultrasound include generalized edema/ana-

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Table 1. Guide to Interpretation of Parvovirus Serology Values

Parvovirus B19 Ig G Result	Parvovirus B19 Ig M Result	Interpretation	Clinical Implication
Negative	Negative	No antibody detected	Susceptible to parvovirus B19 infection
Positive	Negative	Indicative of past exposure	Not susceptible to parvovirus B19 infection
Positive	Positive	Indicative of infection	Infection most likely within the last 2 to 3 months
Negative	Positive	Indicative of infection	Evidence of acute/recent infection with B19. Consider repeat testing in 2 to 4 weeks

sarca, ascites, pleural and pericardial effusion as well as placental edema. Other ultrasonographic manifestations of B19 infection include placentomegaly, polyhydramnios and Doppler findings consistent with anemia. Various mechanisms have been implicated in the occurrence of NIHF including severe fetal anemia leading to hypoxia and high output cardiac failure, development of fetal viral myocarditis leading to cardiac failure and impaired hepatic function [8,21].

The diagnosis of maternal parvovirus infection is based on clinical symptoms and signs and evidence of infection on serological testing for parvovirus specific immunoglobulin (Ig) G and Ig M. Table 1 provides a guide to interpretation of parvovirus Ig G and Ig M serology results in the diagnosis of infection [22]. However, serology may not be useful if infection is suspected after onset of hydrops fetalis due to the lag period between immune response and occurrence of hydrops. Therefore, the method of choice for detection of intrauterine infection is polymerase chain reaction (PCR) amplification of viral DNA *via* amniocentesis or cordocentesis [23].

Prevention of exposure is ideal, but not feasible, in susceptible pregnant individuals as the period of contagion is prior to the onset of symptoms. Women with confirmed exposure should be evaluated in a tertiary care unit by a maternal-fetal medicine specialist. The fetus should be assessed weekly for 8 to 10 weeks for evidence of anemia using middle cerebral artery Dopplers and for hydrops. If hydrops develops at or near term, consideration should be made for delivery or intrauterine transfusion. If hydrops develops in late first or early second trimester, when directed fetal therapy is impractical, management should be expectant or termination of pregnancy could be considered. Management of the hydropic fetus is by cordocentesis to assess fetal hemoglobin and reticulocyte count and facilitate intrauterine transfusion. Currently there are no randomized controlled trials to evaluate the best management for fetal hydrops secondary to parvovirus B19 infection but intrauterine transfusion appears to be a reasonable option [24, 25].

To date, there have been practice guidelines published in Canada [24] and UK [25] regarding management of parvovirus B19 infection in pregnancy but none of these statements systematically review the literature regarding the long-term neurodevelopmental outcomes of infants and children. Further, the impact of clinical presentation on long-term neurodevelopment has not been addressed. The availability of this information is vital to physicians in order to provide appropriate counseling regarding management and therapeutic options to the pregnant couple.

We undertook this systematic review to provide a summary on the long-term neurodevelopmental outcomes of infants and children born to mothers with parvovirus B19 infection in pregnancy.

MATERIAL AND METHODS

Search Strategies

A comprehensive literature search using the OVID search platform was conducted in the following databases: MEDLINE (1950 – March 2009), EMBASE (1980 – March 2009), CINAHL (1982 – March 2009), PsychInfo (1967 – March 2009), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CCRT) (1st Quarter 2009). No language restrictions were applied. The search terms used to identify studies for inclusion in this review are described in Appendix. The articles were scanned initially based on titles and abstracts by two reviewers (AJ, VS). Articles that reported on the long-term neurodevelopmental outcomes following maternal parvovirus B19 infection in pregnancy were retrieved in full and assessed for eligibility by two reviewers (AJ, VS). The reference lists of eligible studies were checked to identify additional studies for inclusion in this review. A log of search strategy, articles scanned, articles retrieved and included and excluded are reported in the results section.

Inclusion Criteria

Studies that reported on long-term neurodevelopmental outcome of infants and children born following maternal parvovirus B19 infection in pregnancy were included irrespective of the type of study design. We included cohort studies (prospective or retrospective), case-control studies, case series and case reports if they described the neuro-developmental outcomes. Information from studies published as full/short report was included.

Exclusion Criteria

Information presented as abstracts, letters, commentaries and editorials were excluded.

Primary Outcome

The primary outcome was neurodevelopmental outcome of infants and children born following maternal parvovirus B19 infection in pregnancy assessed using a validated tool or based on information provided by their physicians or caregivers using a questionnaire. Examples of validated tools include: Snijders-Oomen non-verbal intelligence test [26], Kaufmann assessment battery for children [27], Griffiths Test for infant development [28], Denver Developmental Screening test [29] and Bayley Scales of Infant Development [30].

Data Abstraction and Presentation

Data from each eligible study were extracted individually by two reviewers (AJ, VS) and compared. The reviewers resolved any disagreements through discussion or, if required, consulted a third person (EK).

Data synthesis was performed using qualitative description from the included studies and was categorized based on the clinical presentation: 1) infants and children with clinical presentation of NIHF and 2) infants and children born to mothers with serologic evidence of acute infection during pregnancy.

RESULTS

The electronic searches yielded 1034 citations from all six databases. All references were stored in an EndNote™ library that identified 178 duplicates. The remaining 856 unique references were screened by two authors (AJ, VS) against the inclusion criteria and 12 articles [14, 16, 17, 31-39] were retrieved for additional review (Fig. 1). Eleven studies [14, 16, 17, 31-36, 38, 39] met the eligibility criteria and were included in the systematic review. One study was excluded as it was a letter to the editor [37]. Information on the baseline characteristics of included studies is presented in Table 2. The results from studies are described below based on 1) outcomes of infants and children with NIHF and 2) confirmed maternal infection during pregnancy (based on maternal serology).

Outcomes Based on Clinical Presentation of NIHF

Five studies reported on the neurodevelopmental outcome in infants and children who presented with NIHF secondary to congenital parvovirus B19 infection (Table 2) [32-34, 36, 39]. The type of study designs include retrospective case series (N=3) [32, 33, 36] and case reports (N=2) [34, 39]. Results from individual studies are presented below.

Cameron *et al.* [32] reported outcome of 16 pregnancies complicated by NIHF secondary to parvovirus infection. Three fetuses received intrauterine transfusion (IUT) of packed red blood cells of which only one survived. The only live born infant in this study was followed up regularly and was reported to have normal development at 2 years of age.

Dembinski *et al.* [33] reported neurodevelopmental outcomes of infants and children with NIHF who received IUT from a single tertiary care center in Germany. Of the 67 confirmed cases of congenital infection (based on PCR or specific Ig M positive), 37 cases developed NIHF and received IUT. In this group, intrauterine deaths occurred in five while the remaining 32 were born alive with one infant dying in the neonatal period. Amongst survivors, the authors were able to obtain neurodevelopmental outcome in 20 (35% loss to follow up). The age of infant at the time of assessment ranged from 1.08-9.1 years (median, 4.3 years). A variety of validated assessment tools were used to calculate the developmental quotient (DQ) and intelligence quotient (IQ) depending on the age of the child. For children ≤ 2 years (N=3), Griffiths Test for Infant Development was used to calculate the DQ scores [mean 100, standard deviation (SD) 11]. Intelligence quotient was calculated using either the Kaufmann Assessment Battery for Children > 8 years of age (N=3) or Snijders-Oomen Non-Verbal Intelligence Test for children between 2-6 years of age

(N=14) with a mean IQ of 100 and SD of 15. The mean DQ/IQ score of all children was 101 (range 84-116). Two children had IQ/DQ score of 84 (below one SD) while one child had an IQ/DQ score that exceeded one SD. Neurological examination was reported to be normal in all children. Using a multivariate analysis, the following variables were found not to influence the IQ/DQ scores: minimum fetal haemoglobin ($p=0.64$) or fetal haematocrit ($p=0.97$), gestational age at first IUT ($p=0.1$) or at delivery ($p=0.4$) and number of IUT ($p=0.1$).

Donders *et al.* [34] reported neurodevelopmental outcome on a hydropic fetus secondary to parvovirus infection delivered at 31 weeks gestation for fetal distress. Following aggressive neonatal management and repeated red blood cell transfusion the infant recovered. The infant continued to have persistent anemia necessitating red blood cell transfusion until the age of 4 months. The infant had a positive test for PCR at 4 months which became negative on follow-up. The child was reported to have a normal neurodevelopmental outcome when assessed at 22 months [method of assessment not reported (NR)].

Nagel *et al.* [36] reported adverse neurodevelopmental outcome in fetuses with NIHF treated with IUT. Of the 24 cases in which IUT was performed, information on neurodevelopmental outcome was available in all survivors (N=16). Thirteen children were assessed by the investigators in the out-patient clinic; one was assessed at home while for the remaining two children who were evaluated elsewhere information was retrieved. Age of children at the time of follow up was between 0.4 -8 years. For infants and children between 0.08-3.5 years, The Bayley Scale of Infant Development (N=9) was used to calculate the mental developmental index (MDI) and psychomotor developmental index (PDI). The Snijders-Oomen Non Verbal Intelligence Test was used to calculate IQ for children between 2.5-7 years of age (N=7). The mean (SD) for these scores (MDI, PDI, IQ) is 100 (15). Eleven children (68%) had scores within normal limits with normal neurological examination. Three children had mild delay (defined as scores of 70-84) while two children had severe delay (defined as scores <70). All these children were also noted to have neurological deficits on examination. These deficits include: marked hypotonia of lower limbs (N=1), delayed fine motor coordination (N=2), marked hypertonia and hyperreflexia of upper limbs (N=1) and generalized hypotonia, ataxia and strabismus (N=1). The child with ataxia was further evaluated by MRI scan which showed cerebellar vermis atrophy. Metabolic and laboratory evaluation in this child did not detect any other etiology for the cerebellar vermis atrophy. No correlation was demonstrated between neurodevelopmental outcome and pre transfusion fetal haemoglobin ($p=0.83$), platelet count ($p=0.15$) and intrauterine pH ($p=0.53$) at the time of cordocentesis.

Sheikh *et al.* [39] reported two cases of NIHF secondary to parvovirus infection which resolved spontaneously and were reported to be normal at one year of age.

In summary, only two included studies reported adverse neurodevelopmental outcomes in infants and children who presented with NIHF. [33,36] In the study by Dembinski *et al.* [33], even though 2/20 (10%) children had mild delay (IQ/DQ score < 85), the authors concluded that these

Table 2. Long Term Outcomes Following Maternal Parvovirus B19 Infection in Pregnancy

Study, Year, Country and Design	Number of Cases and Study Period	Fetal Intervention and Outcome	Age at Follow-Up and Method of Assessment	Results	Conclusion and Limitations
Studies Reporting Outcomes Based on Clinical Presentation of NIHF¹					
Cameron <i>et al.</i> 1997, UK Retrospective case series	N=17 cases NIHF (N=16) 1986-1996	IUD (N=16) IUT (N=3) Survival (N=1/3)	2 years NR	Normal development (N=1)	NIHF associated with poor outcome in terms of mortality Interpretation regarding long-term outcome limited due to single survivor
Dembinski <i>et al.</i> 2002, Germany Retrospective case series	N=67 cases NIHF treated with IUT (N=37) Of those treated with IUT, N=31 survived and follow-up data available for N=20 1989-1998	Spontaneous resolution (N=30) IUD following IUT (N=5) Live births (N=32) Neonatal death (N=1/32)	13 to 110 months (median 52 months) Assessment tools: Snijders-Oomen non-verbal intelligence test (N=14) Kaufmann assessment battery for children (N=3) Griffiths Test for infant development (N=3)	Mild delay (N=2) Neurodevelopmental scores ranged within two standard deviation of a normal population and exceeded one standard deviation in three children	Children with successful IUT have good neurodevelopmental outcome Limitations: 1) Conclusion based on small number of participants 2) Different values of scores reported in the abstract and the results section. In addition, unclear whether scores are reported as mean or media value 3) Missing neurodevelopmental outcome on 11/31 (35%) children
Donders <i>et al.</i> 1994, Belgium	NIHF (N=1) Follow-up data (N=1) Study period NR	NIHF at 30 weeks	Follow-up until 22 months Method of neuro-developmental assessment NR	Developmentally normal	No definitive conclusions based on a single case report
Nagel <i>et al.</i> 2007, Netherlands Retrospective case series	NIHF with IUT for anemia or thrombocytopenia (N=24) Follow-up data (N=16) 1997-2005	IUD during the procedure (N=1) IUD after the procedure (N=6) Death at birth (N=1)	0.5 to 8 years Assessment tools: Bayley Scales of Infant Development or Snijders-Oomen test	Mild developmental delay (N=3) Severe developmental delay (N=2)	Fetal parvovirus B19 infection may result in central nervous system damage Limitations: 1) Small sample size with a wide range of follow-up age
Sheikh <i>et al.</i> 1992, USA Case report	NIHF (N=2) Follow-up data (N=2) Study period: NR	Spontaneous resolution Preterm birth at 32 weeks (N=1)	Follow-up at 9 and 18 months for case 1 and 2 respectively Method of assessment NR	Developmentally normal	No definite conclusions can be made based on 2 cases
Studies Reporting Outcomes Based on Serologic Evidence of Acute Maternal Infection²					
Bruu and Flugsrud 1994, Norway Retrospective case series	Acute maternal infection in pregnancy based on serology (N=19) Follow up data (N=16) 1984-1986	Miscarriages (N=1)	2 years Information from local health authority	Normal development (N=15) Hyperactivity and delayed language (N=1)	No evidence of increased adverse neurodevelopmental outcome Limitations: 1) None had evidence of congenital infection 2) Small sample size 3) Method of assessment not reported
Gratacós <i>et al.</i> 1995, Spain Prospective cohort study	Acute maternal infection in pregnancy based on serology (N=60) Live born infants (N=56) Follow-up data (N=55) Study period: dates NR (duration 2 years)	Miscarriages (N=5) and confirmed secondary to B 19 infection (N=1) Serological evidence of congenital neonatal infection at 1 year of age (N=12/48 tested)	1 year Information on neuro-developmental outcome obtained from paediatrician	No severe neuro-developmental outcome reported in any infant	Adverse fetal outcome rare in infants born to mothers with acute parvovirus B19 infection in pregnancy Limitations: 1) No standardized method of neurodevelopmental assessment with short duration of follow-up 2) No report of whether there was mild to moderate adverse neuro-developmental outcome

(Table 2) contd.....

Study, Year, Country and Design	Number of Cases and Study Period	Fetal Intervention and Outcome	Age at Follow-Up and Method of Assessment	Results	Conclusion and Limitations
Studies Reporting Outcomes Based on Serologic Evidence of Acute Maternal Infection²					
Koch <i>et al.</i> 1993, USA Prospective cohort study	Acute maternal infection in pregnancy based on serology (N=19) Live born infants (N=19) Follow-up data (N=19) 1990-1991	No evidence of fetal hydrops or death	3-21 months Denver developmental screening	Normal examination	Acute parvovirus B19 infection in pregnancy can be associated with normal neurodevelopmental outcome Limitations: 1) Information limited to small sample size 2) No information on scores obtained from the screening tool
PHL Service Working Party on Fifth Disease 1990, UK Prospective cohort study	Acute maternal infection in pregnancy based on serology (N=190) Live births (N=156) Follow-up data (N=114) 1985-1988	Therapeutic abortion (N=4) Spontaneous abortion or IUD (N=29) Stillbirth (N=1) Preterm (N=6)	1 year Information on neurodevelopmental outcome obtained from family physicians using questionnaire ³ Further follow-up of 129/156 children 7-10.5 years Information on neurodevelopmental outcome obtained from family physicians using questionnaire	No developmental delay in any infant Developmental delay (N=3)	Majority of the children will have normal neurodevelopment Limitations: 1) Information based on questionnaire only rather than formal assessment
Miller <i>et al.</i> 1998, UK Prospective cohort study	Acute maternal infection in pregnancy based on serology (N=255) Live born infants (N=215) Follow-up data (N=182) 1992-1995	Therapeutic abortion (N=11) Spontaneous abortion or fetal death (N=29)	At least 1 year of age Information on neurodevelopmental outcome obtained from family physicians using questionnaire	Mild developmental delay (N=3)	Majority of the children will have normal neurodevelopment Limitations: 1) Information based on questionnaire only rather than formal assessment and short follow-up duration
Rodis <i>et al.</i> 1998, USA Retrospective case-control study	Cases: Women with serologic evidence of recent parvovirus infection (N=113) Follow-up data (N=108) Control: Pregnant women who were non-immune or with serologic evidence of past infection (N=99) Follow-up data (N=97) 1988-1994	Cases: Spontaneous abortion (N=4) Stillbirth (N=1) Ectopic pregnancy (N=1) Twins (N=2) NIHF (N=2) Control: Spontaneous abortion (N=5) Stillbirth (N=2) Twins (N=5)	6 months to 7 years Information based on questionnaire to caregivers (mothers)	Cases: Delays in motor, speech or language development or significant attention deficits require special education (N=8) Cerebral palsy (N=2) Motor delays (N=1) Attention, speech, learning delay (N=5) Both language and motor delay (N=2) Controls: Significant developmental delays (N=7) Cerebral palsy (N=0) Motor delays (N=3) Attention, speech, learning delay (N=3) Both language and motor delay (N=1) No statistically significant difference in the proportion of developmental delay between cases and control (p>0.05)	No apparent increase in the occurrence of adverse neurodevelopmental outcomes in children exposed to in utero parvovirus B19 infection Limitations: 1) Inadequate power to demonstrate a two fold difference in the risk of adverse neurodevelopmental outcome between groups

IUD: Intrauterine death; IUT: Intrauterine transfusion; NIHF: Non-immune hydrops fetalis; NR: Not reported.

¹[32-34, 36, 39].²[14, 16, 17, 31, 35, 38].³Further follow-up data at 7-10.5 years obtained using same methodology and reported in a separate publication by Miller *et al.* [17].

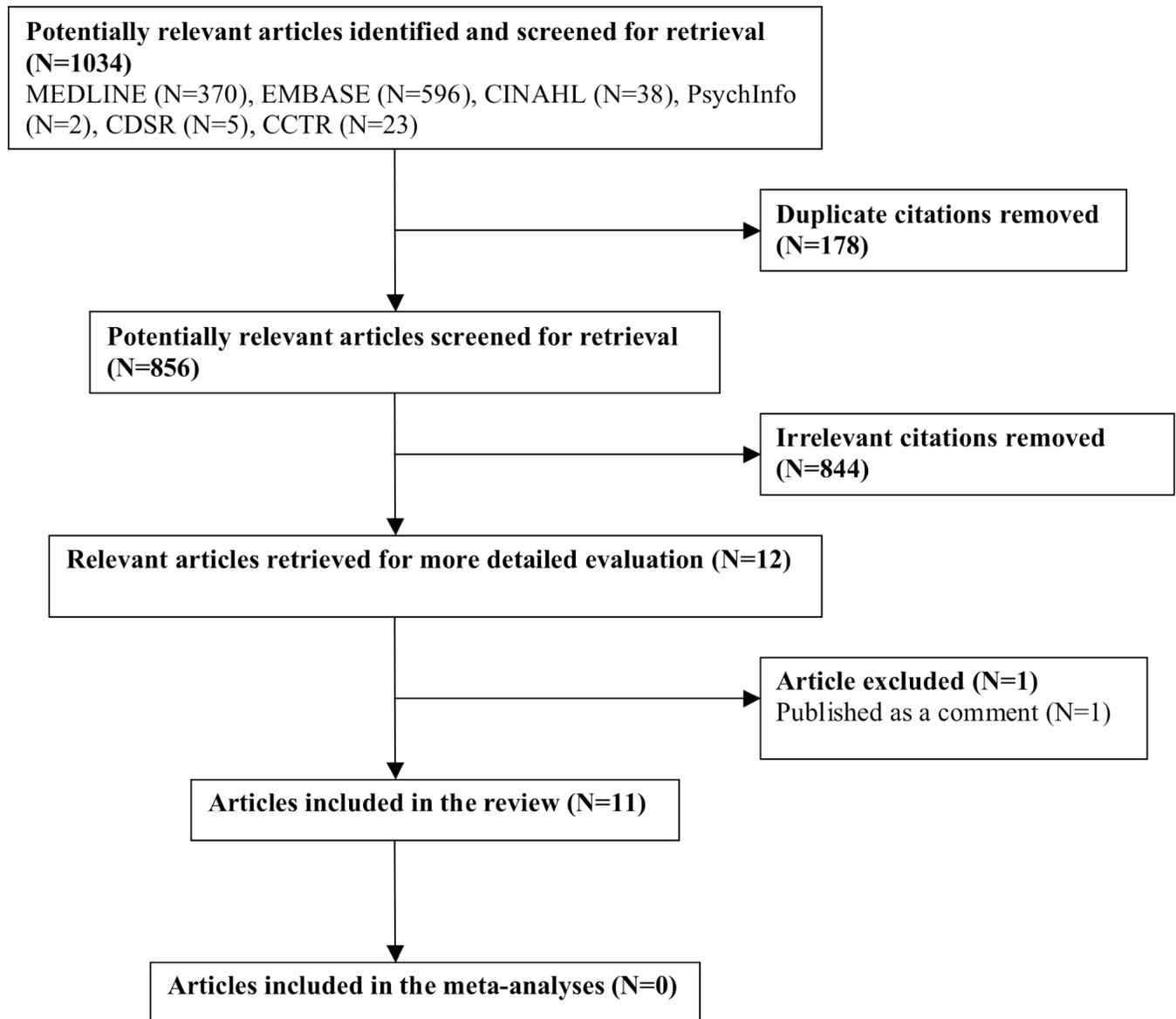


Fig. (1). Flow diagram for selection of studies.

findings were insignificant with all children having normal neurological examination. In contrast, Nagel *et al.* [36] reported that 5/16 (31%) infants and children had evidence of delayed psychomotor development [3/16 (19%) with mild delay and 2/16 (12%) with severe delay]. All five of these infants and children had tone abnormalities with ataxia and strabismus reported in one. None of these studies had a healthy control group for comparison. In total, 7/39 (18%) infants and children who presented with NIHF had adverse neurodevelopmental outcome with a range of 0-31.3%.

Outcomes Based on Serologic Evidence of Acute Maternal Infection

Six studies reported on the neurodevelopmental outcome in infants and children born to mothers with serologic evidence of acute parvovirus infection during pregnancy (Table 2) [14, 16, 17, 31, 35, 38]. The type of study designs include prospective cohort studies (N=4) [14, 16, 17, 35], retrospective case series (N=1) [31], and case control study

(N=1) [38]. Results from individual studies are presented below.

Bruu and Flugsrud [31] reported on 19 pregnant women with serologic evidence of acute parvovirus infection. There were two cases of miscarriage. Follow up data was available for 16 children at two years of age. Except for one child with hyperactivity disorder and delayed language, all were reported to have normal growth and development. There was no evidence of congenital infection in these children based on serological testing.

Gratacós *et al.* [16] identified pregnant women with serologic evidence of acute parvovirus infection (N=60). The incidence of fetal loss secondary to parvovirus infection was reported to be 1.66%. Of the five cases with spontaneous abortion, only one fetus was positive for PCR DNA. Six of the 56 live born infants (one was a twin pregnancy) were positive for Ig M antibodies suggesting congenital infection. Information was obtained for 55 of these infants at 1 year of age from paediatricians. None of the infants were reported to

have severe neurodevelopmental impairment or congenital anomalies.

Koch *et al.* [35] prospectively evaluated 19 pregnant women with confirmed acute parvovirus infection (Ig M positive). All women delivered healthy term infants. Neonatal information was obtained retrospectively from medical records. Of the four infants who had serology testing at birth, three had evidence of congenital infection (Ig M positive). Follow-up evaluation included: physical and neurological examination, developmental assessment using Denver developmental screening and hematological testing. The age range of follow-up was 0.25-1.75 years. All infants were reported to be normal with no evidence of anemia.

The first report on the long-term neurodevelopmental outcomes of infants born to pregnant women with acute parvovirus infection in pregnancy was published from UK. The study was a prospective cohort study conducted during 1985-1988 by Public Health Laboratory (PHL) service working party on fifth disease [14]. Of the 190 pregnant women enrolled in the study, four underwent elective termination of pregnancy, 29 had either spontaneous abortion or intrauterine fetal death, and one pregnancy ended in stillbirth. Out of the 34, 14 fetuses were tested for B19 DNA and six were confirmed positive. Rate of fetal loss was more common if infection occurred before compared to after 20 weeks of gestation though the difference was not statistically significant [17% vs 6%, $p=0.3$, relative risk (RR) 2.87, 95% confidence interval (CI) 0.42 to 19.78]. Out of 129 infants eligible for follow up (age \geq one year), information was obtained from family physicians in 114 cases (12% loss to follow up). Details on infants' physical and neurodevelopment was obtained by requesting family physicians to complete a simple form. No details were provided regarding the method of assessment. None of the infants had any congenital malformation or serious neurodevelopmental problem reported. Of the 114 infants, 21 (18%) had some evidence of congenital parvovirus infection (Ig G positive at 1 year).

In a subsequent study using the same methodology and questionnaire, Miller *et al.* [17] conducted a prospective cohort study following an outbreak of erythema infectiosum in UK between 1992 and 1995. Information was obtained regarding neurodevelopmental outcome from 182 infants at one year of age. The rate of mild delay was 1.6% (N=3). Evidence of congenital infection was found in 20% of infants tested (salivary sample positive of Ig G at 1 year of age).

Miller *et al.* [17] also obtained neurodevelopmental outcome from family physicians of 129 children who were enrolled in the PHL study published in 1990 [14]. The rate of some developmental delay was 2% (N=3) at the age of 7-10.5 years.

In a retrospective case-control study, Rodis *et al.* [38] compared neurodevelopmental outcomes of children born to 113 pregnant women with evidence of recent parvovirus infection during pregnancy (Ig M positive) to 99 pregnant women with evidence of past infection (Ig G positive) or who were susceptible to infection (both Ig G and Ig M negative) during the same period. There were two cases of NIHF in study group (one was a still birth while the second survived following IUT) compared to none in control group. The median age (range) of follow-up was 4 (0.5-7) years. Neurodevelopmental

outcomes were available in 108 children (cases) compared to 97 (controls) from mothers using a questionnaire. There was no statistically significant difference in the rate of children with developmental delays between the study and control group (7.4% vs 7.2%, $p > 0.05$). Two infants in the study group developed cerebral palsy (one with mild spasticity and other with severe ataxic cerebral palsy) compared to none in the control group. Difference in occurrence of cerebral palsy was not statistically significant.

In summary, 3 of the 6 included studies reported adverse neurodevelopmental outcomes in infants and children born to mothers with serologic evidence of acute infection. Bruu and Flugsrud [31] reported hyperactivity and delayed language in 1/16 (6.2%) children. Miller *et al.* [17] reported 3/182 (1.6%) children with mild delay. Rodis *et al.* [38] reported adverse outcome in 8/108 (7.4%) children, however when compared to a control group the incidence was not statistically different. Two of the study infants had cerebral palsy compared to none in the control group which the authors found concerning. Miller *et al.* [17] also obtained information at 7-10 years of age for the original cohort of PHL study [14] and reported the incidence of some delay as 3/129 (2%) children (this cohort was reported by PHL to be normal at 1 year of age). The only study [35] that evaluated neurodevelopmental outcome using validated tools did not report any abnormalities in the study population. The other 2 included studies [14, 16] only reported on absence or presence of severe adverse neurodevelopmental outcomes. In total, 12/494 (2.4%) infants and children who were born to mothers with serologic evidence of acute infection had adverse neurodevelopmental outcome with a range of 0-7.4%.

DISCUSSION

In this review of combined data from studies selected on the basis of well defined inclusion criteria, there is a suggestion that the incidence of adverse neurodevelopmental outcome is higher in infants and children who present with NIHF compared to infants born to mothers with serologic evidence of acute parvovirus infection. Of those with adverse neurodevelopmental outcome, delayed psychomotor development and tone abnormalities seemed to predominate. Methodological challenges of this review include data derived from few studies with small number of participants, not all infants with NIHF received IUT, the diagnostic criteria of congenital parvovirus infection in the neonate was heterogeneous, there was a marked variation in the methods used to assess neurodevelopmental outcome (ranging from validated assessment tools to information derived from parents and physicians using questionnaire or simply reporting that these infants and children were followed at regular intervals), variation in reporting adverse outcomes (i.e. some studies reported on the presence or absence of severe outcome), wide range of age at which neurodevelopmental outcome was assessed making comparison between studies difficult and in most studies a healthy control group was not included as a comparator. In addition, neurodevelopmental outcome was not available for all infants and children with NIHF or those born to mothers with acute parvovirus B19 infection from the initial cohort. Therefore, caution should be exercised in interpreting this finding as the conclusion is based on included studies with methodological differences.

Of the five studies [32-34, 36, 39] that report on outcomes in infants with NIHF, adverse neurodevelopmental outcome was reported in two studies [33-36]. Five of the 16 (31.3%) survivors had adverse outcome which included mild and severe delay in three and two children respectively in the study by Nagel *et al.* [36]. In addition, all these children had neurological deficits. In the study by Dembinski *et al.* [33] 2 children were reported to have mild delay 2/20 (10%) however in this case series 35% of subjects were lost to follow-up. Parents of infants and children with adverse outcome are less likely to be compliant with their follow-up visits and this could have influenced the results of this study [40]. Further, in both these studies there was a wide range in age of follow up and different assessment tools were used. In the remaining three studies [32, 34, 39], the conclusion of normal development was based on case reports/series. Based on individual study information, the range of adverse neurodevelopmental outcome was 0% to 31.3%.

Six studies report on neurodevelopmental outcome in infants and children born to mothers with serologic evidence of acute parvovirus B19 infection in pregnancy. The type of outcomes reported varied from no severe adverse outcome [14, 16] to delays in motor, speech or language development or significant attention deficits requiring special education [17, 31, 38]. Except for the study by Koch *et al.* [35] in which Denver developmental testing was used to assess outcomes, in all the remaining studies information was obtained using questionnaire either from physicians, local health authority or caregivers. None of the studies described the type of questionnaire used. This could put the validity of the study in question. The range of adverse neurodevelopmental outcome varies from 0% to 7.4% based on individual studies.

The mechanisms by which parvovirus B19 can cause central nervous system damage is unclear. Postulated mechanisms include teratogenic effect [41, 42], vasculitis [43], hypoxic-ischemic effects secondary to anemia and intracranial bleeding secondary to thrombocytopenia [44]. In animals, parvovirus B19 has a teratogenic effect causing cerebellar hypoplasia and ataxia in cats and anencephaly, microcephaly, facial defects and ectopic hearts in hamsters [41, 42]. Several studies have reported on the neuropathological findings in fetuses, neonates and adults with parvovirus B19 infection. The findings include development of fetal ventriculomegaly [45] and presence of multinucleated giant cells predominantly in the cerebral white matter and calcifications with a perivascular predilection in the white matter, cerebral cortex, basal ganglia, thalamus and germinal layer. Parvovirus B19 genome DNA was detected in the nucleus of the multinucleated giant cells by PCR amplification and *in situ* PCR methods [46]. Barah *et al.* [47] tested cerebrospinal fluid samples from 162 patients (1 day to 15 years of age) with undiagnosed meningoencephalitis who presented during an outbreak of parvovirus B19. Seven patients were found to be positive for parvovirus (4.3%) [47]. In a subsequent publication from the same population, Kerr *et al.* documented elevated cytokine levels in serum and cerebrospinal fluid in 12 subjects with proven B19 meningoencephalitis [48]. Two of these subjects were newborns with possible perinatally acquired infection. In four cases cerebellar involvement was suggested either clinically (ataxia) or pathologically (atrophy of the molecular and granular layers of the cerebellum with focal loss of Purkinje cells). Neuroimaging (MRI or CT) was

performed in six cases and showed evidence of demyelination. The consequences of anemia secondary to parvovirus B19 can be comparable to neonates with blood group incompatibility where adverse neurodevelopmental outcome have been reported to be in the range of 4.5% to 10% [49-51]. Therefore, one may speculate that the a combination of each of the above pathophysiological mechanisms may be implicated in the occurrence of adverse neurodevelopmental outcome.

Despite a comprehensive review of the literature, we conclude that there is paucity of systematically collected data regarding long-term outcome of children following parvovirus B19 infection on which to base evidence based counseling. However, in spite of these concerns it can be concluded that the outcome of parvovirus B19 in pregnancy is favorable in most cases. Most women exposed to parvovirus B19 do not become infected and most infected mothers will not transmit the infection to the fetus. Further, most infected fetuses remain asymptomatic and do not become hydropic. With the availability of IUT, survival of hydropic fetus has improved. There is some data suggesting that fetal parvovirus B19 infection can cause central nervous system damage.

In order to obtain definitive evidence regarding long-term neurodevelopmental outcome with parvovirus B19 infection, future studies with adequate sample size using standardized neurodevelopmental assessment tools at 18-24 months and school age need to be conducted. In addition, the role of neuroimaging such as MRI (both fetal and neonatal) in identifying the effects of parvovirus B19 on cranial structures should be elucidated. These findings should be correlated with neurodevelopmental outcomes to provide appropriate counseling to women with acute parvovirus infection in pregnancy. It would be unethical to conduct a randomized trial evaluating the efficacy of IUT in fetuses with anemia as its role in improving mortality is already proven. Due to the rarity of number of cases born to mothers with acute parvovirus B19 infection seen at each center/year, a multicenter prospective cohort trial will be needed to address this issue.

DEFINITIONS

Susceptible Individual: An individual without evidence of previous immunity against parvovirus B 19 (i.e. absence of Ig G) and therefore at risk of developing infection if exposed to the virus.

History of Exposure: A significant contact with a person suffering from acute parvovirus B19 infection. Significant contact is defined as contact in the same room (e.g. in a house or classroom or a 2-4 bed hospital stay) for a significant period of time (15 minutes or more), or face-to-face contact with a laboratory confirmed case of parvovirus B19 infection during the period of maximum infectivity (from 7 days prior to appearance of a rash to the date of appearance of the rash) in the absence of respiratory isolation precautions [52].

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APPENDIX: LITERATURE SEARCH STRATEGY

We ran searches using the OVID search platform in the following databases: MEDLINE, EMBASE, CINAHL, PsycINFO, CDSR and CCTR. We retrieved a total of **1034** references from all 6 databases. All references were saved in an EndNote library used to identify the **178** duplicates. Author AJ and VS reviewed the remaining **856** unique references against our inclusion criteria.

The following tables and text record the search strategies and terms used.

MEDLINE

The search strategy for MEDLINE (1950 to March Week 3 2009) retrieved **370** references of which 370 were unique and not duplicated in our other searches. We used a combination of MeSH and free text terms for

Set #	History	Results	Comments
1	parvoviridae/ or parvovirus b19, human/ or Erythema Infectiosum/	3619	Parvovirus MeSH terms
2	exp pregnancy complications/ or exp Pregnancy/	633863	Pregnancy MeSH terms
3	exp "congenital, hereditary, and neonatal diseases and abnormalities"/	792727	Congenital Abnormality MeSH terms
4	1 and 2 and 3	305	Congenital abnormalities base set
5	exp mental disorders/ or exp "behavior and behavior mechanisms"/ or exp "psychological phenomena and processes"/ or exp neurologic manifestations/ or exp human development/ or exp fetal alcohol syndrome/ or exp Nervous System/ or exp Nervous System Diseases/ or child development/ or exp diagnostic techniques, neurological/ or exp neuropsychological tests/ or cerebral arteries/ or cerebrovascular circulation/ or brain chemistry/ or exp nerve growth factors/ or exp nervous system physiology/ or exp neurotransmitter agents/ or exp receptors, neurotransmitter/ or circadian rhythm/ or mental health/ or exp psychological tests/ or exp social behavior disorders/ or child psychiatry/ or exp psychophysiology/ or exp neuropsychological tests/ or hallucinations/ or illusions/ or fetal alcohol syndrome/ or exp psychology/ or communication/ or language/ or exp verbal behavior/ or exp nonverbal communication/ or exp child development/ or fetal alcohol syndrome/ or exp movement/ or exp nervous system physiology/ or exp vision tests/	5016213	Neurocognitive MeSH terms
6	1 and 5	221	Neurocognitive outcomes base set
7	4 or 6	370	Total unique citations

EMBASE

The search strategy for EMBASE (1980 to 2009 Week 12) retrieved **596** references of which **473** were unique and not duplicated in our other searches. There were **123** duplicates from MEDLINE. We used a combination of EMBASE and free text terms for

The following EMBASE search strategy retrieved 596 citations of which 123 were duplicates from MEDLINE

Set #	History	Results	Comments
1	parvovirus/ or Erythema Infectiosum/ or "parvovirus b19".mp. (4720)	4720	Parvovirus EMBASE terms
2	exp pregnancy/ or exp fetus disease/ or exp pregnancy complication/	220475	Pregnancy EMBASE terms
3	exp Congenital Disorder/ or exp Prenatal Disorder/ or prenatal exposure/ or exp postnatal development/ or	402039	Congenital Abnormality EMBASE terms
4	1 and 2 and 3	414	Congenital abnormalities base set
5	exp "Disorders of Higher Cerebral Function"/ or exp motor dysfunction/ or exp sensory dysfunction/ or exp speech disorder/ or exp mental function/ or Cerebral Palsy/ or exp communication disorder/ or exp psychomotor disorder/ or sensation/ or neurocogniti*.ti,ab.	1476624	Neurocognitive EMBASE terms
6	1 and 2 and 5	19	Neurocognitive outcomes base set
7	4 or 6	596	Total unique citations

CINAHL (EBSCOhost)

The search strategy for CINAHL (1982 to March Week 3 2009) retrieved **38** references of which **7** were unique and not duplicated in our other searches. We used a combination of CINAHL and free text terms for

Set #	History	Results	Comments
1	(MH "Parvovirus Infections+")	2120	Parvovirus CINAHL terms
2	(MH "Pregnancy+") or (MH "Pregnancy Complications+")	64853	Pregnancy CINAHL terms
3	(MH "Neonatal, Fetal Diseases and Abnormalities (Non-Cinahl)+")	39982	Congenital Abnormality CINAHL terms
4	1 and 2 and 3	33	Congenital abnormalities base set
5	(MH "Delirium, Dementia, Amnestic, Cognitive Disorders+") or (MH "Behavior and Behavior Mechanisms+") or (MH "Behavioral and Mental Disorders (Non-Cinahl)+") or (MH "Neurodegenerative Diseases+") or (MH "Nervous System Diseases+")	694960	Neurocognitive CINAHL terms
6	1 and 2 and 5	7	Neurocognitive outcomes base set
7	4 or 6	38	Total unique citations

PsycINFO

The search strategy for PsycINFO (1967 to March Week 3 2009) retrieved **2** citations of which **1** was a duplicate from MEDLINE, EMBASE and CINAHL

Set #	History	Results	Comments
1	parvovir*.mp.	2	Parvovirus textword terms

EBM Reviews - Cochrane Database of Systematic Reviews

The following CDSR (1st Quarter 2009) search strategy retrieved **5** citations none of which were duplicated in MEDLINE, EMBASE, CINAHL and PsycINFO

Set #	History	Results	Comments
1	parvovir*.mp.	5	Parvovirus textword terms

EBM Reviews - Cochrane Central Register of Controlled Trials

The following CCTR (1st Quarter 2009) search strategy retrieved **23** citations all of which were duplicated in MEDLINE, EMBASE, CINAHL, and PsycINFO, but not CDSR

Set #	History	Results	Comments
1	parvovir*.mp.	23	Parvovirus textword terms

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