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Outcome of fetuses with congenital parvovirus B19 infection: systematic review and meta-analysis

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KEYWORDS: fetal infection; non-immune hydrops; outcome; parvovirus B19; prenatal care; prenatal diagnosis; ultrasound

ABSTRACT

Objective *To explore the outcome of fetuses affected by congenital parvovirus B19 (PB19) infection, with or without signs of hydrops on ultrasound.*

Methods *PubMed, EMBASE and CINAHL databases were searched for studies reporting on prenatal diagnosis and outcome of fetal PB19 infection. The outcomes explored were miscarriage, perinatal death (PND), intrauterine death, neonatal death, spontaneous resolution of hydrops or fetal anemia, need for intrauterine transfusion (IUT), resolution of hydrops or anemia after transfusion, fetal loss following transfusion, abnormal brain scan after birth and abnormal neurodevelopmental outcome. Outcomes were reported according to the presence or absence of signs of hydrops on ultrasound. A subgroup analysis was performed including hydropic and non-hydropic fetuses diagnosed at* < 20 *weeks and* ≥ 20 *weeks of gestation. Meta-analyses of proportions and meta-analyses using individual-data random-effects logistic regression were performed to analyze the data.*

Results *Thirty-five observational studies were included, involving 611 fetuses affected by PB19 infection. The risks of miscarriage (odds ratio (OR), 11.5; 95% CI, 2.7–49.7) and PND (OR, 4.2; 95% CI, 1.6–11.0) were higher in fetuses with PB19 infection presenting, compared with those not presenting, signs of hydrops on ultrasound. In fetuses affected by hydrops, spontaneous resolution of the infection, defined as disappearance of hydrops without need for IUT, occurred in 5.2% (95% CI, 2.5–8.8%) of cases whereas, in the group of fetuses not affected by hydrops, infection resolved in 49.6% (95% CI, 20.7–78.6%) of cases. IUT was performed in 78.7% (95% CI, 66.4–88.8%) of hydropic and in 29.6% (95% CI, 6.0–61.6%) of non-hydropic fetuses affected by congenital PB19 infection and resolution of the infection after IUT occurred in 55.1% (95% CI, 34.0–75.3%) and in 100% (95% CI, 57.3–100%) of cases, respectively. The risk of fetal loss after IUT was higher in fetuses affected compared with those not affected by hydrops (OR, 9.8; 95% CI, 2.8–34.6). The prevalence of abnormal brain imaging was 9.8% (95% CI, 2.5–21.0%) in fetuses affected and 0.0% (95% CI, 0.0–7.0%) in those not affected by hydrops, whilst the corresponding figures for abnormal neurodevelopmental outcome were 9.5% (95% CI, 2.6–20.2) and 0.0% (95% CI, 0.0–7.5), respectively; however, statistical power to assess these outcomes was inadequate due to the small number of included cases.*

Conclusions *Hydrops is the main determinant of mortality and adverse perinatal outcome in fetuses with PB19 infection. Perinatal outcome in non-hydropic fetuses is generally favorable. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Parvovirus B19 (PB19) is a small, single-stranded DNA virus that is commonly spread by respiratory secretions or from hand to mouth contact, but can also occasionally be transmitted from the mother to the fetus during pregnancy[1]. Approximately 50–75% of women of reproductive age have developed immunity to PB19[1]. Although pregnancy has been shown not to affect the natural history of the infection, seronegative pregnant

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women, once exposed to the virus, can transmit the infection to their fetus in approximately 17–33% of cases[1].

Even though the majority of fetuses affected by PB19 do not show any sign and have a spontaneous resolution of the infection[2], several complications such as miscarriage and stillbirth may occur. Furthermore, fetal PB19 infection is among the most common causes of non-immune fetal hydrops, which carries a high risk of perinatal mortality and morbidity[3]. Long-term sequelae of congenital PB19 infection, such as cardiomyopathy, hepatic failure and abnormal neurodevelopmental outcome, have been reported[4].

The pathophysiology of PB19-related fetal damage is mainly dependent on the occurrence of fetal anemia due to the direct suppression of erythroid precursors in the early stages of hematopoiesis, although impaired myocardial contractility and fetal thrombocytopenia may play a role in this scenario[4,5].

Accurate identification and treatment of fetuses affected by congenital PB19 infection is fundamental in order to improve perinatal outcome. The large majority of affected fetuses are identified due to the presence of signs of fetal anemia such as increased peak systolic velocity in the middle cerebral artery, ascites, cardiomegaly or hydrops. Therefore, identification of women presenting seroconversion for PB19 is fundamental in order to arrange appropriate fetal surveillance[6]. Delivery of the fetus or treatment of fetal anemia by intrauterine blood transfusion (IUT) represents the mainstay in prenatal management of fetal PB19 infection[7].

Despite this, the true prevalence of abnormal perinatal outcome in fetuses affected by PB19 infection has still to be ascertained. Small sample size of the studies, with even smaller number of cases included, and differences in gestational age at infection, fetal status and type of prenatal management once the infection has been established do not allow extrapolation of objective evidence on the burden of the short- and long-term complications occurring in fetuses affected by PB19 infection.

The aim of this systematic review was to elucidate the outcome of fetuses affected by congenital PB19 infection, with or without signs of hydrops on ultrasound.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to an *a-priori*-designed protocol recommended for systematic reviews and meta-analyses[8]. PubMed, EMBASE and CINAHL databases were searched electronically on 20 August 2016 with an update on 23 June 2017 utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'Parvovirus B19', 'Parvovirus infection', 'prenatal diagnosis', 'prenatal ultrasonography' and 'prenatal care' (Table S1). The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were hand-searched for additional reports. PRISMA guidelines were followed[9].

Study selection, data collection and data items

The incidence of the following outcomes in fetuses with congenital PB19 infection was explored: miscarriage, defined as fetal loss at < 20 weeks' gestation; intrauterine death (IUD), defined as fetal demise occurring at ≥ 20 weeks' gestation; neonatal death (NND), defined as death occurring up to 28 days postpartum; perinatal death (PND), defined as occurrence of IUD or NND; spontaneous resolution of hydrops or fetal anemia in fetuses with and those without hydrops, respectively, defined as absence of such signs on ultrasound at follow-up assessment in fetuses not undergoing IUT; rate of IUT performed; resolution of hydrops or anemia after IUT, defined as absence of ultrasound signs suggestive of hydrops or anemia at the follow-up scan after the procedure; fetal loss following IUT, defined as miscarriage (if the procedure was performed before 20 weeks' gestation) or IUD (if IUT was performed after 20 weeks' gestation); abnormal brain scan after birth, defined as the presence on postnatal imaging (ultrasound, computerized tomography or magnetic resonance imaging) of any cerebral lesion suggestive of direct damage to the brain from the virus, or indirect damage resulting from the response of the host to infection or from fetal anemia or hydrops induced by the virus[10]; and abnormal neurodevelopmental outcome, defined as the occurrence of any neurological lesion associated with a direct effect of the virus on the brain or secondary to fetal anemia or hydrops caused by the infection[10].

Observed fetal outcomes were reported according to presence or absence of signs of hydrops on ultrasound. Furthermore, a subgroup analysis was performed of hydropic and non-hydropic fetuses affected at < 20 and ≥ 20 weeks of gestation. Only fetuses with PB19 infection confirmed by serological or virological analysis or fetuses with signs of hydrops on ultrasound whose mothers had confirmed PB19 infection were considered suitable for inclusion.

Only studies reporting on prenatal diagnosis of fetal PB19 infection were considered suitable for inclusion in the current systematic review; postnatal studies or studies from which cases diagnosed prenatally could not be extracted were excluded. Studies including only cases of fetal or neonatal death were also excluded. Only full-text articles were considered eligible for inclusion; case reports, conference abstracts and case series with fewer than three cases of fetal PB19 infection were also excluded in order to avoid publication bias. Studies published before 2000 were not included, as we considered that advances in prenatal imaging techniques and improvements in the diagnosis and definition of fetal anomalies make these less relevant.

Two authors (F.B., D.M.) reviewed all abstracts independently and agreement regarding potential relevance

was reached by consensus. Full-text copies of those papers were obtained, and the same two reviewers extracted independently relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed and consensus reached by the reviewers or by discussion with a third author. If more than one study reported on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS)[11]. According to the NOS, each study is judged on three broad perspectives: selection of the study groups, comparability of the groups and ascertainment of the outcome of interest. Assessment of selection of a study includes evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration that the outcome of interest was not present at the start of the study. Assessment of comparability of a study includes evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, ascertainment of the outcome of interest includes evaluation of the type of assessment of the outcome of interest, and length and adequacy of follow-up[11]. According to the NOS, a study can be awarded a maximum of one star for each of three numbered items within the selection and outcome categories; a maximum of two stars can be given for comparability.

Statistical analysis

Overall, we evaluated the association between hydrops fetalis secondary to PB19 infection and 10 fetal clinical outcomes (miscarriage, PND, IUD, NND, need for IUT, fetal loss after transfusion, resolution after transfusion, abnormal brain imaging, abnormal neurodevelopment, spontaneous resolution of the infection).

Some of the included observational studies reported zero events in one or both the compared groups, and exposed and unexposed group sizes were frequently unbalanced. In these cases, the best performing methods to obtain pooled estimates are the Mantel–Haenszel odds ratio without zero-cell continuity corrections, logistic regression and an exact method[12,13]. Mantel–Haenszel odds ratios cannot be computed in studies reporting zero events in both groups, but the exclusion of these may cause a relevant loss of information and the potential inflation of the magnitude of the pooled exposure effect[14]. Therefore, in order to retain all studies in the analysis, we performed all meta-analyses using individual-data random-effects logistic regression, with single study as the cluster unit. The pooled datasets with individual data were reconstructed using published 2×2 tables. When one of the overall pooled arms showed no events, we used exact logistic regression analysis. Furthermore, only studies providing data for each explored outcome for both fetuses with and those without hydrops were considered eligible for the computation of odds ratios (ORs)[12–15].

The formal tests for funnel plot asymmetry cannot be used when the total number of publications included for each outcome is below 10 or the events are very few, because the power is too low to distinguish chance from real asymmetry[13]. Thus, we assessed publication bias graphically, through funnel plots, and formally, through Egger's regression asymmetry test[16], only in four out of 11 meta-analyses. All analyses were performed using Stata version 13.1 (2013, Stata Corp., College Station, TX, USA).

RESULTS

General characteristics

Of the 896 articles identified through the search, 87 were assessed for their eligibility (Table S2) and 35 studies were eventually included in the systematic review (Figure 1 and Table 1). These 35 studies included 611 fetuses affected by PB19 infection based on serological or virological confirmation or presence of signs of fetal anemia, such as hydrops, on ultrasound in fetuses with infected mothers[6,17–50]. The definition of fetal hydrops in each included study is reported in Table S3.

Quality assessment of the included studies according to the NOS is presented in Table 2. Most of the included studies had an overall good score regarding selection and comparability of the study groups, and ascertainment of the outcome of interest. The main weaknesses of the studies were their retrospective design, small sample

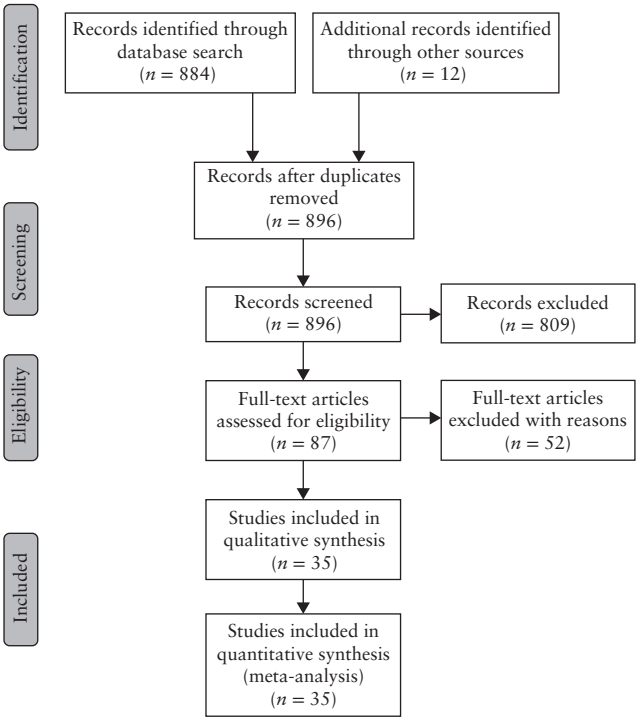

Figure 1 Flowchart showing inclusion of studies on outcome of fetuses with parvovirus B19 infection.

Table 1 General characteristics of studies reporting on outcome of fetuses with parvovirus B19 (PB19) infection included in systematic review

Study	*Country*	*Study design*	*Study period*	*Inclusion criteria*	*GA at diagnosis* (weeks)*	*Maternal infection* (n)	*Fetal infection* (n)
Hellmund (2018)[17]	Germany	Retro	2002–2015	Fetuses receiving IUT for PB19	16 + 6 (13 + 0 to 19 + 6)	NS	55
Zavattoni (2016)[18]	Italy	Retro	2003–2010	Women undergoing serological and virological investigations for PB19	23.5 (5–33)	53	19
Bigelow (2016)[19]	USA	Retro	1988–2013	Fetuses receiving IUT	NS	NS	8
Ota (2016)[20]	Japan	Retro	2000–2012	Fetuses with hydrops due to PB19	20 (17–23)	NS	6
Gillaranz (2016)[21]	Spain	Retro	2009–2014	Fetuses with PB19	19–25	NS	14
Melamed (2015)[22]	Canada	Retro	1992–2014	Pregnancies with PB19 undergoing FBS/IUT	22.5 ± 2.7	37	29
Ishikawa (2015)[23]	Japan	Retro	NS	Fetuses with PB19	13–14	3	3
Mackie (2015)[24]	UK	Retro	2004–2014	Fetuses undergoing IUT for hydrops	< 24	NS	5
Hartge (2015)[25]	Germany	Retro	2000–2014	Fetuses with hydrops due to PB19	1st to 2nd trimester	9	9
Kyeong (2015)[26]	Korea	Prosp	1999–2011	Fetuses with hydrops due to PB19	21 (16.3–24.2)	336	10
Yamada (2015)[27]	Japan	Retro	2011	Fetuses with PB19	NS	NS	69
Macè (2014)[28]	France	Retro	2005–2013	Fetuses with PB19	23 + 4 (± 14 days)	NS	20
Yoshida (2013)[29]	Japan	Retro	2004–2009	Women with confirmed PB19	21 (19–25)	20	20
Puccetti (2012)[30]	Italy	Retro	2005–2009	Fetuses with PB19	20 (4–34)	63	20
Weiffenbach (2012)[31]	Germany	Retro	2003–2009	Fetuses with anemia or hydrops due to PB19	19.5 (9–31)	NS	41
De Jong (2012)[32]	Netherlands	Retro	1997–2009	Fetuses with hydrops receiving IUT	NS	NS	44
Santo (2011)[33]	UK	Retro	1999–2009	Fetuses with hydrops due to PB19	21–25	9	9
Chauvet (2011)[34]	France	Retro	1992–2007	Fetuses with hydrops due to PB19	22.8 (11–30)	NS	27
Fukushima (2011)[35]	Japan	Retro	1983–2010	Fetuses with hydrops due to PB19	NS	NS	8
Enders (2010)[36]	Germany	Retro	1999–2002	Women with confirmed PB19	13–28	236	10
Simms (2009)[37]	UK	Retro	1999–2006	Women with confirmed PB19	NS	46	12
Figueiredo (2008)[38]	Brazil	Retro	1999–2005	Fetuses with hydrops due to PB19	23 (22–25)	NS	20
Beigi (2008)[39]	USA	Retro	1998–2001	Women with confirmed PB19	22 + 2 (2–41)	25	3
Abrams (2007)[40]	USA	Retro	NS	Newborns with hydrops due to fetal PB19	NS	NS	9
Chisaka (2006)[41]	Japan	Prosp	1999–2004	Women with confirmed PB19	5–20	100	5
Hernandez-Andrade (2004)[42]	UK	Retro	NS	Fetuses with hydrops due to PB19	21–27	NS	16
Enders (2004)[43]	Germany	Prosp	1993–1998	Women with confirmed PB19	19 [12–27]	1018	23
Favre (2004)[44]	France	Retro	1993–2000	Fetuses with hydrops due to PB19	NS	NS	6
Cosmi (2002)[6]	USA	Prosp	NS	Women exposed to PB19 or fetuses with hydrops	22.1 (15–37)	32	17
Dembinsky (2002)[45]	Germany	Retro	1998–1999	Fetuses with hydrops receiving IUT	NS	67	37
Nunoue (2002)[46]	Japan	Retro	1986–1999	Women with confirmed PB19	3–33	57	13
Kailasam (2001)[47]	UK	Prosp	NS	Fetuses with hydrops due to PB19	18–25	NS	6
Ismail (2001)[48]	UK	Retro	1996–1999	Fetuses with hydrops due to PB19	22 + 6 (21–28)	NS	8
Suchet (2000)[49]	Canada	Retro	1995–1999	Fetuses with PB19	12–32	NS	7
Heinonen (2000)[50]	Finland	Retro	1987–1996	Fetuses with hydrops due to PB19	NS	NS	3

Only first author is given for each study. *Presented as median (range), range, mean ± SD or median [interquartile range]. FBS, fetal blood sampling; GA, gestational age; IUT, intrauterine blood transfusion; NS, not stated; Prosp, prospective; Retro, retrospective.

size, and heterogeneity in outcome definition, gestational age at assessment and type of prenatal management. Furthermore, not all the included studies were matched case–control series, thus making it possible for the robustness of the results to be affected by other cofactors.

Synthesis of results

The risk of miscarriage was higher in hydropic (pooled proportion (PP), 27.2%; 95% CI, 12.2–45.5%) compared with non-hydropic (PP, 8.8%; 95% CI, 2.8–17.6%) fetuses affected by PB19 infection, with an OR of 11.5 (95% CI, 2.7–49.7) (Tables 3 and 4). The risk of PND in fetuses affected by congenital PB19 was higher in those presenting (PP, 29.5%; 95% CI, 21.4–38.2%) compared with those not presenting (PP, 4.4%; 95% CI, 1.2–9.7%) signs of hydrops on ultrasound, with an OR of 4.2 (95% CI, 1.6–11.0). IUD occurred in 24.0% (95% CI, 16.4–32.5%) of fetuses with PB19 affected by hydrops and in 3.4% (95% CI, 0.8–7.5%) of those unaffected (OR, 3.60; 95% CI, 1.3–10.5), while the corresponding figures for NND were 3.1% (95% CI,

Table 2 Quality assessment of included studies according to Newcastle–Ottawa Scale

Study	*Selection*	*Comparability*	*Outcome*
Hellmund (2018)[17]	★★	★	★★
Zavattoni (2016)[18]	★★	★	★★
Bigelow (2016)[19]	★★	★	★★
Ota (2016)[20]	★★	★	★★
Gillaranz (2016)[21]	★★	★	★★
Melamed (2015)[22]	★★	★	★★
Ishikawa (2015)[23]	★★	★	★
Mackie (2015)[24]	★★	★★	★★
Hartge (2015)[25]	★★	★	★★
Kyeong (2015)[26]	★★	★	★
Yamada (2015)[27]	★★	★	★
Macè (2014)[28]	★★★	★★	★★
Yoshida (2013)[29]	★★	★	★★
Puccetti (2012)[30]	★★	★	★★
Weiffenbach (2012)[31]	★★	★	★★
De Jong (2012)[32]	★★	★	★★
Santo (2011)[33]	★★	★	★★
Chauvet (2011)[34]	★★	★	★
Fukushima (2011)[35]	★★	★★	★★
Enders (2010)[36]	★★	★	★★
Simms (2009)[37]	★★	★	★★
Figueiredo (2008)[38]	★★	★★	★★
Beigi (2008)[39]	★★	★	★★
Abrams (2007)[40]	★★	★	★★
Chisaka (2006)[41]	★★	★	★
Hernandez-Andrade (2004)[42]	★★	★	★
Enders (2004)[43]	★★★	★★	★★
Favre (2004)[44]	★★	★	★★
Cosmi (2002)[6]	★★	★	★★
Dembinsky (2002)[45]	★★	★	★★
Nunoue (2002)[46]	★★	★	★★
Kailasam (2001)[47]	★★	★	★★
Ismail (2001)[48]	★★	★	★
Suchet (2000)[49]	★★	★★	★★
Heinonen (2000)[50]	★★	★	★★

Only first author is given for each study. A study can be awarded a maximum of one star for each of three numbered items within selection and outcome categories. A maximum of two stars can be given for comparability.

0.2–8.1%) and 3.0% (95% CI, 0.6–6.9%), respectively (Table 4).

In fetuses affected by hydrops, spontaneous resolution of the infection, defined as disappearance of signs of hydrops on follow-up ultrasound without the need for IUT, occurred in 5.2% (95% CI, 2.5–8.8%) of cases, whereas in the group of fetuses not affected by hydrops, spontaneous resolution of the infection, defined as absence of signs of fetal anemia on follow-up ultrasound, occurred in 49.6% (95% CI, 20.7–78.6%) of cases (Table 4).

IUT was performed in 78.7% (95% CI, 66.4–88.8%) of hydropic and in 29.6% (6.0–61.6%) of non-hydropic fetuses affected by congenital PB19 infection and resolution of the infection after IUT occurred in 55.1% (95% CI, 34.0–75.3%) of fetuses presenting and in 100% (95% CI, 57.3–100%) of cases not presenting signs of hydrops on ultrasound. Among hydropic fetuses undergoing IUT, 63.2% (95% CI, 39.3–84.0%; I^2, 79.9%) received only one transfusion and 36.8% (95% CI, 16.0–60.7%; I^2, 79.9%) two or more transfusions, whereas all non-hydropic fetuses undergoing IUT received only one transfusion. The risk of fetal loss after IUT was higher in fetuses affected (PP, 28.9%; 95% CI, 19.4–39.4%) compared with those not affected (PP, 5.5%; 95% CI, 1.2–12.5%) by hydrops, with an OR of 9.8 (95% CI, 2.8–34.6) (Tables 3 and 4).

Assessment of abnormal brain imaging and neurodevelopmental outcome was affected by the small number of included cases, which precluded a comprehensive assessment of the risk of such outcomes in the study groups, and therefore results should be interpreted with caution. The prevalence of abnormal brain imaging was 9.8% (95% CI, 2.5–21.0%) in fetuses affected and 0.0% (95% CI, 0.0–7.0%) in those not affected by hydrops, whilst the corresponding figures for abnormal neurodevelopmental outcome were 9.5% (95% CI, 2.6–20.2%) and 0.0% (95% CI, 0.0–7.5%).

Subgroup analysis according to gestational age at infection (< 20 and ≥ 20 weeks of gestation) was affected by the small number of studies and even smaller number of cases included, and thus results were reported only as pooled proportions (Tables S4 and S5). In hydropic fetuses, PND occurred in 15.9% (95% CI, 4.5–32.6%) of cases before and in 36.1% (95% CI, 23.8–49.3%) after 20 weeks of gestation, while spontaneous resolution of hydrops was observed in 10.4% (95% CI, 2.7–22.1%) and 5.2% (95% CI, 1.8–10.4%) of cases, respectively. IUT was performed in 83.2% (95% CI, 58.4–98.0%) of hydropic fetuses infected at < 20 weeks and in 33.1% (95% CI, 18.7–49.3%) of those infected ≥ 20 weeks of gestation, and fetal loss due to the procedure occurred in 39.1% (95% CI, 23.4–56.1%) and 33.1% (95% CI, 18.7–49.3%) of cases, respectively (Table S4).

In non-hydropic fetuses, PND occurred in 2.9% (95% CI, 0.1–8.9%) of cases before and 6.7% (95% CI, 0.03–23.4%) after 20 weeks of gestation, while IUT was performed in 19.7% (95% CI, 0.1–59.4%) and 35.4% (95% CI, 8.7–68.5%) of cases, respectively (Table S5). Fetal loss following IUT occurred in 46.2% (95% CI, 5.3–97.5%) of the cases before 20 weeks and in none after 20 weeks of gestation, whereas infection resolved spontaneously in 58.2% (95% CI, 3.8–99.9%) and in 33.9% (95% CI, 3.3–76.1%) of cases, respectively.

DISCUSSION

Main findings

The findings of this systematic review showed that presence of secondary hydrops is the main determinant in predicting perinatal outcome of fetuses affected by congenital PB19 infection. The risk of PND or IUD was higher in fetuses affected by hydrops, whereas there was no difference in the incidence of NND between the hydropic and non-hydropic groups. Spontaneous resolution of the infection occurred in about half of the cases not presenting with hydrops but in only about 5% of the cases with hydrops. Resolution of the infection after

Table 3 Pooled odds ratios (OR) of outcome of fetuses affected by congenital parvovirus B19 infection, with *vs* those without signs of secondary hydrops on ultrasound

Outcome	*Studies* (n)	*Raw data** (n/N *hydropic* vs n/N *non-hydropic fetuses)*	*Pooled OR* (95% CI)	I^2 (%)	P
Miscarriage†	4	14/31 *vs* 2/41	11.50 (2.7–49.7)	0	0.001
Perinatal death	16	36/193 *vs* 3/156	4.16 (1.6–11.0)	0	0.004
Intrauterine death	15	30/156 *vs* 3/126	3.60 (1.3–10.5)	0	0.014
Neonatal death	14	6/163 *vs* 0/102	3.26 (0.6–18.7)	0	0.186
Need for IUT	12	131/148 *vs* 24/91	159 (41.5–611)	13	< 0.001
Resolution of infection after IUT	3	15/26 *vs* 5/5	0.09 (0.01–1.5)	0	0.096
Fetal loss after IUT	6	23/82 *vs* 2/58	9.81 (2.8–34.6)	0	0.004
Abnormal brain imaging	4	4/38 *vs* 0/45	6.72 (0.81–∞)	22	0.08
Abnormal neurodevelopment	1	0/11 *vs* 0/30	—	—	—
Spontaneous resolution of infection	12	5/128 *vs* 66/124	0.04 (0.01–0.03)	51.4	< 0.001

*When only one study could be included in meta-analysis, OR was computed from raw data of that study. †Computed using data from fetuses with infection before 20 weeks of gestation. IUT, intrauterine transfusion.

Table 4 Pooled proportions (PP) of outcome of fetuses affected by congenital parvovirus B19 infection, with or without signs of secondary hydrops on ultrasound

	Hydropic				*Non-hydropic*			
Outcome	*Studies* (n)	*Fetuses* (n/N)	*PP* (% (95% CI))	I^2 (%)	*Studies* (n)	*Fetuses* (n/N)	*PP* (% (95% CI))	I^2 (%)
Miscarriage*	10	16/53	27.18 (12.2–45.5)	45	7	3/51	8.77 (2.8–17.6)	0
Perinatal death	29	98/372	29.45 (21.4–38.2)	67.5	16	4/158	4.44 (1.2–9.7)	31.5
Intrauterine death	27	68/326	23.96 (16.4–32.5)	65.2	17	3/158	3.38 (0.8–7.5)	18.8
Neonatal death	26	29/335	3.11 (0.2–8.1)	60.2	15	1/104	2.95 (0.6–6.9)	0
Need for IUT	22	218/271	78.70 (66.4–88.8)	80.6	13	22/93	29.61 (6.0–61.6)	89.4
Resolution of infection after IUT	15	79/116	55.11 (34.0–75.3)	80.8	3	5/5	100.00 (57.3–100)	0
Fetal loss after IUT	21	53/188	28.90 (19.4–39.4)	59.3	6	2/58	5.48 (1.2–12.5)	0
Abnormal brain imaging	6	7/63	9.77 (2.5–21.0)	44.6	4	0/45	0.0 (0.0–7.0)	0
Abnormal neurodevelopment	5	7/70	9.52 (2.6–20.2)	29.5	2	0/32	0.0 (0.0–7.5)	0
Spontaneous resolution of infection	22	17/314	5.20 (2.5–8.8)	73.2	14	57/91	49.59 (20.7–78.6)	91.1

Data from individual studies combined using proportion meta-analysis (random-effects model). *Computed using data from fetuses with infection before 20 weeks' gestation. IUT, intrauterine transfusion.

IUT was accomplished in about half of cases affected and in all cases not affected by hydrops, whilst IUD after IUT occurred in about 30% of hydropic and in 5% of non-hydropic fetuses.

Strengths and limitations

The small number of cases, heterogeneity of the populations (due to variability of inclusion criteria) and lack of standardized criteria for the antenatal management represent the major limitations of this systematic review. Assessment of the potential publication bias was also problematic because of the nature of the outcomes evaluated (outcome rates, with the left side limited to a value of zero), which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests. As not all included studies were case–control series reporting matched populations, it is possible that the presence and degree of association between some of the observed outcomes and the study populations might have been affected by several cofactors that were not balanced between cases affected and those not affected by hydrops, such as gestational age at occurrence of the infection, preterm birth and severity of the infection.

One of the major limitations is represented by the populations analyzed in the original studies included in the review. Some of the included studies considered only fetuses affected by hydrops; although the analysis was stratified according to the presence of hydrops, it is possible that mainly cases showing severe degrees of hydrops were diagnosed on ultrasound, thus potentially overestimating the figures for the different adverse outcomes reported in this systematic review. On the other hand, the control group was mainly represented by fetuses showing signs of fetal anemia; in these fetuses, the prevalence of the explored outcomes is likely to be higher compared with that in affected but non-anemic cases.

Furthermore, we could not stratify the analysis according to the gestational age at infection as this information was reported only by a small proportion of the included studies. Finally, a comprehensive assessment of the risk of abnormal brain imaging and neurodevelopmental outcome in fetuses affected by PB19 infection was biased by the small number of cases and by heterogeneity in clinical assessment, neurodevelopmental tool used, time of follow-up and gestational age at birth.

Despite these limitations, the present review represents the most comprehensive published estimate of fetal outcomes associated with congenital PB19 infection.

Implications for clinical practice

Although the outcome of fetuses affected by PB19 infection has been generally reported to be good, several complications such as miscarriage, IUD and hydrops can potentially occur[51]. Identification of the maternal serological status is the first step in stratifying the risk of fetal infection. If the mother is immune, she can be reassured that she will not develop the infection and that exposure will not result in adverse consequences. On the other hand, appropriate follow-up of those mothers showing seroconversion due to PB19 is fundamental in order to identify fetuses with complications. The risk of vertical transmission of PB19 has been estimated to be around 25%[52]. However, the likelihood for fetal infection has been reported to be higher when seroconversion occurs before the 20th week of gestation, during the hepatic stage of hematopoiesis in which red blood cells have a reduced half-life and are more vulnerable to anemia[52]. In this scenario, a closer follow-up may be reasonable. Although there is no randomized trial on the type and frequency of antenatal follow-up of fetuses at high risk, it seems reasonable to perform a weekly ultrasound assessment to rule out signs of fetal anemia or hydrops for at least 8–12 weeks after the diagnosis of fetal infection[2]. Abnormal peak systolic velocity in the middle cerebral artery is the primary imaging marker for fetal anemia and has been shown to have an overall good diagnostic accuracy in identifying anemic fetuses[53]. Other signs include cardiomegaly, hyperechogenic bowel, ascites, polyhydramnios, meconium peritonitis and placentomegaly[51].

The present systematic review shows that the main determinant of adverse perinatal outcome in fetuses affected by congenital PB19 infection is the presence of hydrops. Fetal hydrops may be the consequence of high output heart failure secondary to fetal anemia or myocarditis and to hypoalbuminemia induced by liver failure. On the other hand, fetuses not affected by hydrops have generally an excellent clinical outcome. The rate of spontaneous resolution of the infection without the need for IUT in fetuses without hydrops was about 50%, whereas in all cases that underwent IUT fetal anemia resolved after one transfusion; however, these findings should be interpreted with caution in view of the small number of cases included in the analysis.

Recently, several studies have suggested that fetuses affected by PB19 infection are at higher risk of neurodevelopmental delay[4,54,55]. In the present systematic review, the prevalence of abnormal brain imaging and neurodevelopmental outcome was 9.8% (95% CI, 2.5–21.0%), 9.5% (95% CI, 2.6–20.2%) in fetuses presenting with hydrops and 0% in those without, although the small number of included cases precluded adequate statistical power and thus these findings should be interpreted with caution. Furthermore, the time of follow-up and the type of neurodevelopmental assessment used were not consistent between the included studies.

The association between PB19 infection and abnormal brain imaging and function has not been explained yet. Severe fetal anemia may lead to hypoxic ischemic encephalopathy, which may partially explain the relatively high prevalence of neurodevelopmental delay in children affected by PB19 infection *in utero*. Furthermore, PB19 DNA has been detected in white matter multinucleated reactive microglial cells, suggesting direct damage by the virus to the brain. Finally, acute fetal anemia can lead to a hyperdynamic state, which may impair cerebral perfusion. However, it is possible that several comorbidities, such as prematurity and growth restriction, may be partially responsible for the relatively high prevalence of neurodevelopmental delay in children with congenital PB19 infection. The risk of abnormal brain findings and neurodevelopmental delay should be discussed with parents and appropriate imaging and clinical follow-up arranged after birth.

Large prospective studies sharing objective protocols of prenatal management and postnatal assessment are needed to elucidate the actual prevalence of neurodevelopmental disorders in fetuses affected by PB19 infection.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Search strategy for PubMed, EMBASE and CINAHL for systematic review and meta-analysis

Table S2 Studies excluded from systematic review and meta-analysis and reasons for exclusion

Table S3 Definition of fetal hydrops in included studies

Tables S4 and S5 Pooled proportions of outcome of fetuses affected by congenital parvovirus B19 infection with (Table S4) or without (Table S5) signs of hydrops on ultrasound, according to gestational age at infection

Table S1. Search strategy for PubMed, EMBASE and CINAHL for systematic review and meta-analysis

PubMed

1 exp Parvoviridae Infections/ or exp Parvoviridae/ (15461)
2 exp Parvovirus/ (2216)
3 exp Parvovirus B19, Human/ (2666)
4 exp Prenatal Diagnosis/ (68439)
5 exp Prenatal Care/ (24120)
6 exp Ultrasonography, Prenatal/ (29915)
7 ((prenatal or pregnan*) adj5 (diagnos* or screen* or monitor* or ultraso* or MRI or "magnetic resonance imag*" or surveillance* or treat* or manag* or therap* or care*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (175530)
8 Parvovirus.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (8246)
9 b19.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4343)
10 1 or 2 or 3 or 8 or 9 (17429)
11 4 or 5 or 6 or 7 (180656)
12 10 and 11 (284)

EMBASE

1 exp Parvoviridae Infections/ or exp Parvoviridae/ (11859)
2 exp Parvovirus/ (9759)
3 exp Parvovirus B19, Human/ (1160)
4 exp Prenatal Diagnosis/ (66391)
5 exp Prenatal Care/ (94307)
6 exp Ultrasonography, Prenatal/ (20040)
7 ((prenatal or pregnan*) adj5 (diagnos* or screen* or monitor* or ultraso* or MRI or "magnetic resonance imag*" or surveillance* or treat* or manag* or therap* or care*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (153170)
8 Parvovirus.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (14572)
9 b19.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (4516)
10 1 or 2 or 3 or 8 or 9 (21347)
11 4 or 5 or 6 or 7 (176145)
12 10 and 11 (519)

CINAHL

Search ID#	Search Terms	Search Options	Last Run Via	Results
S9	S7 AND S8	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	81
S8	S4 OR S5 OR S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	46,680
S7	S1 OR S2 OR S3	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	713
S6	(prenatal or pregnan*) N5 (diagnos* or screen* or monitor* or ultraso* or MRI or "magnetic resonance imag*" or surveillance* or detect* or treat* or manag* or therap* or care*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	45,065
S5	(MH "Prenatal Care") OR (MH "Prepregnancy Care")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	12,167
S4	(MH "Prenatal Diagnosis+") OR (MH "Ultrasonography,	Search modes - Boolean/Phrase	Interface - EBSCOhost Research	12,383

	Prenatal+")		Databases Search Screen - Advanced Search Database - CINAHL Plus	
S3	b19	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	422
S2	parvovirus	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	601
S1	(MH "Parvovirus Infections+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	521

Table S2. Studies excluded from systematic review and meta-analysis and reasons for exclusion

Author	Year	Title	Reason for the exclusion
Habibzadeh	2016	The prevalence of parvovirus B19 infection among pregnant women of Ardabil in 2013.	No data on the outcomes explored in this systematic review could be extrapolated from this study
Pasquini	2016	Prevalence of a positive TORCH and parvovirus B19 screening in pregnancies complicated by polyhydramnios.	Only 2 cases of PB19 infection included
Garabedian	2015	Neonatal outcome after fetal anemia managed by intrauterine transfusion	This study is likely to share cases with that by Chauvet et al. because it was carried out in the same centres during the same time period. Thus, in order not to have overlapping cases, it was excluded from the analysis.
Al Shukri	2015	Increased number of parvovirus B19 infections in southeast Scotland in 2012-2013	Only 2 cases of PB19 infection included
Lejeune	2014	Persistent pure red cell aplasia in dicygotic twins with persistent congenital parvovirus B19 infection-remission following high dose intravenous immunoglobulin	Only 2 cases of PB19 infection included
Riipinen	2014	Increased risk of human parvovirus B19 infection in day-care employees: a cohort study among pregnant workers during an epidemic in Finland	no available data
Li	2014	Parvovirus infection: an immunohistochemical study using fetal and placental tissue.	Autopsy based study
Takci	2014	Etiology and outcome of hydrops fetalis: report of 62 cases.	No case of parvovirus infection
Daniilidis	2014	Association of fetal loss with recent parvovirus infection and other demographic prognostic risk factors	This study includes women with I and II trimester miscarriage and explored the occurrence of PB19 infection in such miscarriages. Therefore, it was not possible to extrapolate any data regarding the occurrence of any of the outcomes explored in fetuses with confirmed PB19 infection
Shukri	2014	Increased number of parvovirus B19 infections in southeast Scotland in 2012–2013	It was not possible to extrapolate the number of fetuses infected by PB19 and no data on the other outcomes observed in the present systematic review could be extrapolated from this study

Table S3. Definition of fetal hydrops in included studies

Author	Year	Definition of Hydrops	GA at diagnosis (w)
Hellmund	2018	Not reported	Not reported
Zavattoni	2016	Not provided	20-24
Bigelow	2016	Excessive fluid collection which involves of at least two compartments	NA
Ota	2016	Condition of excessive fluid collection in more than two body cavities and tissues in the fetus secondary to any pathophysiologic process.	24(11-36)
Gillaranz	2016	A combination of at least two of these signs: subcutaneous oedema, pericardial effusion, ascites, pleural effusion	18-25
Melamed	2015	Not provided	NA
Ishikawa	2015	signs of cardiac muscle hyperplasia, pericardial effusion and hyperechogenic bowel	27
Mackie	2015	Not provided	17-23
Hartge	2015	at least two morbidly increased fluid accumulations in the serous fetal compartments: subcutaneous space, pericardial space, pleural space and abdominal cavity	1^{st}-2^{nd} trimester
Kyeong	2015	A combination of at least two of these signs: skin edema, pericardial effusion, ascites and pleural effusion	21(16.3-24.2)
Yamada	2015	Not provided	17 (10-26)
Macè	2014	A combination of at least two serous effusions: subcutaneous edema, pericardial effusion, ascites and pleural effusion	20-30w
Yoshida	2013	Not provided	21+2(19-25^{+6})
Puccetti	2012	Not provided	NA
Weiffenbach	2012	Not provided	NA
De Jong	2012	Not provided	NA
Santo	2011	The presence of fetal subcutaneous tissue oedema associated with serious effusion in one or more cavities including pericardial, pleural and abdominal	27(23-32)

		effusions, in the absence of atypical red cell antibodies.	
Chauvet	2011	A combination of at least two of these four ultrasound signs: ascites, diffuse subcutaneous edema (15 mm), pericardial effusion, pleural effusion.	22.8+-3.7(11-30)
Fukushima	2011	The presence of fetal subcutaneous tissue edema associated with a significant effusion in one or more cavities including the abdominal cavity and pleural or pericardial space, in the absence of atypical red cell antibodies.	25.8 (12-39)
Enders	2010	Not provided	<20
Simms	2009	Not provided	<21
Figuereido	2008	One or more clinical signs, such as peripheral edema, ascites, anemia and congestive heart failure	NA
Beigi	2008	Not provided	NA
Abrams	2007	Tissue edema and effusions of multiple body cavities. Data on fluid accumulation in specific compartments were not reported consistently in the database; therefore, the diagnosis of hydrops fetalis did not always include a report of fluid in >1 body compartment.	NA
Chisaka	2006	Hydrops fetalis diagnosed when the accumulation of fluid in body cavities and subcutaneous edema were evident on ultrasound	15-20
Hernandez - Andrade	2004	Moderate or severe ascites, with or without skin edema, and pericardial or pleural effusions.	17-32
Enders	2004	Not provided	NA
Favre	2004	increased fluid accumulation in fetal soft tissues and serous cavities in >1 site	2^{nd} – 3^{rd} trimester

Cosmi	2002	presence of fluid in two fetal cavities and/or subcutaneous edema	18-28
Dembinsky	2002	Not provided	NA
Nunoue	2002	Not provided	21-26
Kailasam	2001	Not provided	18-25
Ismail	2001	subcutaneous tissue edema accompanied by serous effusion in one or more fetal body cavities without evidence of immune etiology	21 (20^{+5}-24^{+2})
Suchet	2000	Fetal edema (generalized subcutaneous edema greater than 5 mm) and fluid accumulation in the serous cavities (ascites, pleural and pericardial effusion)	NA
Heinonen	2000	effusion in one or more fetal body cavities and generalized subcutaneous edema without evidence of isoimmunization	<20

Garabedian	2014	Is intrauterine exchange transfusion a safe procedure for management of fetal anaemia?	This study is likely to share cases with that by Chauvet et al. because it was carried out in the same centres during the same time period. Thus, in order not to have overlapping cases, it was excluded from the analysis.
Lassen	2013	Parvovirus B19 infection in pregnancy and subsequent morbidity and mortality in offspring	The study includes cases from a national register; no information was available on the course of infection during pregnancy
Lassen	2012	Parvovirus B19 infection in the first trimester of pregnancy and risk of fetal loss: a population-based case-control study.	Only cases affected by fetal losses were included in this study
Leijser	2012	Brain ultrasound findings in neonates treated with intrauterine transfusion for fetal anaemia	This study shares cases with that by De Jong et al. Which was considered as the most representative from the same research group.
Bovincini	2012	Gestational and Fetal Outcomes in B19 Maternal Infection: a Problem of Diagnosis	This study shares cases with that by Puccetti et al. Which was considered as the most representative from the same research group.
Bogers	2011	Parvovirus B19 infection in pregnancy and amniocentesis	Letter to editor, no original case included
Amann	2011	Fetal anemia of unknown cause--a diagnostic challenge	In the present series, the authors mentioned that 23 cases of fetal anemia were assessed during the study period. However, there was no mention on any of the outcomes observed in the present systematic review
Miller	2009	Perinatal outcomes after second trimester detection of amniotic fluid viral genome in asymptomatic patients	No case of parvovirus infection
Kho	2009	Management of an obstetric health care provider with acute parvovirus B19 infection	Although this study states the number of infected mothers, there is no detail description of the outcomes described in the present systematic review
Borna	2009	Middle cerebral artery peak systolic velocity and ductus venosus velocity in the investigation of nonimmune hydrops.	Only 1 case of parvovirus infection
Bovincini	2009	Diagnosis of fetal parvovirus B19 infection: value of virological assays in fetal specimens	This study shares cases with that of Bovincini et al (2009) which was considered as the most representative from the same research group.
Savarese	2008	Atypical manifestations of congenital parvovirus B19 infection.	Only 2 cases of PB19 infection included
Enders	2008	Improved diagnosis of gestational parvovirus B19 infection	This study is likely to share cases with other studies by the same authors

		at the time of nonimmune fetal hydrops	which have been included in the present systematic review
Riipinen	2008	Parvovirus B19 infection in fetal death.	Only cases who experienced miscarriage or fetal death were included in this study
De Haan	2008	Parvovirus B19 infection in pregnancy: maternal and fetal viral load measurements related to clinical parameters	This study shares cases with that by De Jong et al. Which was considered as the most representative from the same research group.
Hsu	2007	Prenatal diagnosis and perinatal management of maternal-fetal congenital parvovirus B19 infection.	Only 2 cases of PB19 infection included
Kempe	2007	First-trimester treatment of fetal anemia secondary to parvovirus B19 infection.	Only 2 cases of PB19 infection included
Elbaz	2007	Erythrovirus B19 as a potential cause of fetal hydrops: assessing awareness	No data on the outcomes explored in this systematic review could be extrapolated from this study
El-Sayed	2007	Relevance of parvovirus B19, herpes simplex virus 2, and cytomegalovirus virologic markers in maternal serum for diagnosis of unexplained recurrent abortions	No data on the outcomes explored in this systematic review could be extrapolated from this study
Glenn	2007	Fetal cerebellar hemorrhage in parvovirus-associated non-immune hydrops fetalis.	Only 2 cases of PB19 infection included
Leung	2007	Fetal parvovirus B19 infection in a twin pregnancy with 1 twin presenting with hydrops fetalis and the other asymptomatic: a case report.	Only 2 cases of PB19 infection included
Liao	2007	Nonimmune hydrops fetalis diagnosed during the second half of pregnancy in Southern China.	Only 1 case of parvovirus infection was included in this series
Nagel	2007	Long-Term Outcome After Fetal Transfusion for Hydrops Associated With Parvovirus B19 Infection	This study shares cases with that of De Jong et al. which was considered as the most representative from the same research group.
Segata	2007	Fetal thrombocytopenia secondary to parvovirus infection	This study is likely to share cases with that by Cosmi et al. And Puccetti et al. et al. Because it was carried out in the same centres. Furthermore, there is no mention on when the cases were collected, thus, in order not to have overlapping cases, it was excluded from the analysis.
Trainor	2006	The emerging pattern of hydrops fetalis--incidence, aetiology and management.	No case of PB19 infection was included in this series

Simpson	2006	Severity of non-immune hydrops fetalis at birth continues to predict survival despite advances in perinatal care.	Only 1 case of PB19 infection
Van Gessel	2006	Incidence of parvovirus B19 infection among an unselected population of pregnant women in the Netherlands: A prospective study	This study includes women with confirmed seroconversion top PB19; however, there was no case of suspected fetal infection based on ultrasound assessment in the study population. Furthermore, it was not clear how many fetuses were tested for the infection at birth.
Suwanrath-Kengpol	2005	Etiology and outcome of non-immune hydrops fetalis in southern Thailand.	No information on PB19 infection
Enders	2005	Human parvovirus B19 infection during pregnancy – Value of modern molecular and serological diagnostics	The present study shared cases with that by Enders et al. 2005 which was considered as the most representative from this research group.
Enders	2004	Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: Prospective evaluation of 1018 cases.	The present study shared cases with that by Enders et al. 2005 which was considered as the most representative from this research group.
Xu	2003	Hydrops Fetalis Secondary to Parvovirus B19 Infections	Only 2 cases of PB19 infection included
Norbeck	2002	revised clinical presentation of parvovirus B19- associated intrauterine death	Only cases affected by fetal loss were included in this study
Liu	2002	Retrospective analysis of 17 liveborn neonates with hydrops fetalis.	No case of parvovirus infection
Tolfvenstam	2001	Frequency of human parvovirus B19 infection in intrauterin fetal death	Only cases affected by fetal loss were included in this study
Sohan	2001	Analysis of outcome in hydrops fetalis in relation to gestational age at diagnosis, cause and treatment	This study shares cases with that by Simms et al. Which was considered as the most representative from the same research group.
Delle Chiaie	2001	Prediction of fetal anemia with Doppler measurement of the middle cerebral artery peak systolic velocity in pregnancies complicated by maternal blood group alloimmunization or parvovirus B19 infection	This study shares cases with that by Cosmi et al. Which was considered as the most representative from the same research group.

Skjöldebrand-Sparre	2000	Parvovirus B19 infection: association with third-trimester intrauterine fetal death	Only cases experiencing IUD in the third trimester of pregnancy were included in this study
Dong	2000	Detection of a human parvovirus intrauterine infection with the polymerase chain reaction.	No available information for the meta-analysis except for the number of fetal infection
Jensen	2000	An epidemic of parvovirus B19 in a population of 3,596 pregnant women: a study of sociodemographic and medical risk factors.	It was not possible to extrapolate the number of fetuses infected by PB19 and no data on the other outcomes observed in the present systematic review could be extrapolated from this study
Dong	2000	Detection of a human parvovirus intrauterine infection with the polymerase chain reaction.	No fetal data
Haverkamp	2000	Good prognosis for psychomotor development in survivors with nonimmune hydrops fetalis.	It was not stated if and how many fetuses had PB19 infection
Hemauer	2000	Seroprevalence of Parvovirus B19 NS1-Specific IgG in B19-Infected and Uninfected Individuals and in Infected Pregnant Women	No data on infected fetuses

Table S4. Pooled proportions of outcome of fetuses affected by congenital parvovirus B19 infection with signs of hydrops on ultrasound, according to gestational age at infection

	< 20 weeks' gestation					≥ 20 weeks' gestation			
Outcomes	**Studies (n)**	**Fetuses (n/N)**	**Pooled proportion %(95% CI)**	**I^2 (%)**		**Studies (n)**	**Fetuses (n/N)**	**Pooled proportion % (95% CI)**	**I^2 (%)**
Perinatal death	9	6/50	15.91 (4.5-32.6)	44		13	32/105	36.08 (23.8-49.3)	45.7
Intrauterine death	9	5/50	13.86 (3.8-28.9)	37.5		14	2/112	34.47 (22.5-47.6)	48.9
Neonatal death	9	1/50	4.87 (0.8-12.1)	0		13	2/105	4.45 (1.4-9.0)	0
IUT	6	20/34	83.24 (58.4-98.0)	59.8		10	17/64	33.06 (18.7-49.3)	42.4
Resolution after IUT	5	7/18	34.72 (8.6-41.5)	21.6		8	28/48	56.45 (42.4-70.0)	4.9
Fetal loss after IUT	4	12/31	39.12 (23.4-56.1)	0		10	17/64	33.06 (18.7-49.3)	42.4
Spontaneous resolution of infection	9	2/32	10.36 (2.7-22.1)	0		12	3/94	5.24 (1.8-10.4)	0

IUT: intrauterine blood transfusion.

Table S5. Pooled proportions of outcome of fetuses affected by congenital parvovirus B19 infection without signs of hydrops on ultrasound, according to gestational age at infection.

	< 20 weeks' gestation					≥ 20 weeks' gestation			
Outcomes	**Studies (n)**	**Fetuses (n/N)**	**Pooled proportions %(95% CI)**	**I^2 (%)**		**Studies (n)**	**Fetuses (n/N)**	**Pooled proportions % (95% CI)**	**I^2 (%)**
Perinatal death	7	1/51	2.86 (0.1-8.9)	0		4	1/24	6.67 (0.03-23.4)	22.5
Intrauterine death	7	0/51	0 (0-7.7)	0		5	1/34	4.10 (0.2-12.9)	0.5
Neonatal death	7	1/51	2.86 (0.1-8.9)	0		4	0/24	0 (0-13.1)	0
IUT	5	3/20	19.65 (0.1-59.4)	72.4		6	15/29	35.40 (8.7-68.5)	65.5
Resolution after IUT	-	-	-	-		2	3/3	100 (45.5-100)	0
Fetal loss after IUT	2	2/5	46.2 (5.3-97.5)	0		3	0/15	0 (0-17.4)	-
Spontaneous resolution of infection	4	9/17	58.21 (3.8-99.9)	86.6		6	5/14	33.93 (3.3-76.1)	68.8

IUT, intrauterine blood transfusion