Journal of Clinical Virology 114 (2019) 12–20

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

The risk of maternal parvovirus B19 infection during pregnancy on fetal loss and fetal hydrops: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Parvovirus B19
Fetal loss
Spontaneous abortion
Fetal hydrops
Meta-analysis

ABSTRACT

Background: Human parvovirus B19 (B19) is widespread infection in humans, yet the impact on adverse pregnancy outcomes is controversial.
Objective: to evaluate the impact of B19 infection during pregnancy on adverse pregnancy outcome, and investigated the incidence of fetal loss and fetal hydrops after maternal B19 infection during pregnancy.
Study design: A systematic literature search was performed using Embase, Medline, PubMed, Web of science, and the Cochrane Library database for relevant publications up to 10th August 2018. Cohort studies and case-control studies were included in analyses.
Results: In total, 36 eligible studies were included. Of these, 18 studies reported the risk of maternal B19 infection during pregnancy on fetal loss and 20 studies reported the incidence of fetal loss or fetal hydrops after maternal B19 infection. Collectively, the results indicated that maternal B19 infection increased the risk of fetal loss, spontaneous abortion, and stillbirth with ORs of 2.68 (95% CI: 2.02–3.55), 2.42 (95% CI: 1.76–3.33), and 3.53 (95% CI: 1.91–6.54), respectively, when compared with uninfected pregnant women. In addition, the incidence of fetal loss and fetal hydrops in B19 infected pregnant women was 7.6% (95% CI: 5.5–9.5) and 9.3% (95% CI: 5.6–13.0), respectively.
Conclusions: maternal parvovirus B19 infection during pregnancy increased the risk of fetal loss, spontaneous abortion, and stillbirth. A high incidence of fetal loss and fetal hydrops was observed in pregnant women with parvovirus B19 infection.

1. Background

Human parvovirus B19 (B19), a single-stranded DNA virus, is the causative agent for erythema infectiosum or fifth disease. B19 is mainly transmitted by respiratory droplets, but also through blood or vertically from mother to fetus [1]. The proportion of pregnant women susceptible to B19 infection ranges from 34% to 65% in various parts of the world [2–4]. The incidence of seroconversion during pregnancy is estimated at between 1% and 1.5% in the endemic period, increasing to 13% in the epidemic period [4].

The adverse risk of B19 infection during pregnancy has been reported extensively, but with controversial conclusions [4–6]. In a prospective study, Jensen et al. reported that B19 IgM seropositivity was associated with events of spontaneous abortions and stillbirths (odds ratio, OR = 9.9) [4]. However, in another population-based case-control study, the association was not significant (OR = 0.8) [5]. Furthermore, obvious differences in incidence of fetal loss or fetal hydrops among women with acute B19 infection during pregnancy are reported.

2. Objectives

Here, we conducted a systematic review and meta-analysis to evaluate the risk of maternal parvovirus B19 infection during pregnancy on fetal loss, and to evaluate its effect on the incidence of fetal loss and fetal hydrops.

3. Study design

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [7].

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https://doi.org/10.1016/j.jcv.2019.03.004
Received 16 October 2018; Received in revised form 11 February 2019; Accepted 7 March 2019

3.1. Inclusion and exclusion criteria

Studies were eligible for screening if they met the following criteria: (1) cohort study or case-control study; (2) reported adverse pregnancy outcomes, including fetal hydrops, fetal loss, intrauterine fetal death, miscarriage, preterm birth, stillbirth, and low birth weight, in patients with B19 infection; (3) B19 infection occurred during pregnancy and was defined as positive for DNA, IgM, or seroconversion; (4) reported corresponding effect estimates (e.g. relative risks, OR, or incidence) or sufficient data to calculate effect estimates. Studies were excluded if they (1) were review articles, editorials, opinions, or case reports; (2) described B19 infections defined as IgG antibody positive.

3.2. Literature search

Embase (Ovid), Medline (Ovid), PubMed, Web of science, and the Cochrane Library database were searched from the earliest date available up until 10nd August 2018. We used both MeSH and free text terms to identify relevant articles. The following free text terms were used: 'parvovirus', 'parvovirus B19', 'B19V', 'pregnancy', 'pregnant', 'fetal loss', 'fetal hydrops', 'miscarriage', 'abortion', 'low birth weight', 'preterm birth', 'stillbirth', 'intrauterine fetal death', 'IUFD', 'non-immune fetal hydrops' and 'NIHF'. Searches were restricted to human studies and there was no language restriction. Manual searches of the reference lists of review articles and studies included in the final publication selection were also conducted.

3.3. Data selection and extraction

Two authors independently evaluated all retrieved articles by title, abstract, and full text according to the above inclusion criteria. Any disagreement was resolved by consensus. Data were independently extracted from each eligible study and included study characteristics (first author, publication year, country of origin, study design, and time of study conducted) and virus detection characteristics (B19 detection method, virus detected tissue, and time of the virus infection). In addition, studies evaluating the risk of B19 infection on pregnancy outcome, the number of B19 infectious participants with or without adverse pregnancy outcomes, corresponding relative risks (RRs) or ORs, and 95% CI value, were extracted. For studies evaluating the incidence of fetal loss and fetal hydrops after B19 infection, the number of B19 infected participants and the number of cases of fetal loss or fetal hydrops were extracted. When data were reported from overlapping study samples (e.g., multiple publications from the same study), the most recent and comprehensive report was considered.

3.4. Quality assessment

Cohort and case-control study quality was assessed using the Newcastle–Ottawa Scale (NOS) [8,9]. This scale scores studies across three categories: selection of subjects, comparability of study groups, and the assessment of outcome/exposure. This rating system was used to indicate study quality, with a maximum score of 9. Studies were graded on an ordinal scoring scale, with higher scores representing higher quality studies. When a study was awarded a score of 7 or more, 5 or 6, or < 5, it was considered a high-, moderate-, or low-quality study, respectively. In addition, we adapted the NOS scale to assess bias risk in single-arm cohort studies, which reported the incidence of fetal loss or fetal hydrops after maternal parvovirus B19 infection during pregnancy. Accordingly, the items applicable to control were excluded, resulting in a maximum score of 6; when a study was awarded a score of ≥5, 3 or 4, or < 3, it was considered as a high-, moderate-, or low-quality study, respectively [10].

3.5. Statistical analysis

The ORs or RRs with their corresponding 95% CIs were selected as the effect size to assess the risk of fetal loss including spontaneous abortion and stillbirth in B19 infected participants. The incidence of fetal loss and fetal hydrops after maternal B19 infection during pregnancy was also pooled. When a study reported more than one result of spontaneous abortion, stillbirth, or intrauterine fetal death, the fetal loss was counted as the sum of adverse pregnancy outcomes. Otherwise, fetal loss was defined as a spontaneous abortion, stillbirth, or intrauterine fetal death when only one result of these outcomes was reported. Inter-study heterogeneity was estimated by the I^2 statistic, and significant heterogeneity was defined as $I^2 \geq 50\%$. Pooled results and corresponding 95% CIs were calculated with a fixed effects model (Mantel and Haenszel method) when heterogeneity was not significant ($I^2 < 50\%$); otherwise, a random effects model (DerSimonian and Laird method) was applied. Forest plots were constructed for visual display of pooled results if necessary. In the pooled risk analysis section, one was added to each cell of a 2 × 2 contingency table when the B19-positive participants were both zero in the case and control groups. In the pooled incidence analysis section, those studies with no observed fetal loss or fetal hydrops were removed from the primary analysis. In the sensitivity analysis section, these studies were included with 1/2 added to both the fetal loss or fetal hydrops groups and the B19 infected group. In the pooled risk analysis section, subgroup analyses were only performed within case-control studies and according to year of study (before 2000 or after 2000), virus detection method (IgM/seroconversion or polymerase chain reaction, PCR), and virus detected tissue (maternal serum, fetal/placenta, or other tissues). In the pooled incidence analysis section, excepting the time (year) of study, subgroup analyses were also conducted according to study design (prospective or retrospective/unclear), clinical maternal symptoms of infection (symptomatic or asymptomatic), and time of infection (first or second trimester). Sensitivity analyses were used to evaluate whether any single study dominated the results of the meta-analyses. A meta-regression analysis was also performed to explore inter-study heterogeneity. Finally, publication bias was assessed by visual inspection of funnel plots and Begg's test. Statistical analyses were conducted using STATA 12.0 (Stata Corp LP, College Station, TX).

4. Results

4.1. Characteristics of the studies included in this meta-analysis

Systematic literature searches identified 3556 potentially relevant studies. Most ineligible studies were excluded based upon title or abstract information. Finally, 36 studies [4–6,11–43], were eligible for analysis, including 18 studies [4–6,11–25], reporting the risk of maternal parvovirus B19 infection during pregnancy on fetal loss and 20 studies [6,12,26–43] reporting the incidence of fetal loss or fetal hydrops after maternal B19 infection. The selection process is shown in Figure S1. No disagreements occurred between the two authors regarding the selection of the included studies. Main study characteristics were showed in Table 1. Among the 36 studies included, two were published in Chinese [11,12], two were published in Polish [24,27] and one was a conference article [35]. Most of the included studies were of high quality, and four case-control studies were of moderate quality [4,17,20,25].

4.2. Risk of maternal parvovirus B19 infection for fetal loss

Eighteen studies, including three cohort studies [6,12,24] and 15 case-control studies [4,5,11,13–23,25], with a total of 20 609 participants, reported the impact of B19 infection on the risk of fetal loss. Pooled results suggested that maternal B19 infection during pregnancy increased the risk of fetal loss [OR of 2.68 (95% CI: 2.02–3.55; I^2 =

Table 1
Basic characteristics of the studies included in this meta-analysis.

Authour (year)	Country	Study design	Period of study	center
Koskiniemi (1996)	Finland	case-control	1988-1990	1
Kinney (1988) [a]	USA	case-control	NA(NIH)/1985 (ATL)	12(NIH)/5(ATL)
Wenstrom (1998)	USA	case-control	1988-1995	1
Harger (1998)	USA	prospective cohort study	1990-1996	1
Jensen (2000)	Denmark	case-control	1992-1994	1
Makhseed (2001)	Kuwait	case-control	NA	1
Friedek (2001)[b]	Poland	cohort study	NA	NA
Li (2001) [c]	China	prospective cohort study	1998	1
Xu (2002)[c]	China	case-control	1991-1997	6
Nyman (2002)	Sweden	case-control	1997-1999	2
Norbeck (2002)	Sweden	case-control	1993-1997	2
Keikha (2006)	Iran	case-control	2001-2002	1
Syridou (2008)	Greece	case-control	2004-2005	1
Johansson (2008)	Sweden	case-control	1993-2002	multicenter
Riipinen (2008)	Finland	case-control	1992-1995/2003-2005	1
Sarfraz (2009)	Norway	case-control	1992-1994	multicenter
Lassen (2012)	Denmark	case-control	1992-1994	multicenter
Daniilidis (2014)	Greece	case-control	2004-2009	1
Daniilidis (2014)	Greece	case-control	2004-2009	1
Hall (1990)	England and Wales	prospective cohort study	1985-1988	multicenter
Rodis (1990)	USA	prospective cohort study	1987-1988	1
Smoleniec (1994)	England	case-series study	1993	NA
Guidozzi (1994)	South Africa	prospective cohort study	NA	NA
Gratacos (1995)	Spain	prospective cohort study	NA	1
Sparre (1996)	Sweden	prospective cohort study	1990-1991	1
Miller (1998)	England and Wales	prospective cohort study	1992-1995	multicenter
William (1998)	USA	case-series study	NA	2
Makhseed (1999)	Kuwait	prospective cohort study	NA	NA
Yaegashl (1999)	Japan	cohort study	NA	multicenter
Enders (2004)	Germany	prospective cohort study	1993-1998	multicenter
Chisaka (2006)	Japan	prospective cohort study	1999-2004	multicenter
Gessel (2006)	Netherlands	prospective cohort study	1998-2000	multicenter
Beigi (2008)	USA	retrospective cohort study	1998-2001	1
Paulina (2008)[b]	Poland	prospective cohort study	2000-2007	1
Enders (2010)	Germany	cohort study	1999-2002	NA
Puccetti (2012)	Italy	retrospective cohort study	2005-2009	1
Simmons (2014)	Ireland	retrospective cohort study	NA	1

Authour (year)	Sample size	Detection method	Virus detection site	Outcome	Study quality assessment
Koskiniemi (1996)	84	IgM	maternal serum	risk of stillbirth	high quality
Kinney (1988) [a]	384(NIH)/46(ATL)	IgM	maternal serum	risk of spontaneous abortion/stillbirth	high quality
Wenstrom (1998)	122	PCR	amniotic fluid	risk of spontaneous abortion	high quality
Harger (1998)	618	IgM	maternal serum	risk and incidence of spontaneous abortion/stillbirth	high quality
Jensen (2000)	3151	IgM	maternal serum	risk of fetal loss	moderate quality
Makhseed (2001)	1047	IgM	maternal serum	risk of spontaneous abortion/stillbirth	moderate quality
Friedek (2001)[b]	32	IgM	maternal serum	risk of spontaneous abortion	high quality
Li (2001) [c]	335	PCR	maternal serum	risk and incidence of stillbirth	high quality
Xu (2002)[c]	222	PCR	fetal tissue	risk of spontaneous abortion	high quality
Nyman (2002)	153	PCR	placenta tissue	risk of spontaneous abortion	high quality
Norbeck (2002)	152	PCR	fetal/placenta tissue	risk of stillbirth	moderate quality
Keikha (2006)	324	IgM	maternal serum	risk of spontaneous abortion	high quality
Syridou (2008)	97	PCR	placenta tissue	risk of spontaneous abortion/stillbirth	high quality
Johansson (2008)	793	PCR	maternal serum	risk of spontaneous abortion	high quality
Riipinen (2008)	535	PCR	fetal tissue	risk of spontaneous abortion/stillbirth	moderate quality

(*continued on next page*)

Table 1 (*continued*)

Authour (year)	Sample size	Detection method	Virus detection site	Outcome	Study quality assessment
Sarfraz (2009)	1238	IgM	maternal serum	risk of stillbirth	high quality
Lassen (2012)	11347	IgM	maternal serum	risk of spontaneous abortion	high quality
Daniilidis (2014)	206	IgM	maternal serum	risk of spontaneous abortion	high quality
Daniilidis (2014)	206	IgM	maternal serum	risk of spontaneous abortion	high quality
Hall (1990)	183	IgM	maternal serum	incidence of fetal loss	high quality
Rodis (1990)	39	IgM	maternal serum	incidence of fetal loss/fetal hydrops	high quality
Smoleniec (1994)	22	IgM	maternal serum	incidence of fetal loss/fetal hydrops	high quality
Guidozzi (1994)	64	IgM	maternal serum	incidence of fetal hydrops	high quality
Gratacos (1995)	60	IgM/seroconversion	maternal serum	incidence of spontaneous abortion	high quality
Sparre (1996)	34	seroconversion/ increasing level of IgG	maternal serum	incidence of fetal loss	high quality
Miller (1998)	408	IgM	maternal serum	incidence of fetal loss/fetal hydrops	high quality
William (1998)	43	IgM	maternal serum	incidence of fetal loss	high quality
Makhseed (1999)	39	IgM/seroconversion/ increasing level of IgG	maternal serum	incidence of fetal loss	high quality
Yaegashl (1999)	48	IgM	maternal serum	incidence of fetal loss/fetal hydrops	high quality
Enders (2004)	1018	IgM	maternal serum	incidence of fetal loss/NIHF	high quality
Chisaka (2006)	100	IgM	maternal serum	incidence of fetal loss/NIHF	high quality
Gessel (2006)	18	IgM	maternal serum	incidence of fetal loss/NIHF	high quality
Beigi (2008)	25	IgM/seroconversion	maternal serum	incidence of fetal loss/fetal hydrops	high quality
Paulina (2008)[b]	243	IgM	maternal serum	incidence of fetal hydrocephalus or ventriculomegaly /spontaneous abortion	high quality
Enders (2010)	236	IgM	maternal serum	incidence of fetal loss/fetal hydrops	high quality
Puccetti (2012)	63	PCR/IgM	maternal serum	incidence of fetal loss/fetal hydrops	high quality
Simmons (2014)	20	seroconversion	maternal serum	incidence of fetal loss	high quality

Note: a, they were two cohorts (NIH and ATL) which were described in one study; b, these two studies were published in Polish; c, these two studies were published in Chinese; PCR, polymerase chain reaction; NIHF, nonimmune hydrops fetalis; NA, not available.

41.9%; Fig. 1)]. When only including the 15 case-control studies, which involved 19 624 participants, the pooled OR was 2.50 (95% CI: 1.86–3.36; I^2 =39.6%; Table 2). Subgroup analyses showed that in the pooled results of different study periods, detection method and B19 detection tissues were consistent, which also indicated that B19 detection increased the occurrence of fetal loss (Table 2).

4.3. Risk of maternal parvovirus B19 infection for spontaneous abortion

These results, based on 13 studies, including two cohort studies [6,24] and 11 case-control studies [11,13–22] (involving 15 171 participants), indicated that B19 infection increased the occurrence of spontaneous abortion [pooled OR of 2.42 (95% CI: 1.76–3.33; I^2 =7.6%)]. In addition, subgroup analyses of pooled results of the different study types, study periods, detection methods, and B19 detection tissues also suggested that B19 infection increased the occurrence of spontaneous abortion (Table 2).

4.4. Risk of maternal parvovirus B19 infection for stillbirth

There were two cohort studies [6,12] and seven case-control studies [5,14,15,17,20,23,25], which included 3057 participants and reported the association of maternal B19 infection and stillbirth. Both the overall pooled analysis and subgroup analysis of seven case-control studies indicated maternal B19 infection was a risk factor for stillbirth [pooled OR of 3.53 (95% CI: 1.91–6.54; I^2 = 31.6%) and 3.11 (95% CI: 1.57–6.14; I^2 = 25.2%), respectively] (Table 2).

In subgroup analysis, the results of five studies [5,15,17,23] detecting virus infection in the maternal serum as positive IgM results or seroconversion did not suggest an association between maternal parvovirus B19 infection and stillbirth [pooled OR of 1.16 (95% CI: 0.45–2.98; I^2 = 0.0%)]. However, when restricted to these studies, which used PCR to detect virus infection in fetal or placenta tissues, the pooled OR was 11.25 (95% CI: 2.59–28.94; I^2 = 0.0%; Table 2).

4.5. Incidence of fetal loss following maternal parvovirus B19 infection

Sixteen studies [6,12,27–3032–3537–42], involving 189 cases of fetal loss and 2455 pregnant women reported the incidence of fetal loss in B19 infected pregnant women. The pooled incidence of fetal loss was 7.6% (95% CI: 5.5–9.5; I^2 = 58.7%; Fig. 2). In addition, the pooled incidence of fetal loss of symptomatic participants (9.3%, 95% CI: 6.2–12.4; I^2 = 0.0%) was higher than that of asymptomatic participants (5.4%, 95% CI: 3.9–6.9; I^2 = 48.0%; Table 3). The results of subgroup analyses of prospective and retrospective/unclear design studies, and studies from different periods are shown in Table 3.

Four studies [28–30,34], reported the fetal loss rate associated with different times of B19 infection. Results showed that the incidence of fetal loss in pregnant women who were infected with the virus in their first trimester (14.0%, 95% CI: 11.2–16.8; I^2 = 24.5%) was higher than that for the second trimester (5.6%, 95% CI: 4.0–7.2; I^2 = 0.0%; Table 3).

4.6. Incidence of fetal hydrops of maternal parvovirus B19 infection

Nine studies [27–30,32,34,40–42], reported the incidence of fetal hydrops in B19 infected pregnant women (151 cases of fetal hydrops and 2462 pregnant women). The pooled incidence of fetal hydrops was 9.3% (95% CI: 5.6–13.0; I^2 = 91.6%; Fig. 3). Subgroup analysis showed that the incidence of fetal hydrops in prospective studies was higher than in other study designs, with pooled incidences of 13.5% (95% CI: 5.2–21.8; I^2 = 95.9%) and 7.7% (95% CI: 2.8–12.5; I^2 = 76.5%), respectively (Table 3). The incidence of fetal hydrops in studies conducted after 2000 (11.4%, 95% CI: 3.1–19.7; I^2 = 93.2%) was higher than that before 2000 (5.2%, 95% CI: 1.5–8.8; I^2 = 86.7%; Table 3).

Four studies [29,30,34,40] reported the fetal hydrops incidence

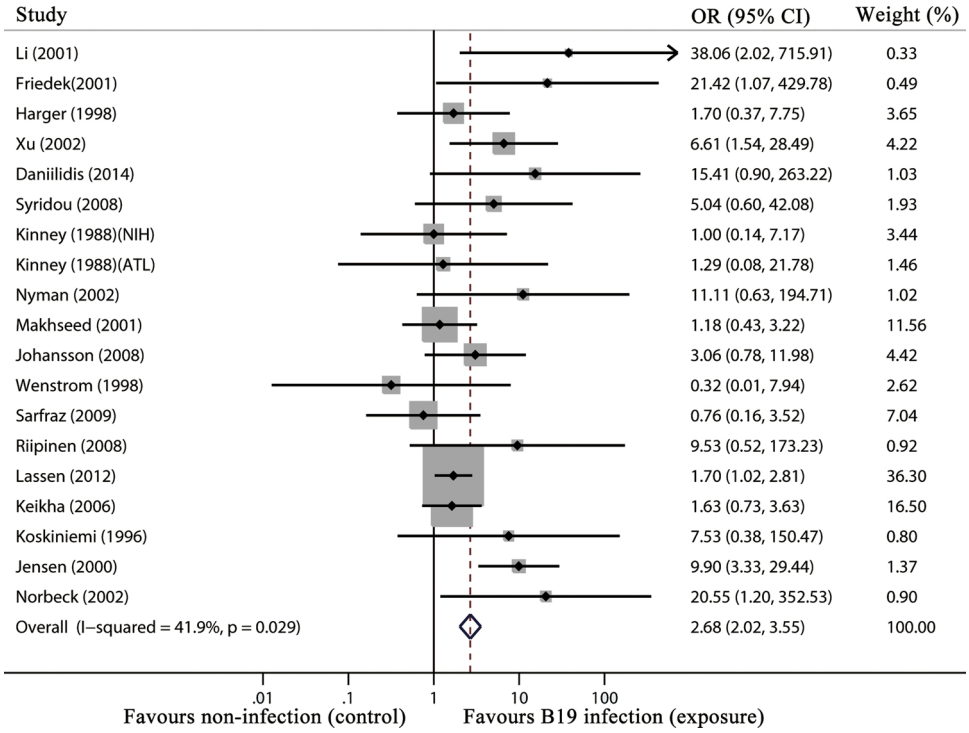

Fig. 1. Forest plot of the association between maternal parvovirus B19 infection during pregnancy and the risk of fetal loss.

Table 2
Subgroup analyses of the association between parvovirus B19 infection during pregnancy and adverse pregnancy outcomes.

			Number of study included	Number of participants (n)	RR/OR	95% CI	Heterogeneity(I^2) (%)
Fetal loss	All studies included		19[a]	20609	2.68	2.02-3.55	41.9
	Type of study	Cohort Study	3	985	6.94	0.87-55.40	57.6
		Case-control Study	16[a]	19624	2.50	1.86-3.36	39.6
	Period of study[b]	Before 2000	11	17934	2.54	1.29-5.01	51.0
		After 2000	5	1690	3.02	1.66-5.47	8.3
	Detection method[b]	IgM/Seroconversion	9	17815	1.86	1.33-2.61	46.0
		PCR	7	1809	5.65	2.75-11.60	0.0
	Detection tissue[b]	Maternal serum	10	18343	1.93	1.39-2.67	40.9
		Fetal/Placenta or other tissues	6	1281	6.63	2.82-15.58	0.0
Spontaneous abortion	All studies included		13	15171	2.42	1.76-3.33	7.6
	Type of study	Cohort Study	2	650	5.49	1.39-21.61	19.1
		Case-control Study	11	14521	2.29	1.65-3.19	3.4
	Period of study[b]	Before 2000	6	13044	2.11	1.43-3.13	23.2
		After 2000	5	1477	2.73	1.48-5.03	0.0
	Detection method[b]	IgM/Seroconversion	5	13077	1.84	1.27-2.68	0.0
		PCR	6	1444	4.43	2.04-9.62	0.0
	Detection tissue[b]	Maternal serum	6	13605	1.92	1.34-2.75	0.0
		Fetal/Placenta or other tissues	5	916	5.07	1.97-13.07	0.0
Still birth	All studies included		10	3057	3.53	1.91-6.54	31.6
	Type of study	Cohort Study	2	953	5.85	0.17-203.82	66.8
		Case-control Study	8	3057	3.11	1.57-6.14	25.2
	Period of study[b]	Before 2000	6	2563	2.36	1.09-5.08	27.5
		After 2000	2	494	7.72	1.38-43.28	0.0
	Detection method[b]	IgM/Seroconversion	5	2411	1.16	0.45-2.98	0.0
		PCR	3	646	11.25	2.59-28.94	0.0
	Detection tissue[b]	Maternal serum	5	2411	1.16	0.45-2.98	0.0
		Fetal/Placenta or other tissues	3	646	11.25	2.59-28.94	0.0

Note: a, there was one study which included two cohorts; b, only case-control studies were included in subgroup analyses; RR, relative risk; OR, odds ratio.

associated with B19 infection at different times: first trimester, 2.1% (95% CI: 0.1–4.2; I^2 = 61.4%); and second trimester, 5.0% (95% CI: 2.0–8.0; I^2 = 68.4%) (Table 3).

4.7. Heterogeneity analysis

Inter-study heterogeneity in analyses of the pooled incidence of fetal loss and fetal hydrops in B19 infected pregnant women were explored by meta-regression analysis. Five variables were included in the meta-regression analysis: (1) country of origin (developed countries vs. developing countries); (2) time of study conducted (before 2000 vs. after 2000); (3) sample size (< 100 participants vs. ≥ 100 participants); (4) number of study centers (multicenter vs. single or unclear); and (5) study design (prospective vs. retrospective or unclear). Results showed

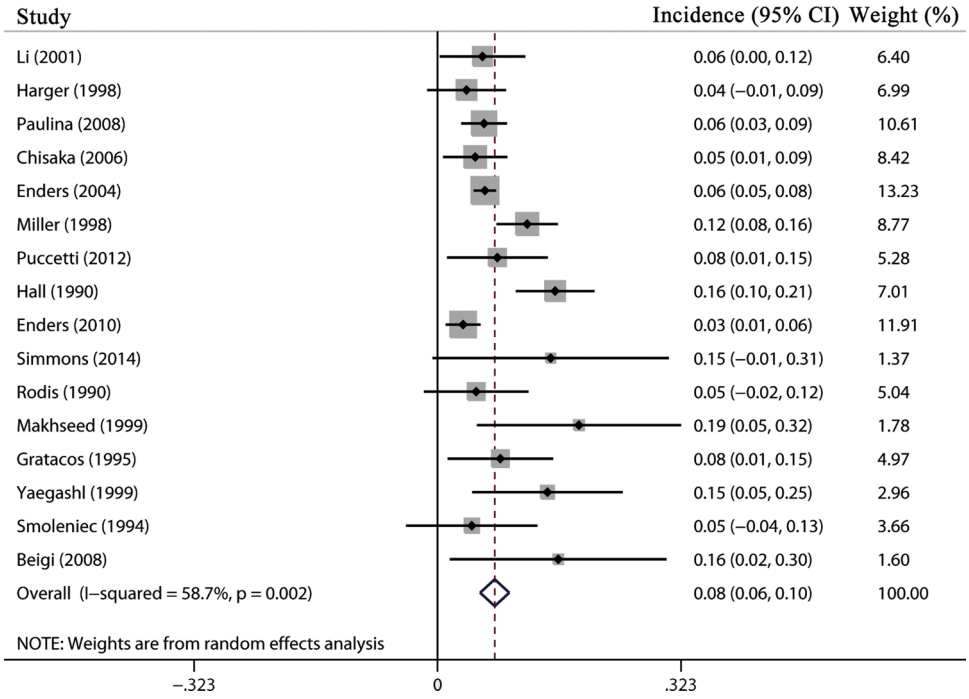

Fig. 2. The pooled incidence of fetal loss after maternal parvovirus B19 infection during pregnancy.

that none of these variables significantly influenced heterogeneity, in the analysis of incidence of either fetal loss or fetal hydrops.

4.8. Sensitivity analysis

By sequentially removing individual eligible studies, we observed that no individual study altered the overall significance of risk of maternal B19 infection for fetal loss, spontaneous abortion, or stillbirth. In addition, when five studies were added [26,31,36,37,43], in which no fetal loss or fetal hydrops was observed in pooled analyses, the pooled fetal loss and fetal hydrops incidence was 6.5% (95% CI: 4.7–8.4) and 6.7% (95% CI: 3.9–9.6), respectively.

4.9. Publication bias

The funnel plots for publication bias were symmetrical, and Begg's test indicated no significant asymmetry in any of the analyses.

5. Discussion

Results of this meta-analysis suggest that when compared with uninfected pregnant women, maternal B19 infection increased the risk of fetal loss, spontaneous abortion, and stillbirth with ORs of 2.68, 2.42, and 3.53, respectively. In addition, the incidence of fetal loss and fetal hydrops in B19 infected pregnant women was 7.6% and 9.3%, respectively. Our results were consistent with a recently published systematic review that explored the outcome of fetuses affected by congenital B19 [35], the risk of miscarriage (OR: 11.5) and perinatal death (OR: 4.2) was higher in fetuses of B19-infected mothers compared to those not presenting with hydrops on ultrasound [35]. Furthermore, the overall risk of death and intra-uterine death was higher in fetuses affected by hydrops [35]. High incidence of fetal hydrops was observed in pregnant

Table 3
Subgroup analyses of the incidence of fetal loss and fetal hydrops of maternal parvovirus B19 infection.

			Number of study included	Number of B19 infected participants (n)	Number of adverse pregnancy outcomes (n)	Pooled rate (%)	95% CI (%)	Heterogeneity(I^2) (%)
Fetal loss	All included		16	2455	189	7.6	5.5-9.5	58.7
	Period of study	Before 2000	10	1768	149	8.7	5.9-11.5	62.4
		After 2000	6	687	40	5.0	3.3-6.6	28.6
	Study design	Prospective	10	2041	161	7.8	5.5-10.0	60.9
		Retrospective/NA	6	414	28	4.8	2.8-6.8	49.7
	Clinical maternal	Symptomatic	3	329	31	9.3	6.2-12.4	0.0
	symptom of infection	Asymptomatic	4	832	49	5.4	3.9-6.9	48.0
	Time of infection	First trimester	5	586	86	14.0	11.2-16.8	24.5
		Second trimester [a]	4	803	47	5.6	4.0-7.2	0.0
Fetal hydrops	All included		9	2163	151	9.3	5.6-13.0	91.6
	Period of study	Before 2000	4	1496	63	5.2	1.5-8.8	86.7
		After 2000	5	667	88	11.4	3.1-19.7	93.2
	Study design	Prospective	4	1769	114	13.5	5.2-21.8	95.9
		Retrospective/NA	5	394	37	7.7	2.8-12.5	76.5
	Time of infection	First trimester	4	581	15	2.1	0.1-4.2	61.4
		Second trimester	3	803	44	5.0	2.0-8.0	68.4

Note: a, fetal loss of second trimester in one study was only observed up to 24 week of gestation.

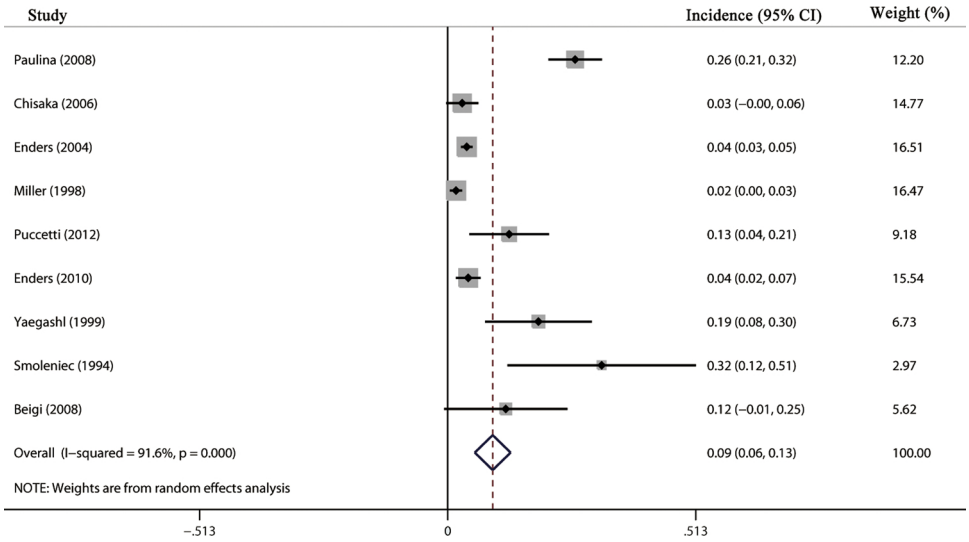

Fig. 3. The pooled incidence of fetal hydrops after maternal parvovirus B19 infection during pregnancy.

women with B19 infection, and hydrops was the main determinant of mortality and adverse perinatal outcome in affected fetuses [35].

After first being described in 1975 [44], B19 infection was identified globally [45]. Jensen et al. reported that 65.7% (1881/2859) of pregnant women were B19 IgG seropositive at their first antenatal visit [4]. In addition, of the IgG-negative women, 10.3% (101/978) were found to have an acute B19 infection during pregnancy [4]. In pregnant women suspected of contracting B19 infection during pregnancy, the infection rate was higher and reported up to 21% (100/478) in a prospective study [28]. Whether gestational age at infection influences the risk of fetal complications is crucially important in clinical practice. The highest risk of fetal loss appears to follow maternal infection during weeks 9 to 16 of pregnancy [46]; risk is reduced with infection in the second half of pregnancy and is rare if infection occurs in the last 2 months [46]. In a large prospective cohort study including 1018 pregnant women with acute B19 infection, Enders et al. reported the incidence of fetal loss associated with maternal infection at 0–8, 9–12, 13–16, and 17–20 weeks of gestation (WG) was 17.2%, 9.9%, 12.7%, and 5.7%, respectively [29]. A high incidence of fetal hydrops was observed at 13–16, 17–20, and 21–24 WG with 7.3%, 7.0%, and 5.2%, respectively [29]. In our study, the pooled incidence of fetal loss and fetal hydrops in B19 infected pregnant women was 7.6% and 9.3%. Meanwhile, our results suggested the incidence of fetal loss associated with maternal infection during the first trimester was higher than that of infection during the second trimester (14.0% vs. 5.6%; Table 3). Large sample, prospective studies are urgently needed to verify the effect of different timings of maternal infection on fetal complications.

To date, the impact of clinical symptoms such as erythema infectiosum on fetal loss or fetal hydrops have not been sufficiently researched and the conclusions of several previous studies are inconsistent [28,29,38,41,42]. Enders et al. reported that the incidence of fetal loss in acute B19 infected pregnant women with a rash and/or arthropathia (9.0%, 25/278) was slightly higher than that of pregnant women without symptoms (5.3%, 39/740) [29]. However, the absence of typical B19-associated symptoms did not correlate with an increased incidence of fetal hydrops (4.3% vs. 3.8%) [29]. In our study, based on limited evidence [28,29,38,42], the pooled incidence of fetal loss of symptomatic participants was relatively higher than that of asymptomatic participants (9.3% vs. 5.4%; Table 3). Further studies are needed to confirm this observation.

Numerous studies showed that infections during pregnancy will increase the risk of adverse pregnancy outcomes, including human immunodeficiency virus, toxoplasma gondii, and some other common viruses, such as human papillomavirus, herpes simplex virus (HSV), and human cytomegalovirus (HCMV) [47–49]. Co-infection of B19 and other infective pathogens is common [50,51]. Although a significant risk of B19 infection for fetal loss was observed in our study, most of the included studies did not state whether pregnant women co-infected with B19 and another infectious pathogen were excluded. Further studies are needed to confirm the sole effect of B19 infection on adverse pregnancy outcomes; also, whether B19 co-infection with other viruses presents a synergistic effect on adverse pregnancy outcomes.

Currently, with no available vaccine, the screening, evaluation, and management of B19 infection in pregnant women is important [46]. To date, systematic screening for parvovirus immunity of all pregnant women is not recommended in pregnancy care guidelines [46]. However, a large proportion of women (about 34%–65%) are susceptible to B19 during pregnancy [2–4]; and, after acute B19 virus infection, adverse pregnancy outcomes are elevated. The benefit of comprehensive screening of B19 IgG and IgM in all pregnant women needs further sociological and economic studies to confirm its value.

The present meta-analysis involved some limitations. Firstly, there was significant heterogeneity among the included studies. Different characteristics between populations occurred in each study, time, and severity of B19 infection, and uncontrolled biases may have introduced heterogeneity. Although we performed meta-regression analyses, the results did not identify the precise reason for heterogeneity. Secondly, B19 infection may play diverse roles in terms of risk at different stages of pregnancy. We did not distinguish the risk of infection for adverse pregnancy outcomes in the first, second, or third trimesters, since most of the included studies were case-control study and it is impractical to time the onset of the maternal infection. Thirdly, since most included studies did not report other risk factors of adverse pregnancy outcomes, only the unadjusted pooled ORs of the risk of B19 infection for pregnancy outcomes were calculated in this study.

Maternal parvovirus B19 infection during pregnancy increased the risk of fetal loss, spontaneous abortion, and stillbirth. A high incidence of fetal loss and fetal hydrops was observed in pregnant women following infection. Whether infectious symptoms in pregnant women increase the risk of adverse pregnancy outcomes needs further investigation.

Funding

This study was funded by The National Key Research and Development Program of Reproductive Health & Major Birth Defects Control and Prevention (No.2016YFC1000406), National Natural Science Foundation of China (No. 71704122, 81590955), The National

Science and Technology Major Project (No. 2018ZX10302206), The National Key Development Plan for Precision Medicine Research (No. 2017YFC0910004), and “Thousand Youth Talents Plan” of China (No. D1024002).

Competing interests

None declared

Ethical approval

Not required

Author contribution

Yi-quan Xiong: Manuscript writing and Project development;
Jing Tan: Manuscript writing and Data analysis;
Yan-mei Liu and Meng Chen: Data collection;
Qiao He: Data collection and Eligible articles evaluated;
Ling Li and Kang Zou: Eligible articles evaluated;
Xin Sun: Manuscript revised and project development;

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2019.03.004.

References

[1] E.P. de Jong, F.J. Walther, A.C. Kroes, D. Oepkes, Parvovirus B19 infection in pregnancy: new insights and management, Prenat. Diagn. 31 (2011) 419–425.
[2] G. Enders, M. Biber, Parvovirus B19 infections in pregnancy, Behring Inst. Mitt. (1990) 74–78.
[3] J.H. Harger, S.P. Adler, W.C. Koch, G.F. Harger, Prospective evaluation of 618 pregnant women exposed to parvovirus B19: risks and symptoms, Obstet. Gynecol. 91 (1998) 413–420.
[4] I.P. Jensen, P. Thorsen, B. Jeune, B.R. Moller, B.F. Vestergaard, An epidemic of parvovirus B19 in a population of 3,596 pregnant women: a study of socio-demographic and medical risk factors, BJOG 107 (2000) 637–643.
[5] A.A. Sarfraz, S.O. Samuelsen, A.L. Bruu, P.A. Jenum, A. Eskild, Maternal human parvovirus B19 infection and the risk of fetal death and low birthweight: a case-control study within 35 940 pregnant women, Bjog Int. J. Obstet. Gynaecol. 116 (2009) 1492–1497.
[6] J.H. Harger, S.P. Adler, W.C. Koch, Prospective evaluation of 618 pregnant women exposed to parvovirus B19: risks and symptoms, Obstet. Gynecol. 91 (1998) 413–420.
[7] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, J. Clin. Epidemiol. 62 (2009) 1006–1012.
[8] A. Stang, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, Eur. J. Epidemiol. 25 (2010) 603–605.
[9] Wells Ga, S.B. OCD PJ, V. Welch, M. Losos, The Newcastle-ottawa Scale (NOS) for Assessing the Quality If Nonrandomized Studies in Meta-analyses, Vailable from: URL: (2009) http://wwwohrica/programs/clinical_epidemiology/.
[10] X. Zhou, L. Li, J.S. Kwong, J. Yu, Y. Li, X. Sun, Impact of bariatric surgery on renal functions in patients with type 2 diabetes: systematic review of randomized trials and observational studies, Surg. Obes. Relat. Dis. 12 (2016) 1873–1882.
[11] D. Xu, G. Zhang, B. Li, X. Wang, X. Sun, Relationship between human parvovirus B19 infection and spontaneous abortion and congenital heart disease in China, Zhonghua Fu Chan Ke Za Zhi 37 (2002) 324–326.
[12] B. Li, X. Qu, S. Wang, [The relationship between maternal infection with human parvovirus B19 and fetal death and congenital malformation], Zhonghua Fu Chan Ke Za Zhi 36 (2001) 24–26.
[13] A. Daniilidis, K. Sidiropoulos, Z.D. Panna, E. Hatzipantelis, A. Loufopoulos, K. Dinas, Association of fetal loss with recent parvovirus infection and other demographic prognostic risk factors, J. Obstet. Gynaecol. (Lahore) 34 (2014) 40–44.
[14] G. Syridou, N. Spanakis, A. Konstantinidou, E.-T. Piperaki, D. Kafetzis, E. Patsouris, et al., Detection of cytomegalovirus, parvovirus B19 and herpes simplex viruses in cases of intrauterine fetal death: association with pathological findings, J. Med. Virol. 80 (2008) 1776–1782.
[15] J.S. Kinney, L.J. Anderson, J. Farrar, R.A. Strikas, M.L. Kumar, R.M. Kliegman, et al., Risk of adverse outcomes of pregnancy after human parvovirus B19 infection, J. Infect. Dis. 157 (1988) 663–667.
[16] M. Nyman, T. Tolfvenstam, K. Petersson, C. Krassny, L. Skjoldebrand-Sparre, K. Broliden, Detection of human parvovirus B19 infection in first-trimester fetal loss, Obstet. Gynecol. 99 (2002) 795–798.
[17] M. Makhseed, A.S. Pacsa, M.A. Ahmed, S.S. Essa, Human parvovirus B19 infection during pregnancy and its possible impact on perinatal outcome in the obstetric population of Kuwait, J. Obstet. Gynaecol. 21 (2001) 485–486.
[18] S. Johansson, S. Buchmayer, S. Harlid, A. Iliadou, M. Sjoholm, L. Grillner, et al., Infection with Parvovirus B19 and Herpes viruses in early pregnancy and risk of second trimester miscarriage or very preterm birth, Reprod. Toxicol. 26 (2008) 298–302.
[19] K.D. Wenstrom, W.W. Andrews, N.E. Bowles, J.A. Towbin, J.C. Hauth, R.L. Goldenberg, Intrauterine viral infection at the time of second trimester genetic amniocentesis, Obstet. Gynecol. 92 (1998) 420–424.
[20] A. Riipinen, E. Vaisanen, M. Nuutila, M. Sallmen, R. Karikoski, M.L. Lindbohm, et al., Parvovirus B19 infection in fetal deaths, Clin. Infect. Dis. 47 (2008) 1519–1525.
[21] J. Lassen, A.K. Jensen, P. Bager, C.B. Pedersen, I. Panum, B. Norgaard-Pedersen, et al., Parvovirus B19 infection in the first trimester of pregnancy and risk of fetal loss: a population-based case-control study, Am. J. Epidemiol. 176 (2012) 803–807.
[22] F. Keikha, E. Miri-Moghaddam, B. Sharifi-Mood, Prevalence of parvovirus B19 infection in successful and unsuccessful pregnancy in Zahedan, southeast of Iran, J. Med. Sci. 6 (2006) 495–497.
[23] M. Koskiniemi, P. Ammala, A. Narvanen, P. Saikku, M. Soderlund, P. Koskela, et al., Stillbirths and maternal antibodies to Chlamydia trachomatis. A new EIA test for serology, Acta Obstet. Gynecol. Scand. 75 (1996) 657–661.
[24] F. Bascietto, M. Liberati, D. Murgano, D. Buca, A. Iacovelli, M.E. Flacco, et al., Outcome of fetuses with congenital parvovirus B19 infection: systematic review and meta-analysis, Ultrasound Obstet. Gynecol. 52 (2018) 569–576.
[25] O. Norbeck, N. Papadogiannakis, K. Petersson, T. Hirbod, K. Broliden, T. Tolfvenstam, Revised clinical presentation of parvovirus B19-associated intrauterine fetal death, Clin. Infect. Dis. 35 (2002) 1032–1038.
[26] L. Skjoldebrand-Sparre, E. Fridell, M. Nyman, B. Wahren, A prospective study of antibodies against parvovirus B19 in pregnancy, Acta Obstet. Gynecol. Scand. 75 (1996) 336–339.
[27] P. Marcinek, D. Nowakowska, K. Szaflik, E. Spiewak, E. Malafiej, J. Wilczynski, [Analysis of complications during pregnancy in women with serological features of acute toxoplasmosis or acute parvovirosis], Ginekol. Pol. 79 (2008) 186–191.
[28] H. Chisaka, K. Ito, H. Niikura, J. Sugawara, T. Takano, T. Murakami, et al., Clinical manifestations and outcomes of parvovirus B19 infection during pregnancy in Japan, Tohoku J. Exp. Med. 209 (2006) 277–283.
[29] M. Enders, A. Weidner, I. Zoellner, K. Searle, G. Enders, Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases, Prenat. Diagn. 24 (2004) 513–518.
[30] E. Miller, C.K. Fairley, B.J. Cohen, C. Seng, Immediate and long term outcome of human parvovirus B19 infection in pregnancy, Br. J. Obstet. Gynaecol. 105 (1998) 174–178.
[31] P.H. van Gessel, M.A. Gaytant, A.C. Vossen, J.M. Galama, N.T. Ursem, E.A. Steegers, et al., Incidence of parvovirus B19 infection among an unselected population of pregnant women in the Netherlands: a prospective study, Eur. J. Obstet. Gynecol. Reprod. Biol. 128 (2006) 46–49.
[32] C. Puccetti, M. Contoli, F. Bonvicini, F. Cervi, G. Simonazzi, G. Gallinella, et al., Parvovirus B19 in pregnancy: possible consequences of vertical transmission, Prenat. Diagn. 32 (2012) 897–902.
[33] Prospective study of human parvovirus (B19) infection in pregnancy. Public Health Laboratory Service Working Party on fifth disease, Bmj. 300 (1990) 1166–1170.
[34] M. Enders, K. Klingel, A. Weidner, C. Baisch, R. Kandolf, G. Schalasta, et al., Risk of fetal hydrops and non-hydropic late intrauterine fetal death after gestational parvovirus B19 infection, J. Clin. Virol. 49 (2010) 163–168.
[35] L. Simmons, N. Burke, E. Kent, F. Malone, Acute parvovirus infection in pregnancy: are we underestimating the risk? Am. J. Obstet. Gynecol. 210 (2014) S14–S15.
[36] F. Guidozzi, D. Ballot, A.D. Rothberg, Human B19 parvovirus infection in an obstetric population. A prospective study determining fetal outcome, J. Reprod. Med. 39 (1994) 36–38.
[37] J.F. Rodis, D.L. Quinn, G.W. Gary Jr, L.J. Anderson, S. Rosengren, M.L. Cartter, et al., Management and outcomes of pregnancies complicated by human B19 parvovirus infection: a prospective study, Am. J. Obstet. Gynecol. 163 (1990) 1168–1171.
[38] M. Makhseed, A. Pacsa, M.A. Ahmed, S.S. Essa, Pattern of parvovirus B 19 infection during different trimesters of pregnancy in Kuwait, Infect. Dis. Obstet. Gynecol. 7 (1999) 287–292.
[39] E. Gratacos, P.J. Torres, J. Vidal, E. Antolin, J. Costa, M.T. Jimenez de Anta, et al., The incidence of human parvovirus B19 infection during pregnancy and its impact on perinatal outcome, J. Infect. Dis. 171 (1995) 1360–1363.
[40] N. Yaegashi, T. Niinuma, H. Chisaka, S. Uehara, K. Okamura, O. Shinkawa, et al., Serologic study of human parvovirus B19 infection in pregnancy in Japan, J. Infect. 38 (1999) 30–35.
[41] J.S. Smoleniec, M. Pillai, E.O. Caul, J. Usher, Subclinical transplacental parvovirus B19 infection: an increased fetal risk? Lancet. 343 (1994) 1100–1101.
[42] R.H. Beigi, H.C. Wiesenfeld, D.V. Landers, H.N. Simhan, High rate of severe fetal outcomes associated with maternal parvovirus b19 infection in pregnancy, Infect. Dis. Obstet. Gynecol. (2008) 524601.
[43] W.C. Koch, J.H. Harger, B. Barnstein, S.P. Adler, Serologic and virologic evidence for frequent intrauterine transmission of human parvovirus B19 with a primary

maternal infection during pregnancy, Pediatr. Infect. Dis. J. 17 (1998) 489–494.
[44] Y.E. Cossart, A.M. Field, B. Cant, D. Widdows, Parvovirus-like particles in human sera, Lancet. 1 (1975) 72–73.
[45] Z. Ergaz, A. Ornoy, Parvovirus B19 in pregnancy, Reprod. Toxicol. 21 (2006) 421–435.
[46] A. Ornoy, Z. Ergaz, Parvovirus B19 infection during pregnancy and risks to the fetus, Birth Defects Res. 109 (2017) 311–323.
[47] S. Giakoumelou, N. Wheelhouse, K. Cuschieri, G. Entrican, S.E. Howie, A.W. Horne, The role of infection in miscarriage, Hum. Reprod. Update 22 (2016) 116–133.
[48] Y.Q. Xiong, Y. Mo, Q.M. Luo, S.T. Huo, W.Q. He, Q. Chen, The risk of human papillomavirus infection for spontaneous abortion, spontaneous preterm birth, and pregnancy rate of assisted reproductive technologies: a systematic review and meta-analysis, Gynecol. Obstet. Invest. (2018).
[49] T.L. Shi, L.J. Huang, Y.Q. Xiong, Y.Y. Zhong, J.J. Yang, T. Fu, et al., The risk of herpes simplex virus and human cytomegalovirus infection during pregnancy upon adverse pregnancy outcomes: a meta-analysis, J. Clin. Virol. 104 (2018) 48–55.
[50] F. Volker, P. Cooper, O. Bader, A. Uy, O. Zimmermann, R. Lugert, et al., Prevalence of pregnancy-relevant infections in a rural setting of Ghana, BMC Pregnancy Childbirth 17 (2017) 172.
[51] R. Tong, L. Shen, W. Yin, W. Zhou, J. Lu, M. Zheng, et al., Prevalence of human parvovirus B19, bocavirus, and PARV4 in blood samples from the general population of China and lack of a correlation between parvovirus and hepatitis B co-infection, PLoS One 8 (2013) e64391.