

Maternal HCV infection is associated with intrauterine fetal growth disturbance

A meta-analysis of observational studies

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Abstract

Since the evidence regarding the association between maternal hepatitis C virus (HCV) infection and impaired intrauterine fetal growth had not been conclusive, the aim of the present study was to evaluate the risk of maternal HCV infection in association with intrauterine fetal growth restriction (IUGR) and/or low birth weight infants (LBW). We performed an extensive literature search of PubMed, MEDLINE, and EMBASE through December 1, 2015. The odds ratios (ORs) of HCV infection and IUGR/LBW were calculated and reported with 95% confidence intervals (95% CIs). Statistical analysis was performed using RevMen 5.3 and Stata 10.0. Seven studies involving 4,185,414 participants and 5094 HCV infection cases were included. Significant associations between HCV infection and IUGR (OR=1.53, 95% CI: 1.40–1.68, fixed effect model) as well as LBW were observed (OR=1.97, 95% CI: 1.43–2.71, random effect model). The results still indicated consistencies after adjusting for multiple risk factors which could affect fetal growth, including maternal age, parity, maternal smoking, alcohol abuse, drugs abuse, coinfecting with HBV/HIV and preeclampsia. Our findings suggested that maternal HCV infection was significantly associated with an increased risk of impaired intrauterine fetal growth. In clinical practice, a closer monitoring of intrauterine fetal growth by a series of ultrasound might be necessary for HCV-infected pregnant population.

Abbreviations: HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IUGR = intrauterine fetal growth restriction, LBW = low birth weight infants.

Keywords: hepatitis C virus, intrauterine fetal growth restriction, low birth weight

1. Introduction

Hepatitis C virus (HCV) infection is a public health issue which affected about 3% of the worldwide population.^[1,2] Accumulative evidence suggested that HCV infection could exist in the

heart, pancreas, kidneys, ovaries,^[3–5] and even in placenta.^[6,7] There is a growing body of data concerning the role of HCV in extrahepatic manifestations, including cardiovascular diseases,^[8,9] immunological disorders,^[10] and neurodegenerative diseases.^[11,12] Placenta is a crucial organ during pregnancy for intrauterine fetal growth. Nie et al^[6] found that HCV could infect trophoblasts cultured in vitro and alter the cellular ultrastructures dramatically, thus might lead to placental insufficiency. The prevalence of HCV infection among women of reproductive age in most western countries varied from 0.5% to 4.8%,^[13,14] our objective was to investigate whether HCV infection was associated with an increased risk of adverse perinatal outcomes.

Low birth weight infants (LBW, defined as a birth weight < 2500 g)^[15] and intrauterine fetal growth restriction (IUGR, defined as birth weight <10th percentile for gestational age)^[16] were common perinatal complications, which remained to be the leading causes and major contributors to perinatal morbidity and mortality.^[17,18] It has been shown that LBW or IUGR fetuses had a higher risk of requiring emergent cesarean section, undergoing hypothermia, neonatal sepsis, respiratory disorders, and neonatal intensive care unit admission.^[19] Moreover, the important contribution of fetal and early childhood development to noncommunicable disease in adult was being recognized. Accumulating evidence indicated that infants born LBW or IUGR were associated with increased risks for cardiovascular diseases, metabolic derangements, neurological and psychiatric disorders in their adulthood life.^[20–22] Therefore, interventions to optimize fetal growth as strategies to prevent adult non-communicable diseases have great potential economic, societal, and individual benefit.

Although the etiology is not completely understood, placental dysfunction caused by excessive systemic inflammation has been

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Table 1
Appraisal of methodological quality (Newcastle-Ottawa Scale) of the including studies.

Study	Population representative	Selection of nonexposed control	Ascertainment of exposure	Outcome negative at start	Comparability by design	Comparability by analysis	Outcome assessment	Duration of follow-up	Score
Berkley et al ^[31]	*	*	×	*	*	*	*	×	6
Connell et al ^[28]	*	×	*	*	*	*	*	*	7
Khaskheli et al ^[33]	*	*	*	*	*	*	*	*	8
Kumar et al ^[34]	*	*	*	*	*	*	*	*	8
Pergam et al ^[30]	*	*	×	*	*	*	*	*	7
Reddick et al ^[29]	*	*	×	*	*	*	*	*	7
Salemi et al ^[32]	*	*	*	*	×	×	*	*	6

* Indicated that a feature is present; × indicated that a feature is absent. For comparability by design this checklist awarded a maximum of 2 asterisks (**), 1 (*), or none if the feature was completely absence (×).

found to play a significant role in infants born LBW or IUGR.^[2,3–26] Earlier studies demonstrated that chronic HCV infection could induce both local and systemic inflammation through various mechanisms.^[27] Therefore, it was proposed women with chronic HCV infection might be associated with increased risk of having infants born LBW or IUGR.

Previously, several studies assessed infants born LBW or IUGR in women with HCV infection.^[28–31] However, there were inconsistency in the results.^[32–34] Thus, we performed a meta-analysis to evaluate whether maternal HCV infection was associated with higher risk of infants born LBW or IUGR when compared to normal pregnant population. Moreover, the findings presented herein may also help informing clinical practice guidelines.

2. Methods

This systematic review and meta-analysis was performed following the guidance provided in the Cochrane Handbook^[35] and was reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.^[36]

2.1. Data sources and search strategy

Two independent investigators searched PubMed, MEDLINE, and EMBASE databases before December 1, 2015. The following terms and phrases were used in the searching strategy: “HCV” or “hepatitis C” in combination with “prenatal” or “perinatal” or “infants” or “fetus” or “neonatal” or “intrauterine growth restriction” or “fetal growth restriction.” References of the relevant reviews were scrutinized. Further, we searched for those articles or citations in the Web of Knowledge, Google Scholar, and Google to obtain additional studies.

2.2. Inclusion and exclusion criteria

Articles were involved if they investigated the association between HCV infection before pregnancy and the risk of infants born IUGR or LBW among pregnant women versus a non-HCV control groups. Studies included in this analysis defined chronic HCV infection status during pregnancy by the presence of HCV antibody in blood during the first prenatal care visit or through medical records reviewed. LBW were defined as a birth weight <2500g^[15] and IUGR was defined as birth weight <10th percentile for gestational age.^[16] No language restrictions were used for study inclusion in this meta-analysis.

2.3. Data extraction

The following information was collected from the included studies: the last name of the first author, publication year, sample

size; study location; scoring of Newcastle-Ottawa Quality Assessment Scale (NOS); adjusted covariates; and/or matched variables in the analysis.

2.4. Assessment of methodological quality

Two independent investigators assessed the quality of each study included using the NOS^[37] (Table 1). On a score scale from 0 to 9, a study with 7 or more asterisks was considered as high quality.

2.5. Statistical analysis

The pooled odds ratio (OR) with 95% confidence intervals (CIs) between HCV infection and infants born IUGR or LBW was used to estimate the effect sizes by a fixed-effects model (when heterogeneity was absent to moderate) or random-effects model (when heterogeneity was high). Homogeneity test was performed with *Q* statistic and *I*² statistic.^[38] The publication bias was investigated by the funnel plots as well as Egger regression asymmetry test.^[39] Subgroup analysis was performed to investigate the impact of various factors (including study types, maternal age, parity, smoking/alcohol abuse status, drug abuse status, coinfecting viral diseases, and rates of preeclampsia, which was defined as new onset of hypertension and proteinuria at or after 20 gestational weeks) that influenced the pooled estimate. RevMen 5.3 and Stata version 10.0 were used to analyze the data.

3. Results

3.1. Selection flow and study characteristics

The detailed search procedures are demonstrated in Fig. 1. Eleven full-text articles were assessed for eligibility. Four articles were excluded because they did not report the incidence of infants born IUGR or LBW, and 1 study compared the perinatal outcomes among HCV-infected population with various viral RNA levels. Finally, 7 articles were included for this meta-analysis. The general information of the 7 identified reports are demonstrated in Table 2.

3.2. Main results

The combined results from 4 cohort and 3 case–control studies are demonstrated in Fig. 2A and B. The pooled results of 5 studies, including 3,888,921 participants and 4183 HCV infection cases, demonstrated a significantly positive association between HCV infection and infants born LBW (OR = 1.97, 95% CI: 1.43–2.71) with significant heterogeneity (*Q* = 25.06, *I*² = 84%, *P* < 0.0001) (Fig. 2A). Meanwhile, the pooled results of 7 studies, involving 4,185,414 participants and 5094 HCV

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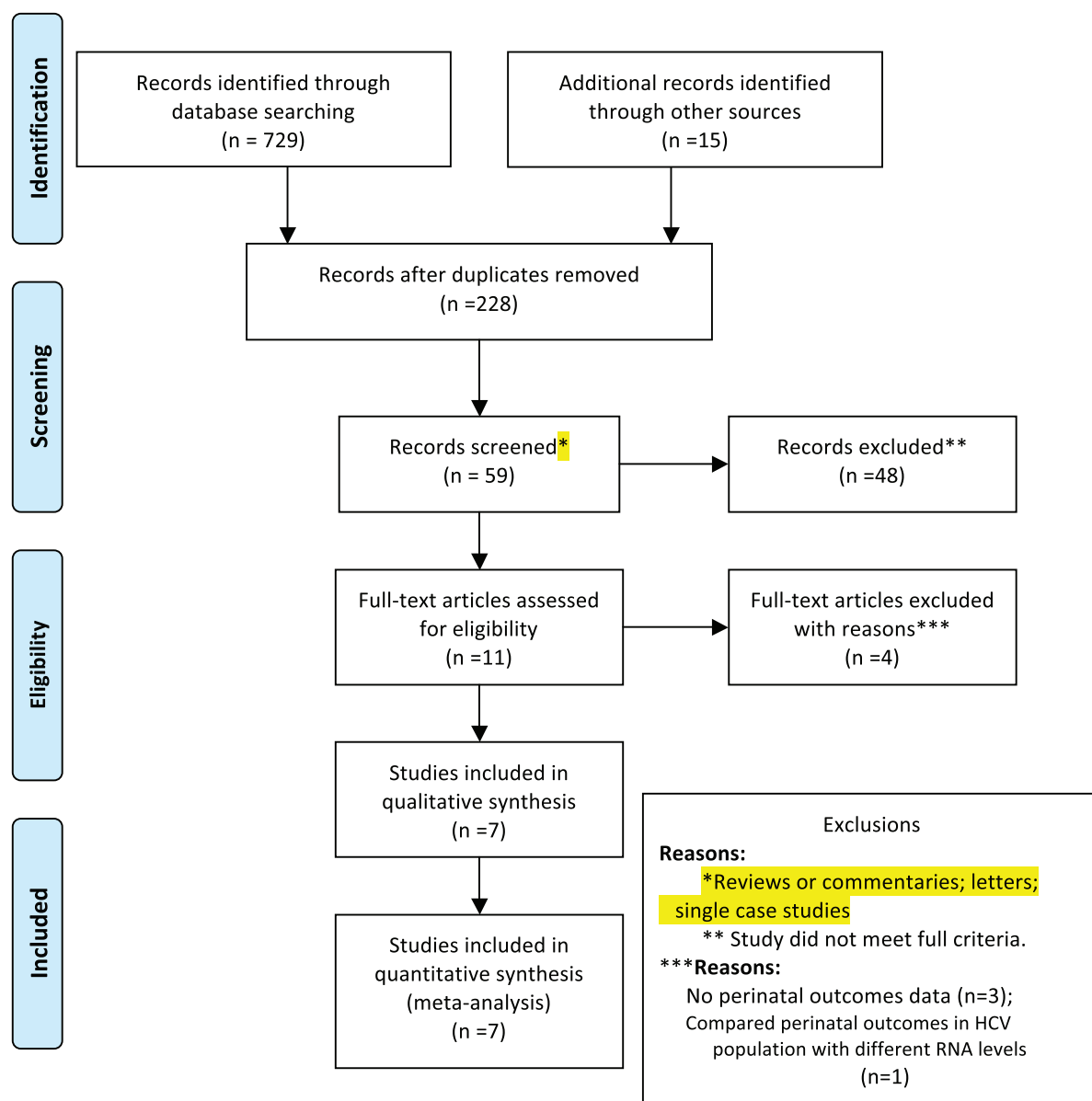


Figure 1. Flow chart of the literature search and article selection.

Table 2

Characteristics of studies of HCV versus control on infants born LBW and/or IUGR.

Author	Year	Study type	Locations	Research interval	HCV diagnostic criterion or assay	HCV (+) population	HCV (-) population	Adjusted covariates/matched variables
Berkley et al ^[31]	2008	Case-control	USA	2000-2006	NR	159	141	2, 3, 4, 6
Connell et al ^[28]	2011	Retrospective cohort	USA	1998-2007	ICD-9	988	1,669,370	1, 2, 3, 4, 5, 6
Khaskheli et al ^[33]	2014	Case-control	Pakistan	2009-2010	Anti-HCV (ELISA)	361	279	1
Kumar et al ^[34]	2007	Case-control	India	2003-2006	Anti-HCV (ELISA)	78	156	1, 2
Pergam et al ^[30]	2008	Retrospective cohort	USA	2003-2005	HCV-RNA	501	2019	1, 2, 3, 4
Reddick et al ^[29]	2011	Retrospective cohort	USA	1995-2005	ICD-9	555	296,218	1, 4, 6
Salemi et al ^[32]	2014	Retrospective cohort	USA	1998-2009	ICD-9	2457	2,217,235	NR

ELISA = enzyme-linked immunosorbent assay, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, ICD = international classification of diseases, IUGR = intrauterine growth restriction, LBW = low birth weight, NR = not reported, RNA = ribonucleic acid, USA = United States of America.

Matched variables for case-control study or adjusted covariates for cohort adjust: (1) maternal age; (2) parity; (3) maternal smoking/alcohol abuse; (4) drugs abuse; (5) coinfecting with HBV/HIV; (6) rate pregnancy complication (preeclampsia).

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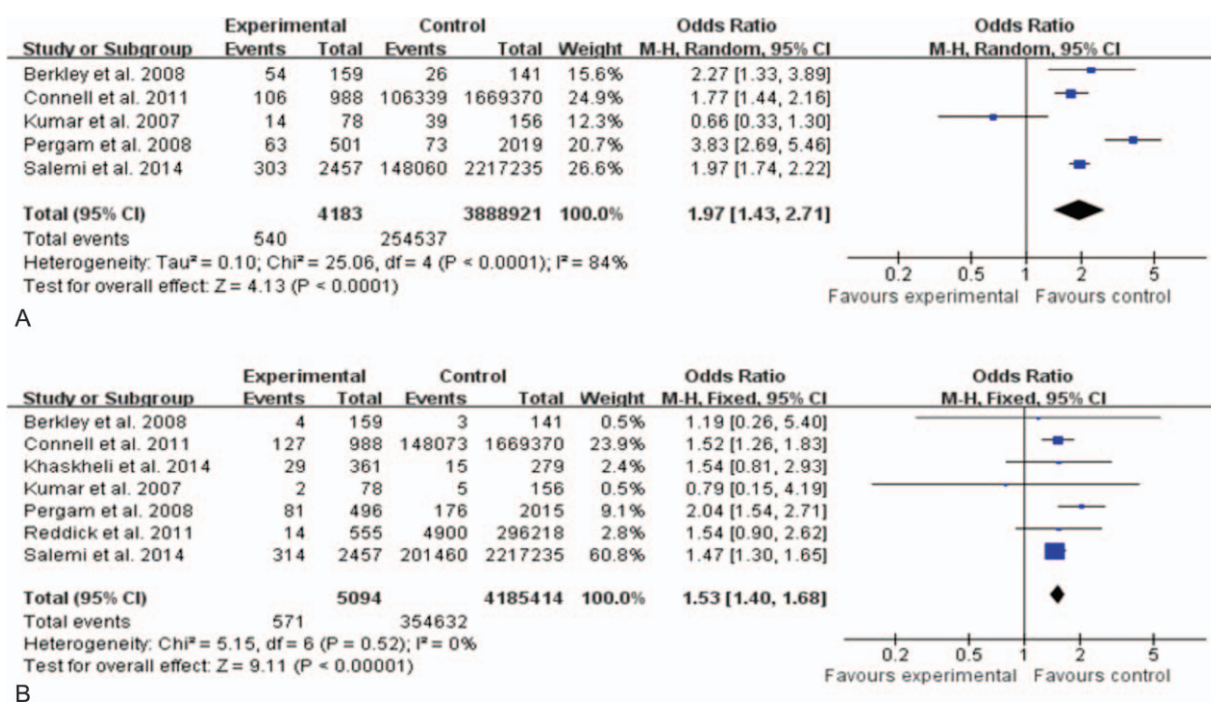


Figure 2. Forest plot of the association between chronic hepatitis C virus infection and risk of infants born (A) low birth weight or (B) intrauterine growth restriction.

infection cases, also suggested a significantly positive association between HCV infection and infants born IUGR (OR = 1.53, 95% CI: 1.40–1.68) without heterogeneity ($Q = 5.15$, $I^2 = 0\%$, $P = 0.52$) (Fig. 2B).

3.3. Subgroup analysis

An analysis of the results according to study type (cohort^[28,30–33] or case-control^[29,34]), maternal age (matched^[28–30,33,34] or nonmatched/not reported^[31,32]), maternal parity (matched^[28,30,31,34] or nonmatched/not reported^[29,32,33]), maternal smoking/alcohol abuse (matched^[28,30,31] or nonmatched/not reported^[29,32–34]), maternal drug abuse (matched^[28–31] or nonmatched/not reported^[32–34]), coinfection with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV) (matched^[28] or nonmatched/not reported^[29–34]) and prevalence of preeclampsia (matched^[28,29,31] or nonmatched/not reported^[30,32–34]) is summarized in Table 3.

Stratification of various factors that may influence the pooled estimate, such as maternal age, parity, smoking/alcohol status, drug abuse, and prevalence of preeclampsia still indicated that women with HCV infection were associated with increased risk of having infants born IUGR or LBW.

3.4. Publication bias

The funnel plots showed a low probability of publication bias (Fig. 3A and B). Consistently, the Egger regression tests demonstrated little evidence of publication bias ($P = 0.685$) for IUGR and ($P = 0.811$) for LBW, respectively.

4. Discussions

Prior studies reported that maternal HCV infection increased the risk of adverse pregnancy outcomes such as premature rupture of

membrane, preterm birth as well as cesarean delivery.^[13,40] However, the association between HCV infection and intrauterine fetal growth disturbance remained inconclusive.^[28–34]

Earlier studies suggested that chronic HCV infection was associated with both excessive local as well as systemic inflammatory response.^[8–12] A higher ratio of proinflammatory/antiinflammatory cytokines has been observed in nondiabetic, nonobese population with HCV infection when compared to HCV-negative individuals.^[41,42] It had been demonstrated that impaired uteroplacental hemodynamics caused by excessive inflammation played a crucial role in adverse perinatal outcomes, such as LBW, IUGR, and stillbirth.^[43–45] Previous studies found that inflammatory lesions in placental histopathological findings were more common in infants born LBW or IUGR.^[46–48] Moreover, pregnant women with chronic diseases characterized by systemic low-grade inflammation like Crohn disease^[49] and/or rheumatoid arthritis^[50] were associated with an increased risk of undergoing LBW or IUGR. Thus, we hypothesized that the higher rate of infants born LBW or IUGR in HCV-infected population may be the results from the excessive inflammatory response caused by the virus infection.

Several perinatal factors, including nulliparous, advanced maternal age as well as low prepregnancy body mass index were associated with increased risk of IUGR and/or LBW.^[51,52] Some large epidemiologic cohort studies indicated that maternal smoking, alcohol, and drugs abuse before conception or during pregnancy were all associated with higher prevalence of intrauterine fetal growth disturbance.^[53–55] It is known that patients with HCV are often associated with higher rates of coinfection with HBV and/or HIV,^[56] which may increase the risk of obstetrical complications and impaired fetal growth. Moreover, pregnancy complication, such as preeclampsia, was also associated with increased risk of infants born LBW or IUGR. Therefore, one common concern was whether these potential confounders would significantly affect the results. To clarify this

Table 3

Subgroup analysis of the association between HCV and infants born LBW and/or IUGR.

	LBW			IUGR		
	Studies no.	OR (95% CI)	I ² (%)	Studies no.	OR (95% CI)	I ² (%)
Study type						
Cohort	3	2.16 (1.84, 2.54)	86	4	1.54 (1.38, 1.71)	20
Case-control	2	1.88 (1.66, 2.11)	90	3	1.51 (1.25, 1.82)	0
Maternal age						
Matched	3	1.95 (1.65, 2.30)	92	5	1.63 (1.41, 1.89)	0
Not matched	2	1.98 (1.76, 2.23)	0	2	1.46 (1.30, 1.65)	0
Maternal parity						
Matched	4	1.98 (1.69, 2.32)	88	4	1.64 (1.41, 1.91)	22
Not matched	1	1.97 (1.74, 2.22)	0	3	1.47 (1.31, 1.65)	0
Maternal tobacco and/or alcohol use						
Matched	3	2.16 (1.84, 2.54)	86	3	1.65 (1.42, 1.93)	36
Not matched	2	1.88 (1.66, 2.11)	90	4	1.47 (1.31, 1.64)	0
Maternal drug use						
Matched	3	2.16 (1.84, 2.54)	86	4	1.64 (1.42, 1.91)	6
Not matched	2	1.88 (1.66, 2.11)	90	3	1.46 (1.30, 1.64)	0
Coinfected with HBV and/or HIV						
Matched	1	1.77 (1.44, 2.16)	—	1	1.52 (1.26, 1.83)	—
Not matched	4	2.04 (1.83, 2.27)	87	6	1.53 (1.38, 1.70)	3
Complicating preeclampsia						
Matched	2	1.84 (1.52, 2.22)	0	3	1.51 (1.25, 1.82)	0
Not matched	3	2.02 (1.81, 2.26)	91	4	1.54 (1.38, 1.71)	20
Location						
America	4	1.82 (1.43, 2.31)	0	5	1.40 (1.26, 1.54)	0
Asia	1	0.66 (0.33, 1.32)	—	2	1.41 (0.78, 2.57)	0

CI=confidence interval, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IUGR=intrauterine growth restriction, LBW=low birth weight, OR=odds ratio.

issue, we provided several measurements to decrease the possible heterogeneity. First of all, we used adjusted ORs to estimate the effect sizes in this meta-analysis. Additionally, we conducted a

subgroup analysis to evaluate the possible impact that each potential confounders such as maternal age, parity, cigarette/alcohol abuse, drugs abuse, HBV/HIV coinfection status, and preeclampsia, which may impose on the pooled results. Our subgroup analysis still indicated that maternal chronic HCV infection was an independent risk factor for intrauterine fetal growth disturbance.

In this meta-analysis, several limitations should be also addressed. First, the included studies were mainly performed in North America and some parts of the Asian countries. Therefore, our findings might be not suitable to be applied to other populations. Second, limited cohort data were available at the moment, which lowering the strength of evidence in this meta-analysis. Third, the subgroup analysis results should be interpreted with caution. Because within matched group, the other covariates adjusted were not the same, while within unmatched group, some studies may be adjusted for other covariates and some were totally not adjusted by any covariate. Further well-designed studies taking potential confounding factors into account may eventually provide a better, comprehensive understanding of the association between HCV infection and the risk of LBW and/or IUGR.

Despite the above-mentioned drawbacks of the analysis, our meta-analysis has some strengths. First, to the best of our knowledge, the current report is the first systematic review and meta-analysis evaluating the association between maternal HCV infection and the risk of infants born IUGR or LBW. It is generally accepted that the analysis of individual studies offer insufficient statistical power. Therefore, we combined all eligible studies in this study which constitutes a large sample size with greatly enhanced statistical power and more reliable results. Second, no publication bias was observed among the studies included. Statistical heterogeneity between the studies was low.

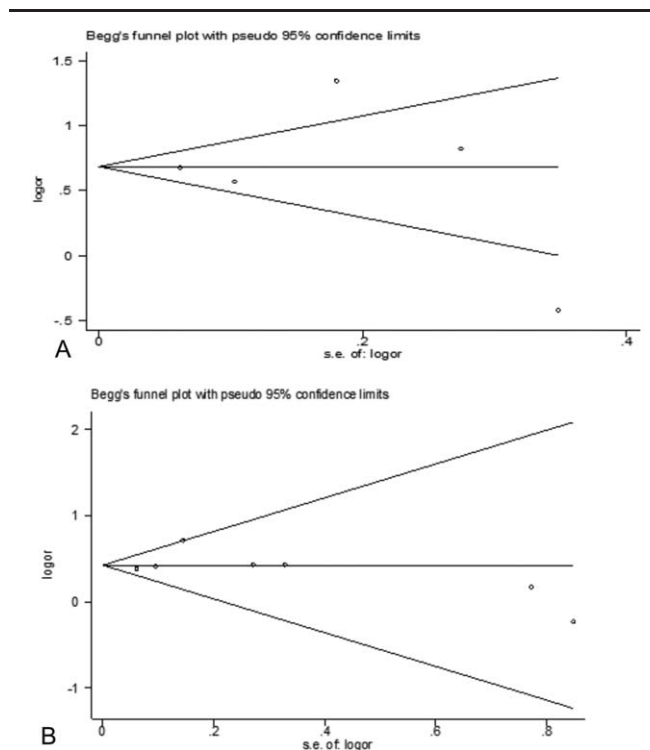


Figure 3. Funnel plot of the association between chronic hepatitis C virus infection and risk of infants born (A) low birth weight or (B) intrauterine growth restriction.

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In summary, women with HCV infection had a significantly higher risk of having an infant born IUGR and/or LBW. Our results indicated closely ultrasound surveillance and follow-up of IUGR fetuses might be necessary for being a part of routine antenatal care in these populations to improve antenatal management and long-term prognosis.

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