

Association between hepatitis C infection during pregnancy with maternal and neonatal outcomes: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Studies of possible implications of the maternal hepatitis C virus (HCV) infection in terms of intrauterine fetal growth restriction (IUGR), preterm birth (PTB), low birth weight (LBW) infants, premature rupture of membranes (PROM), maternal and neonatal mortality are limited and inconclusive. Our study aims to assess the impact of HCV on maternal and neonatal outcomes.

MATERIALS AND METHODS: Systematic literature search was done in PubMed, Scopus, and Google Scholar, Cochrane Library, and TRIP databases for all observational studies published from 1st January 1950 to 15th October 2022. The pooled odds ratio (OR) or risk ratio (RR) with a 95% confidence interval (CI) was estimated. STATA version 12.0 software was used for analysis. Heterogeneity among the included articles was evaluated by sensitivity, meta-regression, and publication bias analyses.

RESULTS: A total of 14 studies involving 12,451 HCV (+) and 56,42,910 HCV (-) pregnant women were included in our meta-analysis. Maternal HCV during pregnancy was significantly associated with the increased risk of PTB (OR=1.66, 95% CI: 1.59-1.74), IUGR (OR=2.09, 95% CI: 2.04-2.14) and LBW (OR=1.96, 95% CI: 1.63-2.36) as compared to healthy pregnant women. Subgroup analysis based on ethnicity also suggested a strong association between maternal HCV infection and a higher risk of PTB in Asian and Caucasian populations. Maternal (RR=3.44, 95% CI: 1.85-6.41), as well as neonatal (RR=1.54, 95% CI: 1.18-2.02) mortality was significantly higher in HCV (+) cases.

CONCLUSIONS: Mothers with HCV infection had a markedly increased probability of PTB and/or IUGR and/or LBW. In clinical practice, standard care of treatment and proper monitoring are needed for the pregnant population with HCV infection. Our findings may provide useful information for selecting appropriate therapy methods for HCV-positive pregnant women.

Key Words:

Hepatitis C virus, Pregnancy, Preterm birth, Infection, Low birth weight, Fetal growth.

Introduction

Hepatitis C virus (HCV) infection is a major global health burden¹⁻³. HCV prevalence in pregnant women is thought to be between 0.7% and 4.4%⁴⁻⁹. However, little is known about how it impacts the course of the pregnancy. Previous studies¹⁰⁻¹³ mostly focused on the vertical transmission and not on the possible implications of chronic HCV infection on the maternal health, labor difficulties, and the health of the new-born. Such information may impact public health guidelines, since the detection of unfavorable outcomes may alter current screening recommendations.

Low birth weight infants (LBW, <2,500 g)¹⁴ and intrauterine fetal growth restriction (IUGR, birth weight 10th percentile for gestational age) significantly contribute to perinatal morbidity and mortality¹⁵⁻¹⁷. LBW or IUGR fetuses are more likely to require an emergency caesarean delivery, suffer from hypothermia, neonatal infections, respiratory problems, or be admitted to a neonatal critical care unit¹⁸.

Recent studies^{19,20} have demonstrated the presence of maternal HCV in placenta, showed HCV and impacts trophoblasts *in vitro*. Therefore, maternal HCV infection could potentially lead to placental insufficiency and subsequent adverse maternal and neonatal outcomes. The diagnosis, medical care, and prevention of hepatitis C are frequently unknown to obstetric nurses. It

is necessary, therefore, to educate nurses who provide care to pregnant women about the pathophysiology, diagnosis, epidemiology, therapy, and prevention of HCV.

Studies²¹⁻²³ show that LBW or IUGR neonates have increased chances of developing adult-onset cardiovascular illnesses, metabolic abnormalities, neurological and mental issues. However, previous research²⁴⁻³² on the relationship between maternal HCV (+) status and the risk of unfavorable pregnancy outcomes has been conducted retrospectively or used from surveillance databases. Therefore, there is very little information on the link between virological parameters and perinatal outcomes.

The effects of chronic HCV infection on maternal and fetal outcomes have been examined only in few studies in literature, even though several have addressed the vertical transmission of HCV infection to the neonate, and only two recent systematic reviews^{33,34} have been published. The association of maternal HCV infection with IUGR, PTB, LBW, premature rupture of membranes (PROM), and maternal and neonatal mortality had not been proven conclusively. Therefore, the study aims to evaluate the effect of HCV infection on maternal and neonatal outcomes.

Materials and Methods

Study Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)³⁵ guidelines were used in this meta-analysis, and we registered the review protocol on PROSPERO with registration ID CRD42022364206.

Search Strategy

Systematic literature search was done in PubMed, Google Scholar, Cochrane Library, Scopus, and TRIP databases for all observational studies published from 1st January 1950 to 15th October 2022, with no restrictions in terms of publication year, language or gender. The search strategy used keywords and phrases such as: “HCV” or “hepatitis C” combined with “pre-natal” or “perinatal” or “infants” or “fetus” or “neonatal” or “intrauterine growth restriction” or “fetal growth restriction”, as well as “maternal” or “pregnant” or “labor” or “delivery” or “mortality”. Bibliography of the selected articles were manually checked for any new relevant human studies.

Study Eligibility Criteria

Inclusion criteria

1. Studies that assess the impact of HCV on maternal or neonatal outcomes among HCV (+) pregnant women vs. HCV (-) pregnant women control group.
2. Studies involving any of the following outcomes: preterm birth defect or LBW or IUGR or maternal or neonatal mortality or premature rupture of membranes in HCV (+) pregnant women vs. HCV (-) pregnant women control group.
3. Chronic HCV infection status during pregnancy established based on the detection of the blood levels of HCV antibody on the first prenatal care visit or through review of medical records.

Exclusion criteria

1. Studies not reporting relevant outcomes.
2. Duplicated studies, case reports or series, systematic reviews, conference abstracts, preprints, and editorials.
3. Full texts unavailable.

Data Collection and Analysis

Selection criteria were used independently by the two authors to screen all eligible studies. Abstract review was the first screening step, followed by a full-text review. A third reviewer was consulted in case of disagreement. Authors' name, country, publication year, design and duration of the study, number of patients, outcome events (preterm birth defect, LBW or IUGR, maternal or neonatal mortality or premature rupture of membranes) were retrieved from each included study.

Quality Assessment

Newcastle-Ottawa Scale (NOS) was used independently by two reviewers to assess the risk of bias³⁶. Selection, comparability, and exposure are the three broad factors used in NOS assessment. The scores ranged from 0 (lowest) to 8 (highest quality). All the differences in the quality score assessments were ruled out through conversation with the corresponding author.

Publication Bias

Publication bias was assessed by funnel plot³⁷, and Egger's regression³⁸.

Statistical Analysis

We used STATA, version 12.0 (StataCorp LP, College Station, TX, USA) for the analysis. The

pooled odds ratio (OR) or risk ratio (RR) with 95% confidence interval (CI) were calculated using a fixed or random effect model. The I^2 statistic was used to calculate heterogeneity in the included studies, which was then adjusted using subgroup analysis and meta-regression using the NOS score. $I^2 > 50\%$ indicated significance. For $I^2 > 50\%$, a random-effects model was used, while a fixed-effect model was used for $I^2 < 50\%$ ³⁹. We performed a sensitivity analysis to validate the pooled observed. $p < 0.05$ was considered to be statistically significant.

Results

Literature Search

Study selection process is shown in Figure 1. Systematic search of five distinct databases identified 1,727 studies. After deleting duplicate articles, 1,094 full text articles were found,

and 82 full text articles were examined for eligibility. Finally, 14 studies^{24-26,28,30,40-48} reporting the association of HCV infection with maternal and neonatal outcomes were included in our analysis.

Characteristics of Included Studies

A total of 14 studies involving 12,451 HCV (+) pregnant cases and 56,42,910 HCV (-) pregnant controls were included. Of them, 12 were cohort studies (10 retrospective^{24-26,28,40-45} and 2 prospective^{46,47}) and two^{30,48} were case-control studies (Table I). Publication dates were between 2000 and 2022, with individual study sample size ranging from 31 to 22,14,778. Seven studies^{24,25,28,30,40,41,44} were conducted in the USA, one study each in India⁴⁸, Pakistan⁴⁵, Ireland³⁹, Italy⁴², Canada⁴³ and two studies^{26,47} in Germany. All included studies had low risk of bias as indicated by the high-quality NOS score (Table II).

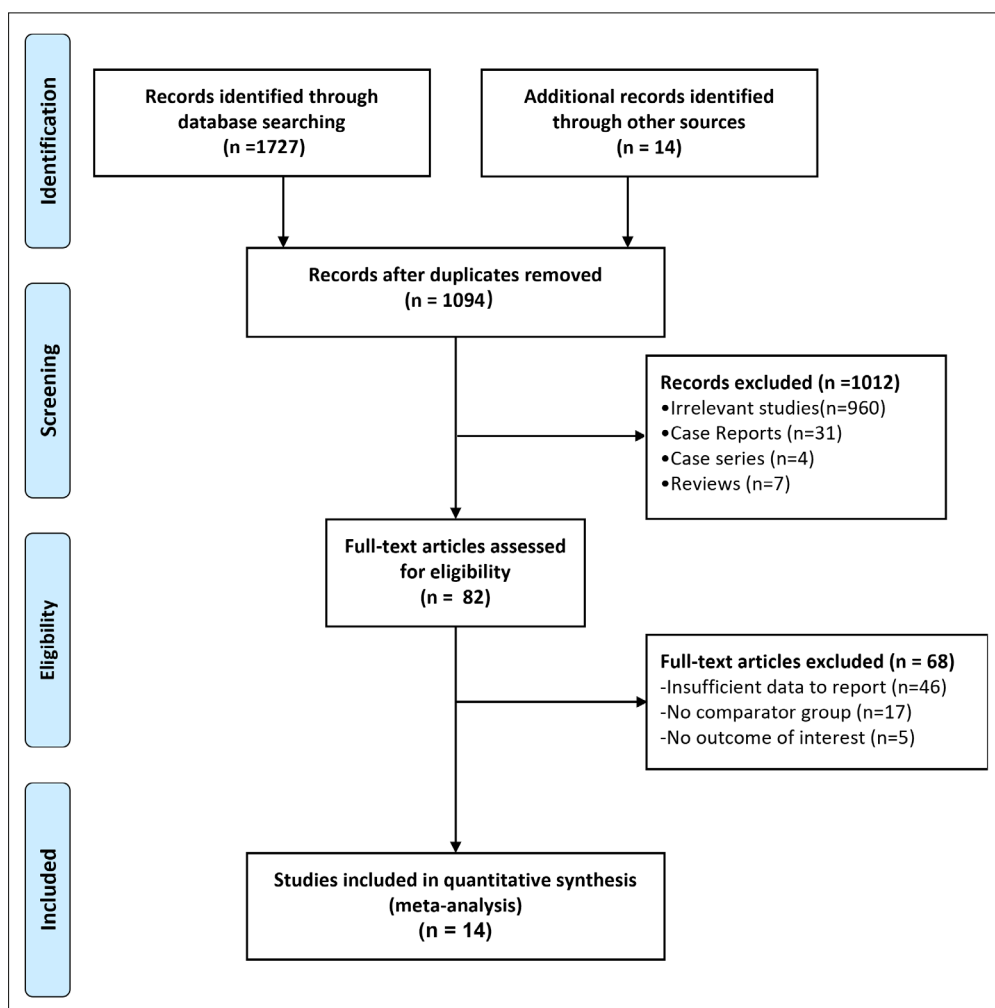


Figure 1. Flow diagram for the selection of studies and specific reasons for exclusion from the present meta-analysis.

Table I. Baseline characteristics of included studies in the meta-analysis investigating for the association of HCV infection with maternal and fetal outcomes.

S. No.	Author, year	Country	Study period	Study design	HCV (+) population	HCV (-) population	HCV diagnostic criteria	Selected population characteristics	Outcome investigated	Adjusted variables
1.	Hillemanns et al ²⁶ 2000	Germany	1992-1996	RCS	31	3,677	Anti- HCV (ELISA) HCV-RNA (RT-PCR)	Pregnant women visiting the Antenatal Clinic	PTB, Cesarean	Maternal age, parity
2.	Jabeen et al ⁴⁰ 2000	Ireland	1977-1978	RCS	89	63	Anti- HCV (ELISA) HCV-RNA (RT-PCR)	Review of the birth history of 36 Rhesus-negative women that were HCV infected after their first pregnancy. Control groups were age and parity-matched Rhesus positive women without any chronic illnesses	PTB, Cesarean, Miscarriage	Maternal age, parity, coinfectd with HIV/HBV
3.	Kumar et al ⁴⁸ 2007	India	2003-2006	CCS	84	8,046	Anti- HCV (ELISA) HCV-RNA (RT-PCR)	Healthy pregnant women at the antenatal clinic	PTB, Cesarean, Miscarriage	Maternal age parity; prior history of liver diseases
4.	Berkley et al ²⁵ 2008	USA	2000-2006	RCS	159	141	NR	Pregnant drug-dependent women who referred to a state-supported drug abuse and treatment program	PTB, IUGR	Parity, alcohol use, maternal drug use
5.	Pergamet al ²⁸ 2008	USA	2003-2005	RCS	500	2,016	ICD-9	Review of the Washington State singleton birth records linked to the Comprehensive Hospital Abstract Reporting System	LBW, PTB	Maternal age, parity, tobacco use, alcohol use, maternal drug use
6.	Reddick et al ³⁰ 2011	USA	1995-2005	CCS	555	2,96,218	ICD-9	Review of the National Inpatient data records on all pregnancy-related discharge	PTB, LBW, Cesarean	Maternal age, maternal drug use, coinfectd with HIV

Continued

Table 1 (Continued). Baseline characteristics of included studies in the meta-analysis investigating for the association of HCV infection with maternal and fetal outcomes.

S. No.	Author, year	Country	Study period	Study design	HCV (+) population	HCV (-) population	HCV diagnostic criteria	Selected population characteristics	Outcome investigated	Adjusted variables
7.	Connell et al ²⁴ 2011	USA	1998-2007	RCS	988	16,69,370	ICD-9	All births using birth certificate records linked to Healthcare Administration's Inpatient Hospital discharge data (Florida)	PTB, LBW, Cesarean	NR
8.	Khaskheli et al ⁴⁶ 2014	Pakistan	2009-2010	PCS	361	279	Anti- HCV (ELISA)	Women having obstetrical hemorrhagic emergencies at the Gynecology and Obstetric University of Medical and Health Sciences Hospital	Maternal mortality, PTB, Cesarean, IUGR	Maternal age
9.	Salemi et al ⁴¹ 2014	USA	1998-2009	RCS	2,457	22,14,778	ICD-9	Birth records linked to maternal and infant inpatient hospital discharge records in Florida	LBW	NR
10.	Rezk et al ⁴⁷ 2017	Germany	May 2012- May 2017	PCS	158	184	Anti- HCV (ELISA) HCV- RNA (RT- PCR)	Pregnant women attending in the Antenatal Care Outpatient Clinic in the first trimester	Neonatal mortality, PTB, Miscarriage, LBW	NR
11.	Rossi et al ⁴² 2017	USA	2006-2015	RCS	7,069	14,48,138	NR	U.S. live birth records	Neonatal mortality, PTB, LBW	Maternal age, year of delivery, pre-gestational diabetes, chronic hypertension, BMI, maternal ethnicity, socioeconomic status, cigarette smoking, parity, and history of prior cesarean delivery

Continued

Table 1 (Continued). Baseline characteristics of included studies in the meta-analysis investigating for the association of HCV infection with maternal and fetal outcomes.

S. No.	Author, year	Country	Study period	Study design	HCV (+) population	HCV (-) population	HCV diagnostic criteria	Selected population characteristics	Outcome investigated	Adjusted variables
12.	Piffer et al ⁴³ 2020	Italy	2009-2018	RCS	182	46,145	Anti- HCV (ELISA) HCV- RNA (RT- PCR)	All pregnant women who delivered between 2009 and 2018, the compliance with HCV serological screening and the seroprevalence trend, also in relation to age group and nationality	PTB, LBW	NR
13.	Kushner et al ⁴⁴ 2022	Canada	Jan 2000- Dec 2018	RCS	1,780	390	HCV RNA test	MOMBABY dataset (routine mother-infant linkage data), and lab data from Public Health Ontario and the Ontario Laboratory Information Systems	PTB	Maternal age, multiple gestation, cirrhosis diagnosis, parity, history of alcohol use, history of substance use, pre-existing diabetes, and HIV coinfection
14.	Chen et al ⁴⁵ 2022	USA	2012-2018	RCS	131,695	28,499,085	ICD-9	Data of pregnancy or delivery-related admissions identified from the National Inpatient Sample Data	IUGR, Caesarean	Age, ethnicity, insurers, hospital teaching status, region, and comorbidities (hypertension, diabetes mellitus, obesity, anemia, alcohol use disorder, smoking, drug abuse)

NR=Not reported, HBV=hepatitis B virus, CCS= Case-control study; RCS=Retrospective cohort study; PCS=Prospective cohort study; HCV=hepatitis C virus, HIV=human immunodeficiency virus, IUGR=Intrauterine fetal growth restriction, LBW=Low birth weight infants; ELISA=enzyme-linked immunosorbent assay, ICD=international classification of diseases, IUGR=intrauterine growth restriction, RNA=ribonucleic acid, USA=United States of America; PROM=Premature rupture of membranes; AIDS=acquired immunodeficiency syndrome; STI=sexually transmitted infection; PTB=Preterm birth.

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Table II. Quality assessment of included studies based on Newcastle-Ottawa Scale (NOS).

Newcastle-Ottawa scale											
S. No.	Authors and year	Selection				Comparability	Outcome				Total-Score
		Representativeness of exposed cohort	Selection of Non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the beginning of study	Comparability of cohorts in terms of design or analysis	Assessment of outcome	Follow-up was long enough for outcomes to occur		Adequacy of Follow-up of cohorts	
1	Hillemanns et al ²⁶ 2000	1	1	0	1	1	1	1	0	6	
2	Jabeen et al ⁴⁰ 2000	1	1	0	1	1	1	1	1	7	
3	Kumar et al ⁴⁸ 2007	1	1	1	1	1	1	1	1	8	
4	Berkley et al ²⁵ 2008	1	1	0	1	1	1	1	0	6	
5	Pergam et al ²⁸ 2008	1	1	0	1	1	1	1	1	7	
6	Reddick et al ³⁰ 2011	1	1	0	1	1	1	1	1	7	
7	Connell et al ²⁴ 2011	1	1	0	1	1	1	1	1	7	
8	Khaskheli et al ⁴⁶ 2014	1	1	1	1	1	1	1	1	8	
9	Salemi et al ⁴¹ 2014	1	1	1	1	0	0	1	1	6	
10	Rezk et al ⁴⁷ 2017	1	1	1	1	1	1	1	1	8	
11	Rossi et al ⁴² 2017	1	1	0	1	1	1	1	1	7	
12	Piffer et al ⁴³ 2020	1	1	1	1	1	1	1	1	8	
13	Kushner et al ⁴⁴ 2022	1	1	1	1	1	1	1	1	8	
14	Chen et al ⁴⁵ 2022	1	1	1	1	1	1	1	1	8	

Thirteen studies^{24-26,28,30,40-44,46-48} reported the data of preterm birth (PTB), five studies^{25,30,45-47} for intrauterine fetal growth restriction (IUGR), six studies^{24,28,41-43,47} with low birth weight (LBW) infants, three⁴⁵⁻⁴⁷ for premature rupture of membranes (PROM) and maternal mortality^{24,25,47} and two studies^{42,47} for neonatal mortality respectively. Of 14 studies, 10 studies^{25,26,28,30,40,42,44-46,48} reported the details about the adjusted variables list (Table I) that were used for multivariate analysis.

Pre-Term Birth (PTB)

As shown by the pooled analysis of 13 studies^{24-26,28,30,40-44,46-48} using the fixed effect model, HCV infection during pregnancy had significant association with the risk of PTB (OR=1.66, 95% CI: 1.59-1.74) as compared to HCV (-) during pregnancy. Overall, no significant heterogeneity ($I^2=36.3%$, $p=0.09$) was observed, which further suggested the good reliability of our findings (Figure 2). Subgroup analysis based on ethnici-

ty also suggest a strong link between maternal HCV infection and a higher risk of PTB in both Asian (OR=1.47, 95% CI: 1.16-1.85, $I^2=0%$) as well as Caucasian (OR=1.67, 95% CI: 1.60 - 1.75, $I^2=47.6%$) populations.

Low Birth Weight (LBW) Infants

Only six studies^{24,28,41-43,47} of Caucasian patients reported the data for LBW. Our pooled analysis showed higher risk of LBW in HCV (+) as compared to HCV (-) pregnant women (OR=1.96, 95% CI: 1.63 - 2.36). Due to the existence of heterogeneity ($I^2=82.4%$, $p<0.001$), effect size was estimated by the random effects model (Figure 3).

Intrauterine Fetal Growth Restriction (IUGR)

An overall significant higher risk of IUGR was detected in the HCV (+) group as compared to the HCV (-) group (OR=2.09, 95% CI: 2.04-2.14). Fixed effect model was applied as no significant

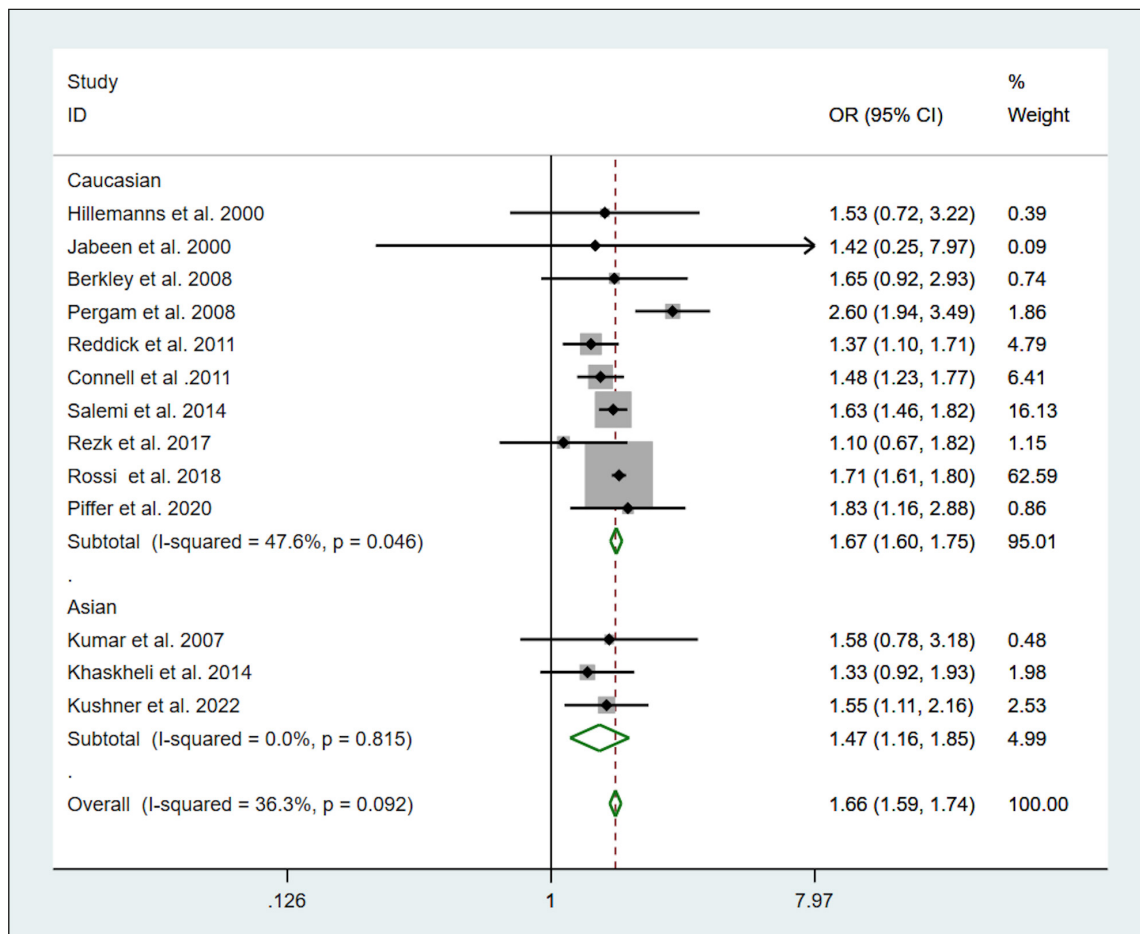


Figure 2. Forest plot for the association between chronic hepatitis C virus infection and risk of preterm birth.

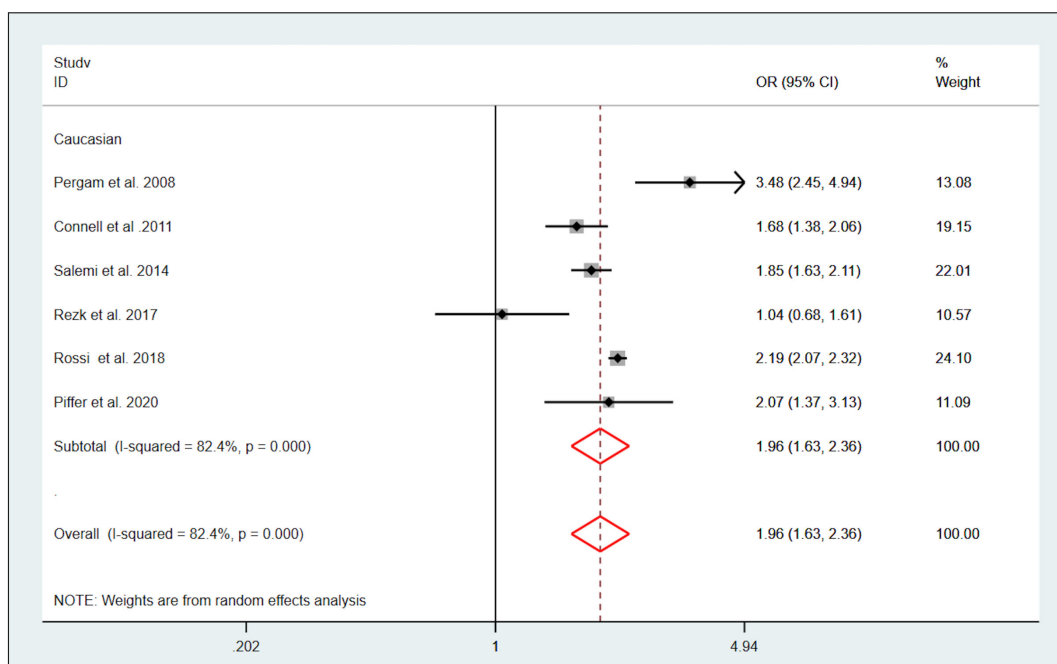


Figure 3. Forest plot for the association between chronic hepatitis C virus infection and risk of low birth weight (LBW) infants.

degree of heterogeneity ($I^2=0\%$, $p=0.07$) was observed (Figure 4). Stratified analysis revealed that higher risk of IUGR was present in the stud-

ies performed in Caucasian (OR=2.09, 95% CI: 2.04-2.14, $I^2=0\%$) but not in Asian population (OR=1.49, 95% CI: 0.79 - 2.44, $I^2=0\%$).

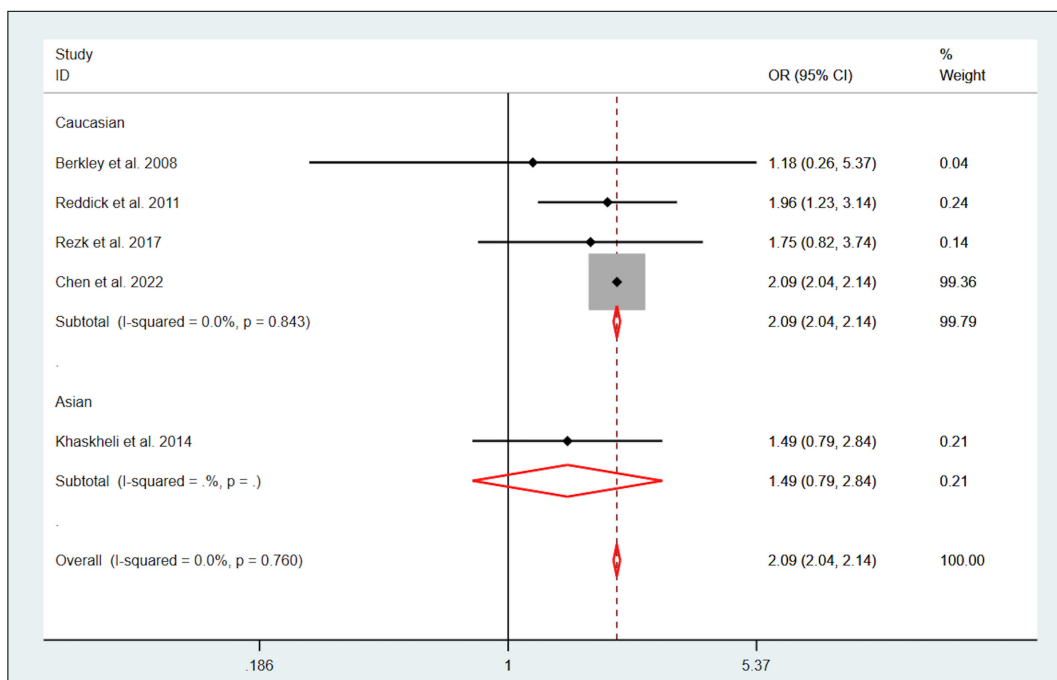


Figure 4. Forest plot for the association between chronic hepatitis C virus infection and risk of intrauterine fetal growth restriction (IUGR).

Maternal Mortality

Three studies^{24,25,47} reported maternal mortality outcomes. HCV infection was associated with higher rate of maternal mortality as compared to HCV (-) group (RR=3.44, 95% CI: 1.85 - 6.41). Due to higher degree of heterogeneity ($I^2=62.5\%$, $p=0.07$), we conducted a random effects model to estimate the effect size (Supplementary Figure 1). A higher maternal mortality rate was also observed in both Asian (RR=2.55, 95% CI: 1.11-5.80, I^2 =Not Estimable owing to only one study in Asian population %) and Caucasian (OR=3.88, 95% CI: 1.75-8.2, $I^2=63.8\%$) populations.

Neonatal Mortality

Only two studies^{42,47} reported the data for neonatal mortality and the pooled analysis suggested higher rate of neonatal mortality in HCV (+) as compared to HCV (-) groups (RR=1.54, 95% CI: 1.18-2.02) (Supplementary Figure 2).

Premature Rupture of Membranes (PROM)

A trend of association of HCV infection during pregnancy with a risk of PROM (OR=1.26, 95% CI: 0.96-1.74) was detected using a fixed effect model (Supplementary Figure 3).

Publication Bias

No significant publication bias was noted for the association between (a) PTB ($p=0.31$); (b) LBW ($p=0.38$); and (c) IUGR ($p=0.12$) and the maternal HCV infection. No obvious asymmetry was detected on the funnel plot (Figure 5a-c).

Sensitivity Analysis

Sensitivity analysis omitting single study in each turn did not detect overall impact for the association of HCV infection with the risk of PTB, IUGR and LBW compared to HCV (-) status during pregnancy (Supplementary Figure 4).

Meta-Regression Analysis

We next conducted a meta-regression analysis based on NOS quality score to assess the impact of heterogeneity. No significant heterogeneity was detected for the association of HCV infection with the risk of PTB ($p=0.16$), IUGR ($p=0.34$); and LBW ($p=0.92$) (Supplementary Figure 5).

Discussion

Our findings suggest a strong association between chronic HCV infection in mothers and a

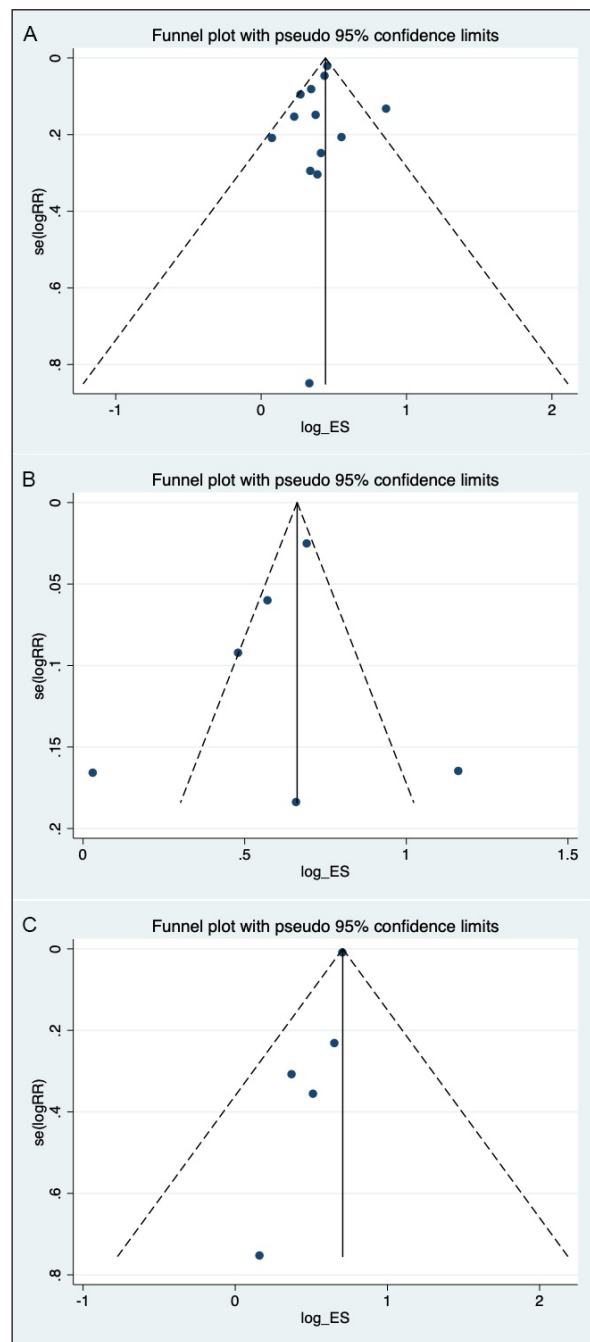


Figure 5. Funnel plot for the association of (A), Preterm birth; (B), low birth weight (LBW) infants; and (C), intrauterine fetal growth restriction (IUGR).

higher incidence of PTB, LBW, IUGR, as well as maternal and neonatal mortality. A trend of association of HCV infection during pregnancy with a risk of PROM was observed.

While earlier research^{24,25,28,30} showed that HCV infection in mothers increased the risk of gestational diabetes mellitus, PROM, LBW, and

stillbirth, only our study provided evidence on the association of PTB with the HCV infection. To the best of our knowledge, our systematic review and meta-analysis of 14 studies for the first time has provided the evidence of the association of maternal HCV infection with the PTB, LBW, IUGR, and stratifies the pooled evidence on the basis of ethnicity (Asian and Caucasian).

The association between a higher risk for PTB and HCV infection may be due to a number of different processes. Inflammation has been suggested^{49,50} as an independent etiological variable for PTB, despite the fact that the pathophysiology of PTB is not fully known. PTB risk was elevated in conditions including Crohn's disease⁵¹ and rheumatoid arthritis⁵² that are characterized by chronic inflammation. An increasing body of evidence^{53,54} suggests that chronic HCV infection is linked to increased systemic and hepatic inflammations. In HCV-infected patients who are not diabetic or obese, pro-inflammatory cytokine levels are higher and the pro-inflammatory/anti-inflammatory cytokine ratio is higher than in HCV-negative people^{55,56}. Previous research⁵³ has shown that an elevated level of pro-inflammatory cytokines is linked to a majority of PTB cases. It has been established that unfavorable perinatal outcomes were significantly influenced by disturbed utero-placental hemodynamics brought on by excessive inflammation.

Previous studies⁵⁷⁻⁵⁹ have shown that infants born with LBW or IUGR had a higher prevalence of placental inflammatory lesions as discovered by placental histopathology. Additionally, expectant women with chronic illnesses such as Crohn's disease⁶⁰ and/or rheumatoid arthritis⁶¹, that are characterized by systemic low-grade inflammation, had higher risk of LBW or IUGR neonates. Therefore, we might hypothesize that the greater proportion of newborns with LBW or IUGR in the HCV (+) patients may be a result of the disproportionate inflammatory response to the viral infection. Nurses traditionally play an important role in both education and management of pregnant women. Therefore, they may be pivotal in helping HCV (+) pregnant patients to better manage their condition, educating patients about the disease, its prevention, lifestyle choices, psychosocial factors, testing, and diagnosis, as well as how to access support services. Nurses must develop a level of knowledge that will allow them to practice independently within established protocols and guidelines.

Numerous perinatal variables, including nulliparity, advanced maternal age, and low pre-pregnancy BMI, were linked to an elevated risk of IUGR and/or LBW^{62,63}. Large epidemiologic cohort studies⁶⁴⁻⁶⁶ revealed a link between the intrauterine fetal growth restriction and maternal drug, alcohol, and smoking usage prior to conception or throughout pregnancy. It is well recognized that HCV population has often a higher incidence of hepatitis B Virus (HBV), human immunodeficiency virus (HIV), and/or other co-infections, and therefore are at higher risk of obstetrical problems and poor fetal growth⁶⁷. Additionally, there is a link between pregnancy complications including hypertension and a higher chance of LBW or IUGR births. Therefore, a frequent question was whether these putative confounders have a major impact on the outcomes.

In this study, we undertook several measures to reduce any potential heterogeneity. First, in this meta-analysis, we estimated the effect sizes using adjusted ORs. In addition, we performed a subgroup analysis to assess the potential influence that each major confounder, such as age, parity, drug and alcohol misuse, preeclampsia, and HBV/HIV coinfection status may have on the combined results. Even after performing a subgroup analysis, it was clear that chronic HCV infection in the mother posed a risk factor on its own for intrauterine fetal development disruption.

Limitations

Our study has certain limitations. There was a substantial variability in ethnicity, age and environmental factors among the included studies. Most of the included studies were of retrospective nature. Multiple comparisons that were made in our analysis may lead to a risk of the false discovery. Additionally, there was a variability in the adjustment of covariates between studies in our review. There was a marked heterogeneity in several comparisons that were made in our study. Therefore, we used a random-effect model and conducted meta-regression analysis to address potential inter-study heterogeneity, as well as assess the heterogeneity in the quality of the included studies.

Further studies that would take into consideration potential confounding factors are needed to better understand the relationship between the HCV (+) status and the risk of LBW and/or IUGR. Despite the limitations, our meta-analysis has several advantages. The current study is, as far as we are aware, the first systematic review

and meta-analysis to assess the relationship between HCV infection in the mother and the likelihood of IUGR or LBW births in the neonates.

Conclusions

Mothers with HCV infection had markedly increased probability of delivering a PTB and/or IUGR and/or LBW neonate. In clinical practice, standard care of treatment and proper monitoring are needed for the pregnant population with HCV infection. Our findings may provide a useful information for selecting appropriate therapy methods for pregnant women with HCV (+) infection.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

No funding was received for this study.

Authors' Contribution

GS conceived and designed the study, WS, YL and XH collected data and performed data analysis. GS wrote the draft of this manuscript. CG edited the manuscript.

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