Hepatitis C Virus Viral Load And Mother-To-Child Transmission: a Systematic Review and Meta - Analysis

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Abstract

Background: Hepatitis C virus (HCV) infection is increasing among pregnant women own to the opioid epidemic, and mother-to-child transmission (MTCT) was considered to be the leading cause of hepatitis C in the future. Thus, our aim of this study was to assess the association of maternal HCV viral load and human immunodeficiency virus (HIV) coinfection with the risk of MTCT in pregnant women infected by HCV.

Methods: We performed a literature searching using MEDLINE, EMBASE, CENTRAL, SCIE, CPCIS, SCOPUS, LILACS and WHO Global Index Medicus from inception to 1 March 2021. Manuscripts were included if they reported the incidence of HCV MTCT. Pooled effect estimates were obtained by using random-effects model and Holm-Bonferroni correction was performed for multiple pooled associations.

Results: a total of 26 studies involving 4491 newborns with maternal HCV infected were identified. Pregnant women with HCV viremia had increased risk of MTCT (odds ratio [OR]: 8.14, 95% confidence interval [CI]: 4.62-14.31) compared with those with negative HCV-RNA. Multiple-subgroup analysis showed HCV viremia/HIV+ group experienced the highest risk for HCV MTCT and then HCV viremia mono-infected group; HCV-RNA negative women experienced the lowest risk for HCV MTCT. Among HCV viremia women, elevated risk of MTCT was found in subjects with viral load ≥ 6 log copies/ml as compared with those with viral load < 6 log copies/ml (OR=4.93, 95% CI: 2.38-10.21).

Conclusions: The HCV MTCT incidence is increased in pregnant women with detectable HCV viremia, and is even higher in those with viral load ≥ 6 log copies/ml. HIV coinfection further increases the risk of HCV MTCT.

Background

Hepatitis C virus (HCV) infection is a major global health issue which affect 2-3% of population in the world¹. HCV infection causes acute and chronic hepatitis, and increases the risk of liver cirrhosis, hepatocellular cancer, liver failure^{2,3}. In the last decade, the prevalence of HCV in reproductive aged women was increasing own to opioid use⁴, resulting in a dramatic rise of HCV infection among pregnant women⁵. HCV viremia were detected in 30-40% infected neonates within the first three days of life, indicated that intrauterine transmission may occur⁶. Therefore, mother-to-child transmission (MTCT) was considered to be the leading cause of hepatitis C in the future⁷, and current guidelines recommend universal HCV screening during pregnancy^{8,9}.

Antiviral treatment is considered as proven interventions to decrease the risk of perinatal transmission and neonatal infection, such as human immunodeficiency virus (HIV) and hepatitis B virus infection during pregnancy^{10,11}. For HCV antiviral treatment, direct-acting antiviral (DAA) regimens are able to reduce HCV viremia to undetectable level within two weeks^{12,13}. Although it was recently reported effective to reduce HCV-RNA titer in pregnant women with DAA regime¹⁴, there are no epidemiologic studies or clinical trials have confirmed the reduction of HCV viral load in pregnancy contributes to the prevention of MTCT.

Although with some debates, HCV viremia has been considered as a main risk factor of MTCT during pregnancy¹⁵. Existing studies show when the viral load greater than or equal to 6 log₁₀ copies/ml, the risk of MTCT is higher than women with a lower viral load^{16–18}. Placenta express multiple HCV-receptors and/or entry cofactors (e.g., claudin-1, occludin, SR-B1, LDLr or DC-SIGN), resulting in HCV transmission of placenta barrier and fetal infection^{19,20}. In addition, exposure to maternal infected blood during birth is another important pathway of HCV vertical transmission²¹, potentially because of peripheral mononuclear cells infection of HCV²⁰. However, some clinical studies did not support this hypothesis^{22,23}. For example, Jhaveri et al. found HCV MTCT even when maternal HCV RNA load below 20000IU/ml²².

Injection drug use and the opioid epidemic is the leading cause of both HCV and HIV infection in the last decades²⁴, and HIV/HCV co-infection is frequently observed in HCV pregnant women²⁵. The most recent systematic review and meta-analysis showed maternal HIV coinfection is a main risk for MTCT of HCV. HIV down regulates the immune responses, in particular of the T cell mediated reactivity with expansion of Treg cells¹⁹. In immunodeficiency status, HCV replication may be increased and therefore facilitate transmission^{7,26}, and it is suggested that HIV antiviral treatment may prevent HCV MTCT. However, whether HCV-viremia mono-infection or HCV-viremia coinfection of HIV increases MTCT of HCV has not been fully clarified.

In this study, therefore, we aim to compare the risk of MTCT of HCV between pregnant women with and without HCV viremia detected in circulation, and to study how HCV viral load associated with MTCT did. In addition, the relationship of HIV coinfection with MTCT was investigated in the current meta-analysis.

Methods

Search strategy and selection criteria

We conducted this systematic review according to a protocol registered in PROSPERO (CRD42021239499), available at: <https://www.crd.york.ac.uk/PROSPERO/>. A comprehensive search of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Science Citation Index Expanded (SCIE), Conference Proceedings Citation Index-Science (CPCIS), SCOPUS, Literature Latino-Americana e do Caribe em Ciências da Saúde (LILACS) and WHO Global Index Medicus was conducted from database inception to January 7, 2021. Detailed search strategy and search terms are available in supplementary Table 1.

To minimize differences between studies, we imposed the following methodological restrictions for the inclusion criteria: (i) study designs: cohort studies or case-control studies, (ii) including data on both anti-HCV positive mothers and their children with documented HCV serology, (iii) comparing MTCT incidence between HCV viremia women and those with negative HCV-RNA. MTCT was confirmed when HCV-RNA was detected in newborns. In instances of multiple

publications, the most up-to-date or comprehensive information was used. Citations initially selected by systematic search were first retrieved as a title or abstract and preliminarily screened. Potentially suitable citations were then retrieved as complete manuscripts and assessed for compliance to inclusion criteria.

Data extraction

Articles were reviewed and crosschecked independently by two authors. Data on the following characteristics were independently extracted: first author, publication year, country, study type, year of enrollment, number of mother-child pairs, maternal age of delivery, HCV-RNA detection method, number of live births, duration and frequency of newborns follow-up, HCV MTCT incidence, maternal HCV-RNA titer, and crude numbers of newborn with HCV infected and not. HCV MTCT incidence was defined as the ratio of the number of infected newborns to the total number of newborns. High level of viremia was defined as the HCV-RNA titers greater than or equal to $6 \log_{10}$ copies/ml¹⁶. The most comprehensive data were included if multiple articles were reported on the overlapping study population. Any disagreements were resolved by consensus.

Quality assessments

We used the Newcastle-Ottawa Scale (NOS) to evaluate the methodological quality of the included observational studies. NOS includes three dimensions to assess the overall quality and a maximum of 4, 2, and 3 stars can be rated for selection, comparability, and outcome assessment respectively. Two authors independently assessed the risk of bias of included studies. Study scored ≤ 5 on the NOS was regarded as being of low quality and was excluded²⁷.

Statistical analyses

We assessed the risk of the HCV MTCT by conducting two meta-analysis to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for individual studies and then pool the estimates using the DerSimonian and Laird random-effects models. First, we compared the HCV MTCT risk between HCV viremia women and those with negative HCV-RNA. Then, we performed a meta-analysis for relationship between HCV-RNA titers and HCV MTCT incidence.

Multiple-subgroup analysis among maternal HCV viremia/HIV+ group, HCV viremia mono-infected group and HCV-RNA negative group was further conducted after the comparison between HCV viremia and negative HCV-RNA women. In order to control the increased type I errors triggered by multiple comparison²⁸, Holm-Bonferroni method²⁹ was used to figure out adjusted *P*-value.

We used the χ^2 -based *Q* test to assess heterogeneity across studies, expressed as Cochran's *Q* and *I*² statistics, together with 95% confidence intervals. We also determine the possibility of publication bias by using the funnel plot, Begg's test, and Egger's test. Sensitivity analyses were further conducted by only included prospective studies with a sample size larger than 100. Subgroup analysis was conducted by country income according to the World Bank's list of economies³⁰, and region of different incidence of HCV infection according to the WHO Global Hepatitis Report²³. Lower middle income countries and upper middle income countries were further aggregated into middle income countries. We also undertook meta-regression by publication year and MTCT incidence.

All statistical analyses were performed using the software R version 4.0.2.

Results

Characteristics of included studies

We identified 717 papers and 202 of which were removed due to duplications. Finally, 26 publications, published between 1993 and 2015, were eligible for inclusion (Figure 1). The studies examined 4491 newborns of HCV infected mother, with a follow up of at least 6 months. There were 3 retrospective cohorts and 23 prospective cohorts. Of the primary studies, 100% had described independent, consecutive sampling of their cohort. All studies detected HCV-RNA by polymerase chain reaction, and the MTCT incidence ranged from 1.3–38.5%.

Of the twenty-six studies, twenty-three independent eligible studies evaluated the risk of HCV MTCT between maternal HCV viremia group and negative HCV-RNA group (Table 1). Thirteen independent eligible studies evaluated the risk of HCV MTCT between HCV viremia/ HIV+ co-infected mothers and HCV viremia mono-infected mothers (Table 1). Nine independent eligible studies estimated the risk of HCV MTCT based on different HCV-RNA titers (Table 2).

Table 1
Characteristics of studies assessing maternal HCV-RNA and MTCT risk.

ID	First author	Year	Country	Study design	Year of enrollment	Mother-child pairs, n	Mother age, years	HCV-RNA detection method	Total no. of newborns	Follow-up	HCV MTCT incidence, %	Maternal RNA (+) MTCT (+)
2	Saez A et al.	2004	Italy	prospective	1992.1-2000.12	119	32 (16-48)	PCR	122	0, 6, 12, 24, 36 months from delivery	1.6%	2
3	Elmagd EKA et al.	2011	Egypt	retrospective	NR	8	20-40	PCR	8	up to 12 months after delivery	25.0%	2
5	Mariné-Barjoan E et al.	2007	France	prospective	1998.10-2002.9	214	34 (30-37)	PCR	214	at birth and at 3, 6 and 12	6.1%	12
9	Granovsky MO et al.	1998	America	prospective	1986.1-1991.1	NR	NR	PCR	122	up to 4 years after delivery	6.7%	6
11	Ngo-Giang-Huong N et al.	2010	Thailand	prospective	1997.6-1999.12	41	NR	PCR	41	at between 6 weeks and 6 months	9.8%	4
12	Steininger C et al.	2003	Australia	retrospective	1994-1999	73	NR	PCR	75	NR	12.0%	9
18	Dal Molin G et al.	2002	Italy	prospective	1994.1-2000.12	105	30.25 ± 4.95	PCR	105	at 1 month, 3-4 months, and 8-13 months of age	4.8%	5
20	Money Det al.	2014	Columbia	prospective	2000-2003	117	30 (26-34)	PCR	117	at three, six, 12, and 18 months after birth	2.8%	4
26	Tajiri H et al.	2001	Japan	prospective	1993 to 1998	114	NR	PCR	114	at 0, 3, 6, 9, 12 months and every year thereafter	7.9%	9
27	Mazza C et al.	1998	Italy	prospective	1994.1-1996.1	70	29.8 ± 5.3	PCR	70	was first detected between 2 and 6 months	8.0%	6
28	Ferrero S et al.	2003	Italy	prospective	1990.3-2000.3	170	30.8 ± 5.3	PCR	188	at birth and at 3, 6, 9, 12 and 18 months of age	2.7%	5
31	Murakami J et al.	2012	Japan	prospective	1992.6-1998.12	NR	31.2 ± 4.0	PCR	125	at least 6 months after delivery	8.8%	11
32	Mast EE et al.	2005	America	prospective	1993.11-1996.7	242	NR	PCR	244	at 1, 2, 4, 6, 9, 12, 15, 18, and 24 months of age	3.7%	9
33	Garcia-Tejedor A et al.	2015	Spain	retrospective	1986-2011	710	NR	PCR	711	at 1, 3, 6, 9, 12, 15, 18 and 24 months of age	2.7%	12

Notes: NR: not reported.

ID	First author	Year	Country	Study design	Year of enrollment	Mother-child pairs, n	Mother age, years	HCV-RNA detection method	Total no. of newborns	Follow-up	HCV MTCT incidence, %	Maternal RNA (+) MTCT (+)
43	Ruiz-Extremera Á et al.	2013	Spain	prospective	1991-2009	122	NR	PCR	122	at birth and at 2, 4, 6, 8, 10, 12, 18 and 24 months, and thereafter at 3, 4, 5 and 6 years.	5.6%	15
40	OHTO H et al.	1994	Japan	prospective	1990.5-1992.12	54	NR	PCR	54	at birth and were followed for at least 6 months after birth	6.7%	3
42	Spence JD et al.	1997	Australia	prospective	1995-1997	125	NR	PCR	125	at birth and at 6, 12, 18 and >18 months of age	12.3%	6
45	Ceci O et al.	2001	Italy	prospective	1995.1-1997.6	78	30 (21-42)	PCR	78	at birth, 4, 8, 12, 18 and 24 months of age	38.5%	30
49	Resti M et al.	1998	Italy	prospective	NR	403	NR	PCR	403	at birth and then at least three times during the follow up	3.2%	13
50	Zuccotti GV et al.	1995	Italy	prospective	1991.1-1993.1	37	26 (19-33)	PCR	37	at birth and at 1 month of age, and then every 3 months until 18 months of age	16.2%	6
53	Zanetti AR et al.	1998	Italy	prospective	1990	291	NR	PCR	291	at birth and at 3, 6, 9, 12 months of age and then every 6 months.	27.0%	17
52	Paccagnini S.	1995	Italy	prospective	1990	70	NR	NR	70	at 0, 3, 6, 9, 12, 15 and 18 months	8.2%	9
54	Resti M et al.	2002	Italy	prospective	1993.4-1996.12	1372	NR	PCR	1372	at birth or within 3 months and then >3 times during the subsequent 2-year follow-up period.	7.6%	97
Notes: NR: not reported.												

Table 1
(Continued)

ID	First author	Maternal HCV viraemic/HIV+ co-infection		Maternal HCV viraemic/HIV-	
		MTCT (+)	MTCT (-)	MTCT (+)	MTCT (-)
2	Saez A et al.	NR	NR	NR	NR
3	Elmagd EKA et al.	NR	NR	NR	NR
5	Mariné-Barjoan E et al.	NR	NR	NR	NR
9	Granovsky MO et al.	4	43	2	23
11	Ngo-Giang-Huong N et al.	NR	NR	NR	NR
12	Steininger C et al.	NR	NR	NR	NR
18	Dal Molin G et al.	NR	NR	NR	NR
20	Money Det al.	0	15	4	89
26	Tajiri H et al.	NR	NR	NR	NR
27	Mazza C et al.	NR	NR	NR	NR
28	Ferrero S et al.	2	28	3	102
31	Murakami J et al.	NR	NR	NR	NR
32	Mast EE et al.	2	6	7	175
33	Garcia-Tejedor A et al.	NR	NR	NR	NR
43	Ruiz-Extremuera Á et al.	NR	NR	NR	NR
40	OHTO H et al.	NR	NR	NR	NR
42	Spence JD et al.	NR	NR	NR	NR
45	Ceci O et al.	NR	NR	NR	NR
49	Resti M et al.	NR	NR	NR	NR
50	Zuccotti GV et al.	4	9	2	6
53	Zanetti AR et al.	9	23	8	167
52	Paccagnini S.	7	10	2	4
54	Resti M et al.	22	136	75	664
Notes: NR: not reported.					

Table 2
Characteristics of the included studies assessing HCV viral load and MTCT risk

ID	First author	Year	Country	Study design	Year of enrollment	Mother-child pairs, n	Mother age, years	HCV-RNA detection method	Total no. of newborns	Follow-up	HCV MTCT incidence, %	HCV-RNA category, log ₁₀ copies/mL
2	Saez A et al.	2004	Italy	prospective	1992.1-2000.12	80	32 (16-48)	PCR	80	at birth and at 6, 12, 24 and 36 months of age	2.5%	<10 ⁶ copies/mL
												≥10 ⁶ copies/mL
5	Mariné-Barjoan E et al.	2007	France	prospective	1998.10-2002.9	194	34 (30-37)	PCR	194	at birth and at 3, 6 and 12 months of age	6.2%	<10 ⁶ copies/mL
												≥10 ⁶ copies/mL
22	Lin HH et al.	1994	China	prospective	1989.3-1992.4	8	NR	PCR	8	at 1 week and 1, 3, 6, 9, and 12 months of age	12.5%	<10 ⁶ copies/mL
												≥10 ⁶ copies/mL
25	Okamoto M et al.	2000	Japan	prospective	1992.6-1998.12	84	NR	PCR	84	NR	8.3%	<10 ⁶ copies/mL
												≥10 ⁶ copies/mL
32	Mast EE et al.	2005	America	prospective	1993.11-1996.7	182	NR	PCR	182	at 1, 2, 4, 6, 9, 12, 15, 18, and 24 months of age	3.8%	≤10 ⁶ copies/ml
												>10 ⁶ copies/ml
33	Garcia-Tejedor A et al.	2015	Spain	retrospective	1986-2011	227	NR	NR	227	at 1, 3, 6, 9, 12, 15, 18 and 24 months of age	1.3%	<10 ⁶ copies/ml
												≥10 ⁶ copies/ml
39	Ketzinel-Gilad M et al.	2000	Israel	prospective	1992-1997	17	23-41	PCR	17	at 2 days after birth and up to 4 years	11.8%	<10 ⁶ copies/mL
												≥10 ⁶ copies/mL

Notes: NR: not reported.

ID	First author	Year	Country	Study design	Year of enrollment	Mother-child pairs, n	Mother age, years	HCV-RNA detection method	Total no. of newborns	Follow-up	HCV MTCT incidence, %	HCV-RNA category, log ₁₀ copies/mL
40	OHTO H et al.	1994	Japan	prospective	1990.5-1992.12	37	NR	PCR	37	at birth and were followed for at least 6 months after birth	18.9%	<10 ⁶ copies/mL
												≥10 ⁶ copies/mL
42	Spence JD et al.	1997	Australia	prospective	1995-1997	52	NR	PCR	52	at birth and at 6, 12, 18 and >18 months of age	11.5%	<10 ⁶ copies/mL
												≥10 ⁶ copies/mL
Notes: NR: not reported.												

All of the 26 studies included in the present meta-analysis were regarded as acceptable quality, with NOS scores between 6 and 9. (supplementary Table 2, Table 3.)

Comparison of HCV MTCT risk between maternal HCV viremia and negative HCV-RNA group

Twenty-three publications^{17,18,31-51} with 4382 newborns of HCV infected mother and 296 MTCT children were identified. The pooled MTCT incidence in the maternal HCV viremia group was 9.55% (95% CI: 8.55%-10.64%), compared with 0.30% (95% CI: 0.11%-0.80%) in negative HCV-RNA group (Table 1).

Heterogeneity was not presented in the included studies ($Q = 8.21$, $P = 1.000$; $I^2 = 0.00\%$). The pooled OR of MTCT in maternal HCV viremia compared to negative HCV-RNA group was 8.14 (95% CI, 4.62-14.31; $P < 0.0001$) by random-effects model (Fig. 2A). A sensitivity analysis including only prospective studies with a sample size larger than 100 showed the pooled OR of MTCT was 8.83(95% CI: 4.18–18.65), indicating good robustness of the results (supplementary appendix Fig. 1A)

The funnel plot showed symmetric distribution which indicated the absence of publication bias (supplementary appendix Fig. 2A). However, Begg's test ($P = 0.010$) and Egger's test ($P = 0.357$) suggested the existence of publication bias.

Multiple-subgroup analysis was conducted among maternal HCV viremia/HIV+ group, HCV viremia mono-infected group and HCV-RNA negative group. The pooled OR was 2.33 (95% CI: 1.16–4.68) for MTCT in HCV viremia/ HIV+ versus HCV viremia mono-infected group, 8.16 (95% CI: 3.19–20.88) for HCV viremia mono-infected versus HCV-RNA negative group, 15.41(95% CI: 5.69–41.74) for HCV viremia/ HIV+ versus HCV-RNA negative group, respectively. All the three significant pooled ORs survived Holm-Bonferroni correction (adjusted P values are 0.0174, 0.0003 and 0.0003 respectively) (Fig. 2A).

Subgroup analysis by country income showed the pooled OR of MTCT was 8.79 (95% CI: 4.85–15.95) in the high-income country subgroup, and 4.06 (95% CI, 0.68-24.21) in the middle-income country subgroup.

Subgroup analysis by regions of the different risk level showed the pooled OR of MTCT was 9.48 (95% CI, 4.77–18.85) in the moderate risk region subgroup; in the high-risk region subgroup, the overall MTCT OR was 5.00 (95% CI: 0.17-146.64) and in the low-risk region subgroup, the overall MTCT OR was 6.01 (95% CI: 2.13-16.97).

Meta-regression analysis indicated that publication year ($Z = 0.13$, $P = 0.897$) and MTCT incidence ($Z = 0.92$, $P = 0.359$) were not correlate to HCV MTCT risk.

Comparison of HCV MTCT incidence between different HCV-RNA titers

Nine publications^{18,31,41-44,52-54} with 881 newborns of HCV infected mother met eligibility for comparing MTCT incidence between mothers with high (≥ 6 log₁₀ copies/ml) or low level of viremia (< 6 log copies/ml) (Table 2). The pooled MTCT incidence in high viremia group was 11.30% (95% CI: 8.15%-15.47%) and 2.38% (95% CI: 6.57%-27.95%) in low viremia group.

No significant heterogeneity observed across studies ($Q = 9.28$, $P = 0.320$; $I^2 = 0.00\%$). Pregnant women with high level of viremia experienced an elevated risk of HCV MTCT (OR=4.93, 95% CI: 2.38,-10.21; $P < 0.001$) compared with those with low HCV viremia titer by random effects model analysis (Fig. 2B). We conducted further sensitivity analysis by limiting studies to those prospective studies with a sample size larger than 100, and the pooled OR of MTCT was 3.82 (95% CI: 1.35-10.79), indicating good robustness of the results (supplementary appendix, Fig. 1B).

The funnel plot showed symmetry, which indicated insufficient evidence of publication bias (supplementary appendix, Fig. 2B). Begg's test ($P = 0.920$) and Egger's test ($P = 0.455$) also suggested the absence of publication bias.

Subgroup analysis by country income showed the pooled MTCT OR was 5.00 (95% CI: 2.54–11.24) in the high-income country subgroup, and 0.69 (95% CI: 0.02–26.90) in the middle-income country subgroup.

Subgroup analysis by region of the different risk level showed the pooled MTCT OR was 3.84 (95% CI, 1.22-12.09) in the moderate risk region subgroup, and the overall MTCT OR was 7.21 (95% CI, 1.62-32.12) in the low-risk region subgroup.

Meta-regression analysis indicated that publication year ($Z = -0.27$, $P = 0.784$) and MTCT incidence ($Z = 0.31$, $P = 0.754$) were not relevant to MTCT risk.

Discussion

The current meta-analysis, involving 4382 newborns with maternal HCV antibody positive, found a significantly increased risk of HCV MTCT in pregnant women with HCV viremia, and an even higher MTCT incidence in pregnant women with high level of viremia. In addition, we found that HIV coinfection further increase risk of MTCT in women with HCV viremia.

In spite of the clear association of HIV co-infection and HCV MTCV during pregnancy, HCV viremia was been confirmed as an independent risk factor HCV transmission according to the result of the present meta-analysis. Although HCV MTCT was found in 4 out of 1291 newborns with maternal HCV-RNA negative, this could be explained by variation of HCV RNA titers during pregnancy, or false negative results due to low sensitivity of testing kits^{33,42,49,51}. In addition, mothers with HCV viremia titer greater than or equal to 6 log copies/ml were with even higher incidence of MTCT than those with HCV viremia titer lower than 6 log copies/ml. It indicates pregnant women with HCV viremia should be considered for antiviral treatment and 6 log copies/ml could be considered as the threshold for who is proposed to receive antiviral treatment. DAA treatment is an effective and safe strategy to reduce HCV RNA viral load in patient with chronic HCV infection⁵⁵. Recently, DAA treatment with Ledipasvir and sofosbuvir regimens showed its effectiveness among pregnant women¹⁴. However, up to 79% women refused to receive DAA treatment during pregnancy, concerning the safety and cost of DAA⁵⁶. The findings of this study suggested the emergency of DAA treatment for HCV infect pregnant women, and strengthening health promotion among pregnant women and reducing the cost of DAA are future measures to be taken.

Maternal HIV coinfection is considered as another risk factor of MTCT⁵⁷. In this meta-analysis, pregnant women co-infected of HIV experience significantly highest prevalence of HCV-MTCT. This result is consistent with the report by Benova et al⁵⁷. The role of HCV/HIV coinfection in HCV transmission seems to depend on HCV-RNA titer, since women taken HAART therapy, by reducing HIV-RNA level, also reduces the risk of HCV-MTCT¹⁸. Whereas, for the same level of HCV-RNA titer, the risk of HCV MTCT is probably higher in HCV/HIV co-infected women than HCV viremia mono-infected women according to the present meta-analysis. This suggests that other mechanisms could be involved to explain HCV-MTCT. Further studies are necessary to explore the interaction between HCV and HIV. Our findings suggested for HIV/HCV co-infected pregnant women antiviral treatments for both HIV and HCV virus could be considered; however, further clinical trials are needed to confirm the safety and effectiveness of the combined treatment.

Inevitably, the present meta-analysis has some limitations. First, because of data source, we were only able to include cohort study for analysis. Second, due to the heterogeneity of studies regarding to HCV viral load, the dose-response relationship between HCV RNA and MTCT could not be obtained. In addition, the difference of MTCT among diverse HCV gene type is not clear, because the gene type of HCV was not available in literature¹⁴. Although with these limitations, our study is the first meta-analysis to determine the association between HCV viral load and MTCT during pregnancy.

Conclusion

In conclusion, detectable HCV viremia is an independent factor of MTCT in pregnant women. HCV/HIV co-infection can further increase the risk of HCV-MTCT. The 6 log copies/ml of maternal HCV viral load may be considered as the threshold for MTCT. Further randomized controlled trials are needed to confirm the indication of DAA treatment in pregnant women.

Abbreviations

HCV: hepatitis C virus; HIV: human immunodeficiency virus; MTCT: mother-to-child transmission; OR : odds ratio; CI =confidence interval; DAA: direct-acting antiviral; CENTRAL: the Cochrane Central Register of Controlled Trials; SCIE: Science Citation Index Expanded; CPCIS: Conference Proceedings Citation Index-Science ; LILACS: Literature Latino-Americana e do Caribe em Ciências da Saúde

Declarations

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Authors' contributions

Songqing Deng and Wenfang Zhong: project development, data management, data analysis, and manuscript writing. Chen Wen and Zilian Wang: manuscript revise and project development. All authors read and approved the final manuscript.

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Availability of data and materials

All data can be obtained from the manuscript.

Ethics approval and consent to participate

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Consent for publication

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Competing interests

Not applicable.

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Figures

Figure 1

Flowchart of selection of studies included in meta-analysis

Figure 2

A Forest plot of MTCT risk of maternal HCV viremia group compared with HCV-RNA-negative group. MTCT= mother-to-child transmission, HCV=Hepatitis C virus B Forest plot of MTCT incidence for maternal HCV-RNA titer ≥ 6 log copies/mL Compared with <6 log copies/mL. MTCT= mother-to-child transmission, HCV=Hepatitis C virus

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