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Review Article

HCV INDUCED COMPLICATIONS DURING PREGNANCY AND NEONATAL RISKS

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Abstract: *Hepatitis C Virus (HCV) is a frequent health concern that causes pregnancy-related disorders such as intrahepatic cholestasis, preeclampsia, preterm delivery, gestational diabetes mellitus, and increased bile acid concentration in pregnant women. The cause of premature delivery in HCV-infected pregnant women is unknown, however alcohol is a risk factor. Many variables contribute to a higher likelihood of HCV transfer from mother to newborn, including a high viral load along with HIV co-infection, protracted membrane breach, and vaginal laceration. Neonatal problems caused by HCV include low birth weight due to a maternal placental inflammatory lesion, fetal distress, in which the infant suffers from oxygen shortage and preterm birth. Antiviral treatment for HCV pregnant women is contradictory. Ribavirin and interferon are not utilized as treatments for HCV in pregnant women due to the potential for teratogenicity and psychological adverse effects. In addition to causing pregnancy-related complications, HCV may have several harmful impacts on the fetus.*

Keywords: Hepatitis C Virus (HCV), Maternal Problems, Vertical Transmission of HCV, Fetal Complications, Treatment of HCV in Pregnant Women

Introduction

Hepatitis C virus (HCV) is one of the most common infections worldwide and spreads quickly (1-6). About 1% to 8% of pregnant women globally have HCV, and between 0.05% and 5% of children are infected with the virus (7, 8). Intravenous drug use is one of the main risk factors for chronic HCV infection, which affects 1 to 2% of women of reproductive age (9). HCV infection can result from blood exposure, which is climaxed by sexual or perinatal transmission (10, 11).

Many studies with large sample sizes suggest that there is a significant increase in the risk of preterm birth in mothers with HCV infection (12, 13), membranes rupture at a premature stage (14, 15), intrahepatic cholestasis (16) as well as gestational diabetes (17) and low birth weight (18), fetal distress (19) and prematurity abnormalities in neonates (20).

Complications during Pregnancy:

Intrahepatic Cholestasis of Pregnancy (ICP):

The global incidence of ICP falls between 0.2% to 2.5% (21), with the highest spread in South America, up to the limit of 15% (22). According to a study conducted in New Mexico, pregnancy-related cholestasis occurred in 6.3% of HCV antibody-reactive individuals but not in HCV antibody-nonreactive patients. Furthermore, all of the cholestasis patients were Hispanic, and 9.3% of pregnant Hispanic women with HCV antibody-reactive disease had pregnancy-related cholestasis (9). The given data clearly shows that cholestasis during pregnancy is substantially more common in the Latino community (23). One study's link between HCV infection and pregnancy-related cholestasis provides evidence that 15.9% of pregnant women who test positive for the HCV antibody experience cholestasis (24); conversely, the second study reports that 20.3% of HCV pregnant women with positive RNA test results also had cholestasis (25).

The most common liver disease among pregnant mothers is gestational cholestasis, also known as intrahepatic cholestasis. While it usually poses little risk to the mother, it may cause significant harm to the developing fetus (26). Hormonal and environmental variables most likely carry the gene for ICP in genetically sensitive women (28, 29). HCV infection in ICP can alter liver transaminase levels and cause bile acid concentrations in the blood to rise (30). Based on clinical data, a research investigation diagnosed gestational cholestasis. It noted that pruritus existed at the start of pregnancy, persisted until birth, and then vanished without any associated medical disorders (31,32). ICP is more prevalent in women with HCV infection than in women without HCV infection, suggesting a clear correlation between the two (33). Compared to women who have both ICP and HCV infection have a much greater viral content, while women who have HCV infection have a lower viral content (34, 35).

Association of HCV and ICP:

Pregnancy-related cholestasis can occur due to changes that HCV infection causes in hepatocytes and biliary epithelial cells (36). According to a research study by Paternoster et al. (25), bile salt levels were significantly lower post-delivery than when the patients were admitted. Still, alanine transaminase (ALT) and aspartate transaminase (AST) levels were higher in the ICP females who were HCV-RNA positive in the post-delivery period than during the pregnancy and at the time of delivery. Hepatitis C and ICP have a robust positive correlation before and after the ICP diagnosis. Since the precise mechanism underlying the correlation between HCV and ICP is unclear (37). The prevalent ABCB11 genotype also causes elevated bile acid levels in HCV-infected patients. Additionally, it has been demonstrated that this ABCB11 polymorphism is linked to ICP (29, 38).

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According to in vitro research, HCV inhibits the liver's ABC transporter multidrug-resistance-protein 2 (MRP2), which prevents the liver from transporting several dangerous substances (39). This may result in elevated progesterone and estrogen levels as well as an increased risk of ICP during pregnancy (40). The cellular surface transfer of cholestatic metabolites by MRP2 is necessary before inhibiting bile salt export pump (BSEP) activity (41). One could assume that inhibiting MRP2 activity would be beneficial for controlling bile acid efflux (41, 42). To find this disparity, more investigation is required. According to a different in vitro research, people with chronic HCV infection tend to have greater levels of fibrosis and reduced expression of activated aryl hydrocarbon receptor (AhR), which can affect how Na+-taurocholate co-transporting polypeptide (NTCP) is regulated (43). Despite the observed changes, some studies revealed no apparent variation in NTCP expression in individuals with chronic HCV infection. More studies are needed to clarify this disparity. Systemic bile acid accumulation is a defining feature of intrahepatic cholestasis of pregnancy (ICP), a disease caused by bile acid transport dysfunction. Pregnant women who test positive for HCV have a greater risk of ICP, according to several studies (44).

A research study compared obstetric and laboratory parameters between the HCV-RNA-positive and control groups. Their results showed that the ICP HCV-RNA positive group had lower ALT and AST serum levels than the ICP HCV-RNA negative group and a significantly lower gestational week (27 ± 4 weeks) at the onset of symptoms. The gestational week of the ICP HCV-RNA negative group was reported to be 31 ± 5 weeks (25). The fluctuation in AST and ALT values between HCV-RNA positive and negative individuals can be explained by the discharge of endogenous interferon from the placenta during pregnancy (45, 46). Interferon production may be the source of changes in the viral load or a reduction in liver enzymes. Conversely, other research revealed that interferon has little effect on removing viruses. Other factors, such as immunological tolerance or hemodilution, may also lower serum transaminases during pregnancy (20, 47). Immunosuppressive cytokines and other hormones synthesized during pregnancy, including sex hormones, may alter the immunological response against HCV (48).

HCV antibody-positive pregnant women on methadone face a greater risk of developing cholestasis during pregnancy, and even at modest doses of maternal methadone, their newborns experience higher withdrawal symptoms (49). Because of this, it is highly recommended that all pregnant women, those at risk of contracting hepatitis C, and those with abnormal transaminase levels be screened for HCV antibodies (50).

Preterm Birth:

Preterm birth, or birth before the 37th week of pregnancy, is more common in women who have HCV infection (49, 51). There is contradictory evidence regarding the link between HCV infection and the probability of preterm delivery. Maternal chronic HCV infection increases the risk of perinatal and obstetrical illness (52). Preterm birth is the primary cause of perinatal illness and death (53). Intraventricular hemorrhage, respiratory distress, necrotizing enterocolitis, sepsis, and hyperbilirubinemia are among the many conditions premature newborns are susceptible to (54). According to Almario et al., there is a higher chance of long-term neurodevelopmental damage and behavioral aftereffects (55). Co-infection with HBV and HCV increases a woman's risk of preterm birth and cesarean delivery (10). Chronic HCV is linked to preterm birth, but numerous other factors can influence how well an HCV woman's pregnancy goes (56).

Insulin resistance during pregnancy is the cause of gestational diabetes mellitus. Elevated levels of VEGF and Ang-2 in the placenta are linked to preeclampsia in women infected with HCV. For mothers who drink alcohol, HCV increases the risk of premature birth.

Serious consequences include a high risk of preterm birth, gestational hypertension, low birth weight, and small gestational age at delivery for pregnant women with HCV. (57). Premature delivery is associated with chronic inflammation brought on by HCV infection and alcohol use throughout pregnancy (58). HCV-positive women were likely to have alcohol dependence in their sample investigation. Therefore, alcohol is the major risk factor for preterm birth (Fig. 1) (58, 59). When a pregnant woman has a liver illness or other chronic inflammatory conditions, her chance of preterm birth is markedly enhanced (60).

Preeclampsia:

Preeclampsia is a severe pregnancy condition in which trophoblast invasion failure results in an inadequate blood supply for the fetus (61). Preeclampsia during pregnancy can have detrimental effects on both the mother and the unborn child (62). The risk of preeclampsia and HCV are inversely correlated. However, a prior investigation established a high-risk percentage of preeclampsia in HCV (63). According to Stokkeland et al., preeclampsia is not very common in mothers with HCV (51). According to a previous study, preeclampsia is a systemic sickness that develops in the placenta and is characterized by substantial maternal endothelial dysfunction (64). Because of severe endothelial dysfunction and an angiogenic imbalance, preeclampsia is a severe systemic illness that results in maternal hypertension (65). According to a study, the clinical manifestation of preeclampsia is caused by an angiogenic imbalance, which is brought on by an excess of placental anti-angiogenic factors and a deficiency of pro-angiogenic factors like VEGF and Ang-2 (66). Two studies discovered that HCV patients had elevated levels of VEGF and Ang-2 in their bloodstream (Fig. 1) (67).

Gestational Diabetes Mellitus (GDM):

Intolerance to glucose at varying concentrations is known as GDM, and it is initially identified in pregnant mothers (68). Among the perinatal and maternal effects of GDM in later life for women are cesarean delivery, birth trauma, macrosomia, and diabetes; the risk can be reduced with various treatments (69). Chronic hepatitis C (CHC) and chronic hepatitis B (CHB) infection are linked to insulin resistance (IR), which raises the likelihood of developing GDM (70).

If a pregnant woman has HCV infection, her pregnancy may not go well, and her newborn may have various results (71). Pregnant HCV-positive women are more prone to develop GDM as they gain weight. Babies delivered to HCV-positive moms require hospitalization to the newborn intensive care unit (NICU) and assisted

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ventilation due to low birth weight (LBW) and small gestational age (SGA). Instead of being drug users, HCV-positive mothers need these treatments very much (15, 71). GDM is more common in pregnant women who test positive for HCV and have insulin resistance (Fig. 1). HCV is detected in the pancreas and causes dysfunction of beta cells (72, 73, 74).

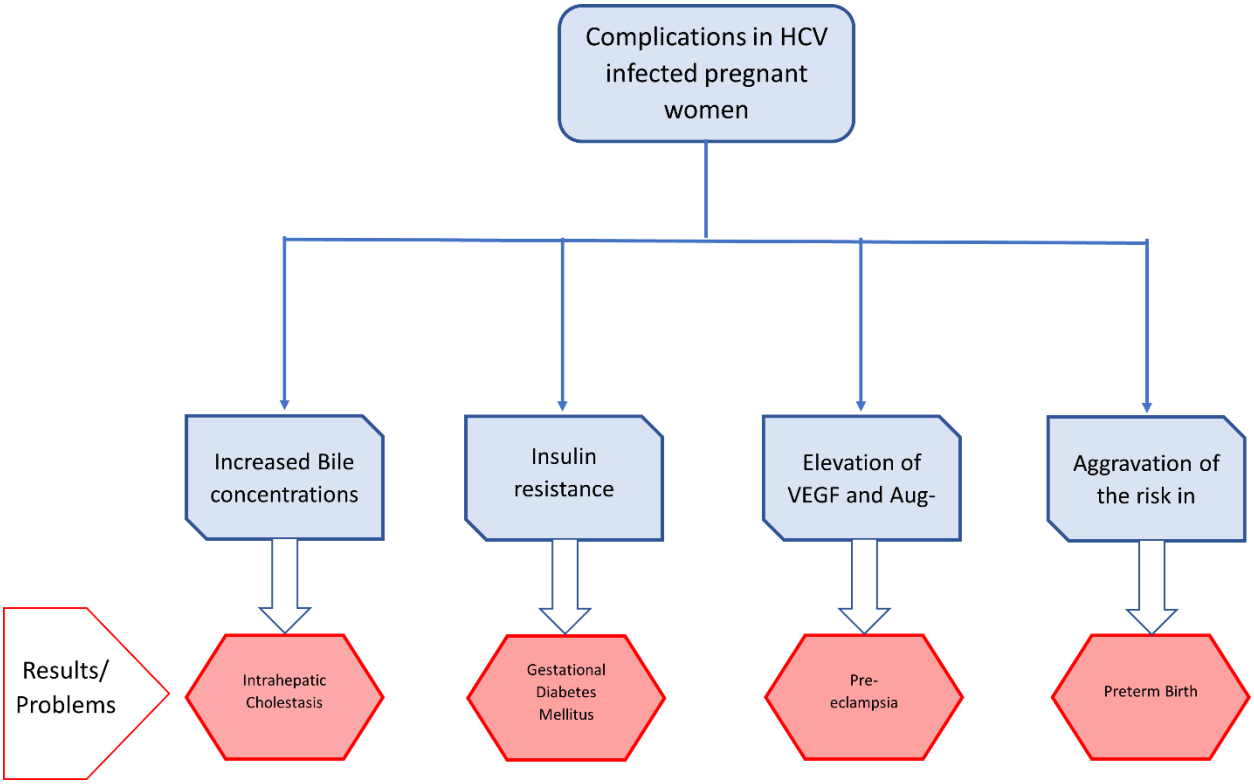

Figure 1. HCV associated maternal complications during pregnancy.

Vertical Transmission of HCV from Mother to Infant:

Numerous investigations have documented the vertical HCV transmission rate in the literature, which falls between 0.7 and 6.7% (75, 76). There is a considerable chance of HCV transfer from a woman to her child due to several variables. A contributing factor to an increased risk of vertical transmission is a high viral load during pregnancy or at the time of delivery (77, 78, 79, 80). According to certain studies, co-infection with the human immunodeficiency virus (HIV) and an elevated viral load are critical determinants in the transfer of viruses from mother to child (75, 81). More recently, contradictory results from other investigations have emerged, demonstrating no relationship between viral load and vertical transmission (82, 83).

While many studies have demonstrated that women who inject drugs are at a higher risk of transmitting HCV to their offspring (83, 84), other research has found no meaningful correlation between a mother's history of injecting drugs and the risk of HCV transmission (85). Other factors, such as gestational age or birth weight (BW), showed no HCV transmission (85, 86, 87). There is no proof to suggest that the HCV genotype encourages the vertical transmission of HCV (88). Another sizable investigation found no link between vaginal birth and a higher risk of vertical transmission in pregnant HCV patients (84). There was a significant correlation between the perineal or vaginal laceration and a higher likelihood of vertical transmission (89). An extensive investigation conducted in UK and Irish centers demonstrated a significant correlation between a lower risk of vertical transmission and elective cesarean sections (90).

According to two studies, girls were more likely than boys to contract HCV, possibly as a result of the hormonal or genetic responses that differ between them in response to HCV infection (85, 91). Accordingly, the female transmission rate was 3.5%, while the male rate was 1.4% (Table 1). Numerous studies found no link between breastfeeding and the risk of perinatal HCV transfer to newborns (85, 91, 92). Therefore, breastfeeding should be permitted in HCV-positive mothers (85, 92).

Table 1. Risk Factors for Vertical Transmission of HCV

Risk factors for vertical transmission of HCV	Rate of vertical transmission
High viral load	Conflicting results
High viral load together with HIV co-infection	Increased risk of transmission
Intravenous drug use	Conflicting results
Gestational age of the fetus or low birth	There is no risk of transmission
Viral genotype	There is no risk of transmission
Vaginal delivery	There is no risk of

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	transmission
Vaginal laceration	Increased risk of transmission
Elective cesarean section	Lowered risk of transmission
Gender of the baby-female fetus	Increased risk of transmission
Breast-feeding	There is no risk of transmission
Prolonged premature rupture membrane	Increased risk of transmission

Premature Rupture of Membrane (PROM):

The membranes usually rupture during the first contraction; however, if the rupture occurs prior to the contraction, it is deemed premature. It has also been observed that these early ruptures do not affect the transmission of HCV from mothers to their offspring (93). Nevertheless, a protracted rupture of the membrane after delivery raises the possibility that the newborn will get HCV-positive mother blood, which would then infect the offspring (77, 94). Premature fetal membrane rupture was significantly more likely in HCV-positive children than in HCV-negative children. Therefore, compared to uninfected children, infected children typically require longer times for membrane rupture and labor (77). Because of the PROM and intra-amniotic infection, the HCV-positive women underwent a cesarean surgery. The primary cause was a placental rupture with preterm ruptured membranes (95). Transmission of HCV increases with a more prolonged rupture of the membrane (96).

According to an observational study, cesarean section delivery of newborns before membrane rupture may lower the expected rate of perinatal HCV infection transmission from HCV-positive moms (86). Another study shows that elective cesarean sections are preferred instead of emergency cesarean sections (89). Before membrane rupture, an elective cesarean section is advised since this may reduce the amount of blood transfer from the mother to the fetus. Women who had HIV and HCV infections at the same time were also included in this investigation (97, 98).

Neonatal Complications:

Low Birth Weight:

HCV can persist in the kidney, heart, ovaries, pancreas, and placenta (99). During pregnancy, the placenta is a vital organ for the intrauterine growth and development of the fetus (100). In numerous investigations, it has been shown that excessive inflammation impairs uteroplacental hemodynamics, which is crucial for adverse perinatal outcomes such as low birth weight, IUGR, and mortality (101,102). Infants of HCV-positive women have more chances of LBW (100). HCV increases systemic and local inflammatory responses linked to atherosclerosis (103, 104, 105).

Compared to HCV-negative people, the HCV-positive populations that are neither diabetic nor obese had higher levels of anti-inflammatory cytokines (106, 107). Previous investigations confirm that placental inflammatory lesions are more prevalent in LBW newborns (108, 109).

Low birth weight (LBW) or intrauterine fetal growth restriction (IUGR) newborns were found to have a higher chance of being admitted to a neonatal intensive care unit (NICU), developing hypothermia, developing neonatal sepsis, and having respiratory issues, according to a 2014 study (110). A newborn born with LBW has a higher chance of metabolic abnormalities, neurological and behavioral diseases, and cardiovascular problems in later life (111).

Fetal Distress:

The primary cause of liver infections is hepatitis B virus (HBV) transmission during pregnancy (112). Prenatal transmission risk is predicted by maternal co-infection with HIV and HCV, maternal history of IDU, and maternal HCV infection of the mother's sexual partner. According to a 2009 study, cesarean delivery is not recommended for pregnant women with HCV infection due to the associated risk of perinatal transfer of the virus from mother to child during the surgery (91). However, a meta-analysis of eight research, including the significant European Pediatric HCV Network study, discovered that cesarean delivery does not lessen the risk of perinatal HCV transmission from mothers with HCV RNA positive to their offspring (113).

HCV-induced maternal anemia, one of the most common nutritional deficiency issues pregnant women face, is linked to fetal discomfort. It's frequently regarded as a risk factor for unfavorable pregnancy outcomes (114).

Pregnant women with HCV infection and drug abusers have more excellent rates of perinatal morbidity and mortality. Pregnant women who abuse opiates are more likely to give birth to babies who are born with lower birth weights (115, 116).

Prematurity:

A baby born prematurely is born before 37 weeks of pregnancy, as opposed to the standard 40 weeks (116). Maternal HCV infection is significantly associated with an increased risk of preterm birth (117). Maternal hepatitis B or C carrier status is associated with several outcomes during the prenatal and neonatal period, including low birth weight, preterm birth, early gestational age, jaundice, fetal distress, and congenital abnormalities (12, 118). It appears that babies born to women infected with hepatitis C may have unfavorable birth outcomes, such as preterm, low birth weight, and congenital abnormalities (119).

Treatment of HCV in pregnant women:

Antiviral treatment is not recommended in pregnant women with HCV infection (120). Treatments with interferon and ribavirin are typically avoided during pregnancy (121) because of their psychiatric side effects; pegylated interferon could be difficult for women who have previously had postpartum depression (122). The risk of teratogenicity associated with ribavirin persists for up to 7 months after therapy ends. Therefore, preventive therapy for newborns or during pregnancy is not indicated (123). Treatment options should be made available to HCV-positive women before pregnancy. By prioritizing treatment over pregnancy, the drawbacks are addressed, including the elimination of the risk of HCV transmission to infants and the reduction of the risk of hepatic advancement in mothers (124).

Screening for HCV infection is suggested for pregnant women with risk factors for HCV exposure (125). Pregnant women with risk factors for HCV exposure should be screened for HCV infection, and postnatal hepatitis C therapy is available for mothers with the disease and their children who carry the virus by vertical transmission from the mother (49). It is essential to create

non-teratogenic medicines since they can lower the likelihood of mother-to-child transmission (MTCT) by up to 10% and the long-term health effects of vertical transmission of HCV infection (9,126). Moreover, the increased effectiveness of contemporary pharmacological therapies necessitates reevaluating the value of routine HCV screening for expectant mothers (127,128).

Conclusion and Future Perspectives:

In addition to posing pregnancy-related issues, HCV may have a variety of adverse effects on the fetus. Antiviral therapy is not recommended in HCV pregnant women because of its adverse impact on the recipient. The concern regarding the association of HCV-induced preterm birth and antiviral therapy along with neonatal complications in pregnant women needs additional research to be entirely resolved. Future research is required in the context of neonatal complications caused by HCV. Laboratory and experimental investigations on the long-term effects of antiviral medicine in pregnant women with HCV may promote the development of more effective HCV therapies for pregnant women.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

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Approved by the department Concerned.

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Approved

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The authors declared absence of conflict of interest.

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