

Hepatitis C virus infection and pregnancy – not the simplest combination

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ABSTRACT

Hepatitis C virus (HCV) infection has a rather noticeable effect on pregnancy, considering the fact that two entities are involved: the mother and the fetus. It has become a worldwide health threat, so forward actions are to be taken in order to minimize the impact on morbidity and mortality caused by this virus. We conducted this review article based on data from 33 articles published between 2016 and 2021 that assessed both maternal and fetal outcomes, long term effect on children born to HCV infected mothers, screening for HCV among pregnant women, vertical transmission, recommendations for the management of HCV infected pregnant patient, available medication and the need for treating HCV during pregnancy. The majority of authors concluded that HCV has a greater impact on the fetus/child rather than on mother and also, most of them are calling in for the need to treat this infection during pregnancy in order to diminish the risk of vertical transmission, therefore to reduce the incidence of HCV infection among infants. The necessity for further studies, especially on safety data for antiviral medication is imperative, as well as the need for new steps in downsizing the impact of HCV infection on individuals around the globe.

Keywords: HCV infection, pregnancy, outcomes, screening

INTRODUCTION

Hepatitis C virus (HCV) infection has become a real health problem globally, the latest estimations made by the WHO revealed around 58 million cases of chronic infection worldwide [1]. According to European Center for Disease Control (ECDC), in 2016 there were nearly 5.6 million cases of HCV infection in Europe [2]. It is worth mentioning that 1% to 8% of pregnant women across the world suffer from HCV infection [3,4]. The first step in trying to stop HCV infection from being a public hazard was the EU HCV Policy Summit in Brussels in 2016 whose main goal was to elaborate a plan to eliminate HCV in Europe until 2030 by reducing death rate and

new infections by 65% and 90% respectively [1,5,6,7].

Hepatitis C is an RNA-enveloped virus, from the Flaviviridae family [8]. It is classified into 7 genotypes which give the differences in genomic RNA length leading to various clinical manifestations, pathogenicity, responses to treatment and to the inability of creating an efficient anti-HCV vaccine [9]. HCV can cause both acute and chronic infection and a diverse range of clinical manifestations, from totally asymptomatic (almost 75% of cases) to mild symptoms such as abdominal pain, jaundice, malaise, anorexia or nausea or to a chronic, life lasting disease [3,10,11]. After the first 6 months of infection, which is considered the period of acute infec-

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tion, spontaneous viral clearance can be observed in 15% to 20% of the cases; the remaining cases develop chronic HCV infection ranging from gradually evolving liver impairment to more serious complications, such as cirrhosis (which could eventually lead to the necessity of liver transplant) or hepatocellular carcinoma [3,12].

Transmission of HCV occurs primarily via blood-to-blood contact, but other routes of infection are also feasible: sharing contaminated objects, uncertain medical procedures, occupational exposure to contaminated blood, vertical transmission (mother-to-child), and, although considered very low, sexual intercourse [3,4,7,8,13]. With regards to mother-to-child transmission (MTCT), it is approximated to nearly 5% and rising to 10% in case of HIV co-infected mothers [8].

Lately there has been a substantial improvement regarding cure rates of HCV infections alongside the development of direct acting antivirals (DAA), setting aside pegylated interferon alpha and Ribavirin from the first line of treatment [13,14]. Even so, considering the minute number of studies on pregnant people and the insufficient safety data, no antiviral medication is yet approved to be administered during pregnancy [4,12].

EFFECT OF HCV INFECTION ON THE PREGNANT WOMAN

There could be a debate on whether the changes in the pregnant patient's wellbeing are the consequences of the infection on the gravid or the consequences of pregnancy on the chronically infected woman. Truthfully, in this matter it would be necessary to know the HCV infection status of the patients before conception. Nonetheless, many authors observed a tendency of hepatic transaminase level to decrease during the last two trimesters of pregnancy, whereas the level of HCV RNA rises to a peak in the third trimester, reverting to the pre-pregnancy levels after delivery [3,13,15]. These changes occur due to the under expression of the maternal immune system as a result of the immunosuppressive cytokines released during pregnancy [6,15]. Therefore, it is thought that this very immune modulation is responsible for the hepatic damage, rather than the direct HCV cytotoxicity [3,4,15]. Additionally, Page et al. [4] cite in their article studies demonstrating the diminished risk of fibrosis progression during pregnancy and opines that pregnancy has a favorable effect on HCV related hepatocellular damage. Further interesting observation was made by Hashem et al. in his study published in 2017 [16] regarding spontaneous clearance of HCV. His team revealed undetectable viremia 12 months after delivery in 26.9% of the eligible cases and they considered this phenomenon to be related to an escalation of

HCV-specific T cells after parturition due to the immune system rebound.

At the same time, there have been observed several adverse maternal outcomes related to chronic HCV infection, including preterm birth, premature rupture of membranes, gestational diabetes, preeclampsia, miscarriage, intrahepatic cholestasis of pregnancy (ICP) or poor birth outcomes in infants [3,6,10]. However, authors could not clearly stipulate that all these complications are directly related to the HCV infection and not to other confounding factors [3,6]. With regard to the risk of preterm birth, there are some possible explanations, namely: placental changes and disproportionate local/systemic inflammatory response caused by the HCV infection [6,13]. As far as gestational diabetes is concerned, various articles present this maternal complication as being associated with excessive weight gain during pregnancy [3,4,12]. What is more, Terrault et al. [17] describes in their article published in 2020 additional complications in HCV infected pregnant patients, e.g. antenatal or postpartum hemorrhage, which are directly related to the progressive hepatic damage, prolonged time of prothrombin particularly, rather than to HCV per se. Likewise, they mentioned a possible association between HCV infection and fertility issues. In agreement with the last cited study, Rezk et al. [18] states in his article that anemia and low prothrombin level are the main causes for postpartum hemorrhage, also that maternal mortality was predominantly caused by the consequences of chronic hepatic disease, such as hematemesis, postpartum hemorrhage, and hepatic coma.

Wijarnpreecha et al. [19] published in 2016 a meta-analysis regarding the association and risk of ICP in HCV infected pregnant women. According to them, ICP is among the commonest origins of liver damage in pregnant population and it becomes clinically manifested during the last trimester of pregnancy when level of transaminase and bile acids rise and patients report pruritus. They found a higher rate of ICP in the HCV infected group and also a substantial higher rate of later HCV infection in pregnant women with ICP compared to those who did not present with ICP. Moreover, they present some theories that might account for the occurrence of ICP in HCV infected pregnant women, as follows: a) down-regulation of the multidrug resistance protein 2 by the HCV in parallel with high levels of pregnancy hormones (e.g. estrogen and progesterone) resulting in a deficiency in transportation of numerous toxic substances; b) cytopathic effects of HCV on biliary epithelial cells and hepatocytes conducting to a decreased biliary excretion and an enhanced intracellular storage of bile acids. Later on, Hamburg-Shields et al. [12] presented in their

article an increased risk of still-birth among women with ICP and they recommend intensive antenatal surveillance and delivery at 36-38 weeks gestation.

One interesting study was published in 2018 by Hagstrom et al. [20] on pregnancy outcomes in women suffering from cirrhosis. The authors investigated the risk of adverse pregnancy outcomes in a cohort of more than 1.3 million cases of cirrhosis among pregnant patients. Although they analyzed all kinds of cirrhosis etiology, 74% of the cases were due to viral and autoimmune liver diseases. There were no cases of maternal mortality found in their study, hence pregnancy modifications of the abdominal pressure and Valsalva maneuvers exerted during child-delivery corroborated with portal hypertension and the increased possibility of esophageal varices (as consequences of cirrhosis) can lead to a high risk of bleeding from the varices. The aforementioned study of Rezk et al. [18] also describes the risk of variceal hemorrhage in pregnant women suffering from chronic viral hepatitis and recommends avoidance of pregnancy among women with previous episodes of bleeding from esophageal varices, as well as those suffering from cirrhosis.

Among HCV infected people, there is a subcategory of HIV co-infected patients and Benhammou et al. [21] conducted a study investigating whether co-infections (HBV + HIV and HCV + HIV) lead to unfavorable pregnancy outcomes and poor response to antiretroviral medication. Their results indeed showed a higher rate of ICP, gestational diabetes or preterm delivery in the HCV-HIV co-infected group. In addition, a lower immunological response to antiretroviral treatment during pregnancy was observed in the co-infected group compared to the HIV mono infected group, which is associated to the extensive CD4 cell apoptosis triggered by the HCV co-infection.

VERTICAL TRANSMISSION OF HCV INFECTION

Vertical transmission (VT) is defined as viral passage from the infected mother to the child, transmission that can occur during the pregnancy, during labor or in the postpartum period [3,4]. VT is responsible for the majority of HCV infection cases in children [3]. With regard to in utero transmission of the virus, many authors reached the conclusion that neonates with positive viremia at birth or shortly after birth were exposed to the virus during pregnancy, therefore the transmission occurred in utero [6,17,22]. One of the incriminated theories of in utero transmission suggests transcytosis or trophoblast-mediated endocytosis of viral particles [22].

Risk factors involved in VT mentioned in various articles are maternal viral load (VL), prolonged rup-

ture of membranes and a long lasting labor, HIV co-infection, invasive fetal monitoring [3,23,24,25]. Generally speaking, there is a 3% to 10% risk of VT, and it rises in women with HCV-HIV coinfection [15]. In 2016, Bal et al. [23] published a study conducted over a period of 16 years, resulting in a rate of 3.5% of HCV infection transmission in children born from chronically HCV infected mothers. In the before mentioned study of Benhammou et al. [21], the ratio of HCV vertical transmission from HCV-HIV coinfecting mothers was 5.9%. Chappell et al. [26] also studied the incidence of MTCT and their article revealed a 8.4% rate of HCV transmission and a 7.2% rate of chronic HCV infection in children.

A substantial number of articles attribute maternal viremia to MTCT, stipulating that only detectable viral load could be responsible for or increase the risk of VT [4,14,17,25], or even that the level of maternal viremia might be related to the type of HCV infection in children (chronic versus transient) [27].

With respect to postpartum transmission, breastfeeding might be the only way of VT, and although breast milk contains small amount of viral load, breast feeding is considered safe and it is not discouraged amongst HCV infected mothers [3,8,14,24]. Breastfeeding should only be suspended in case of cracked or bleeding nipples [15,17,24].

Unfortunately, there is no available procedure or technique that could downsize the risk of HCV transmission to the child, but there are several which can increase the risk and need to be avoided [4,27]. To begin with, in case a pregnant patient is in need of an invasive prenatal procedure, it is recommended to avoid transplacental procedures, thus they should be advised in favor of amniocentesis over chorionic villus sampling [3,14]. With regard to labor and delivery, it has been noticed that invasive fetal monitoring, prolonged labor, more than 6 hours of ruptured membranes or episiotomy could increase the risk of VT, whereas type of delivery has no influence on the risk of transmission [3,4,14,15]. Therefore, women with chronic HCV infection should not be discouraged to deliver vaginally and usual obstetric management should be applied in spite of the HCV infection [3,15]. Cesarean section is not decreasing the risk of VT, thereby C-section it is not a recommendation for HCV infected women, unless they are HIV coinfecting, in which case elective cesarean operation does lower the risk of VT [4,14,22].

As Chappell et al. [24] properly stated in their article published in 2020, the most efficient solution to considerably reduce the incidence of perinatal HCV transmission would be to acquire antenatal viral clearance.

IMPACT OF HCV INFECTION ON FETAL OUTCOMES AND THE RISK FOR LONG TERM MORBIDITY IN CHILD

The most commonly encountered fetal outcomes in case of HCV infected mother listed in the medical literature are low birth weight, small for gestational age, fetal growth restriction and the necessity for assisted ventilation and admission to the neonatal intensive care unit (NICU) [3,4,6,14]. Also, HCV infection in mothers appears to constitute a risk factor for feeding difficulties noted in newborns and other neonatal complications, such as intraventricular hemorrhage, cephalhematoma, brachial plexus injury, fetal distress or neonatal seizures [3].

Rezk et al. [18] assessed in their study also fetal outcomes and they found a rate of low birth weight of 32.2%, a percentage of low Apgar score at 5 minutes of 25.7% and a ratio of neonatal mortality of 6.4%. In addition, 16.9% of the neonates required admission to NICU and 13.4% necessitated assisted ventilation.

In recent years, several studies evaluating long-term complications in children born to HCV infected mothers were published. For instance, in 2019 were issued two valuable articles assessing the risk of respiratory and gastro-intestinal morbidity in this subpopulation. Govrin-Yehudain et al. [28] proved the association between HBV and HCV infections in mother and long term respiratory complications in children. Their hypothesis that sustain this association are related to the immune-mediated mechanisms that chronic HCV infection implies, among them a higher tendency to autoimmune diseases leading to depositions of immune complexes, therefore to the development of vasculitis as well as the effect of excess TNF-alpha released in the circulation of infected organisms on surfactant, more precisely higher levels of TNF-alpha lead to lower levels of surfactant protein C. A noticeable information from this study regards the rate of HCV infected infants, which was zero. Yoles et al. [29] described in their article published in 2019 HCV chronic infection in mother as an independent risk factor for the long-term gastro-intestinal outcomes in children. They incriminate changes of the microbiota along with epigenetic changes in mother caused by infectious hepatitis, which can lead to changes in infant's microbiota and fetal lipid and glucose metabolism. The same team published in 2021 a study they conducted over 24 years [30] showing the association between HCV carrier status in mother and further neurological morbidity in their offspring. They found a higher rate of hospitalization for neurological complications such as developmental or movement disorders in children born to chronic viral hepatitis infected mothers. Once more, epigenetic changes and changes of microbiota seem to be responsible for these outcomes, along with alteration

of the immune system, but further studies on the subject are needed in order to accurately claim these phenomena as responsible for neurological consequences in this subpopulation. Moreover, Freha et al. [31] conducted a study which revealed that HCV infection in mother could be responsible for endocrine morbidity in their children. They found an elevated incidence of hospitalizations due to endocrine disorders in the specified category of children concluding that mothers' HCV infection is an independent risk factor for endocrine morbidity among their offspring. As previously mentioned, HCV infection leads to a higher incidence of autoimmune phenomena, therefore to a higher risk of developing anti-thyroid antibodies which cross the placenta, increasing the risk among children for developing further hypothyroidism.

TREATMENT OF HCV INFECTION IN PREGNANCY

Up until last decade, the standard treatment scheme for HCV chronic infection consisted of pegylated interferon alpha and Ribavirin, a therapy resulting in a sustained viral response (SVR) in 40% to 80% of patients [4]. By that time, taking into account that Ribavirin has embryocidal and teratogenic effects, it is contraindicated in pregnancy [3,4]. Apart from malformations observed in studied animals (malformations of the skull, gastro-intestinal tract, palate, jaw, limbs, skeleton and eye), it has been noticed that Ribavirin can cause sperm abnormalities and that it can be detected in non-plasma compartments for up to 6 months after administration [3,4,13]. Therefore, medical societies strongly recommend avoidance of pregnancy in female patients administering Ribavirin as well as female partners of patients who are under treatment with Ribavirin and up to 6 months after finishing therapy [3,4,13].

Sinclair et al. [32] published in 2017 a study regarding the risk of teratogenicity of Ribavirin exposure during pregnancy and over the 6 months before conception. Their study resulted in 11 birth defects outcomes, 9 of them consisting in structural defects and the remaining 2 in genetic/chromosomal diseases; these last 2 cases they considered to be hardly likely caused by Ribavirin exposure. The authors consider that the analyzed group is rather small to be considered significant and that their results might also have an alternate etiology.

Introduction of direct antiviral agents (DAA), whose SVR reaches up to 90% or above, not to mention their superior tolerance and shorter period of administration (8 to 12 weeks), redefined the treatment of chronic C virus hepatitis [3,4,13]. In present times, data on DAA's safety in pregnancy are still limited. Taking all these into account, specialists

had a rather reticent attitude towards HCV infection treatment during pregnancy, pleading for treating infected women before pregnancy or after finishing breastfeeding [3,4,6,13,27]. Though recently, based on the ongoing studies, medical position related to DAA therapy in pregnancy might incline towards administering it [6,12,22,33]. One interesting fact regarding treatment of pregnant HCV infected patients is the possibility of spontaneous postpartum viral clearance, meaning that this small category of women will not need further antiviral medication; consequently, one thought might be to wait for 12 months after delivery, check on mother's VL and then decide whether or not should they receive treatment [6,12].

Frericksen et al. [22] published a review in 2019 assessing that moment's knowledge of maternal exposure and safety of DAA during pregnancy and lactation. The authors found researches on DAA effects during pregnancy as one area of interest in the scientific world, not only for their potential of curing the mother, but also for preventing VT. Available studies showed DAA do pass the placental barrier, therefore their effects on the fetus can be achieved directly (with the potential of producing malformations) or by causing placental dysfunctions. All things considered, Frericksen and his team opine the ideal scenario would be to obtain a negative VL in pregnant women by the moment of delivery, thus taking into account the risk of preterm birth in HCV infected patients and the duration of treatment, antiviral therapy should be administered from 23/24 to 27/28 weeks of gestation, by-passing in this manner the critical period of organogenesis.

It is common sense to accept that complementary studies are needed in order to establish a standardized guide for treatment of HCV during pregnancy, though current findings might seem optimistic. Additionally, a recent survey addressed to both pregnant and not pregnant women with current or previous HCV infection [34]. More than 50% were in favor of receiving antiviral treatment during pregnancy if it would decrease VT despite the lack of safety data.

MANAGEMENT OF HCV INFECTION IN PREGNANT PATIENTS

At the time being it is well known that no antiviral medicine has been proved to be safe in pregnancy. At the same time, it is absolutely necessary to have knowledge of the HCV carrier status among pregnant women, firstly to be able to scan for further possible complications or comorbidities and secondly to have a record of potential cases of HCV infection in the pediatric population [4,35]. To dig deeper into this subject, the concept of universal

screening for HCV infection in pregnant patients still stands for a disputable issue. Whilst some medical societies plead for risk-based screening during pregnancy [3,4], others try to draw attention on the importance of universal screening and ground their proposal on studies regarding cost-efficiency [24, 33,36,37].

Implementing HCV screening as a general recommendation, would give us the opportunity to identify HCV infection in female patients before conception, in which case antiviral treatment can be administered and the risk of VT becomes null [35], or in early pregnancy and medical specialists are able to discover and manage correctly pregnancies at risk: refer patients to a hepatologist, submit them to additional blood tests and specific investigations, monitor closely their pregnancy in order to prevent adverse outcomes [3,4]. What is more, in the event of antiviral therapy approval during pregnancy, viral clearance could be achieved by the time of delivery, thus decisively lowering the risk of VT [6,22]. Another aspect regarding antiviral approval concerns children's therapy. At this time, DAAs are not approved for use in children under 6 year old [6]. One interesting observation has been made in various studies, namely spontaneous clearance of C virus by the age of 3, pushing many specialists to plead for delaying therapy up until 36 months [24, 26,27].

Doctors insistencies to treat infected mothers during their pregnancy period is related to their facilitated access to health care, naming it their "window of opportunity" as many are lost to follow-up after giving birth [6,22,33,38].

Further advantages of universal screening aim proper diagnose of HCV infection among children born to infected mothers. Vertical transmission of HCV is considered the main cause of chronic infection in pediatric population [15,23] even though only a modest number of cases are being identified or correctly screened due to the lack of universal recommendations for HCV screening in pregnancy and neonatal period [26,35,38]. Consequently, identifying the HCV carrier status of the mother, neonatologists will be aware of the potential cases of viral infection in newborns, acknowledging the real magnitude of HCV infection situation among infants [35].

One aspect often disregarded aims the psychological impact this entire phenomenon has on both the mother and the child, as well as on the whole family. First of all, HCV infected children tend to be stigmatized and considered social outcasts by their peers [38] and we can blame this on offspring's immaturity. Moreover, risk based screening for HCV infection among female patients culminates in mistakenly marginalization of infected pregnant wom-

en [39]. Not in the least, it has been observed a poor quality of life in families confronting with a sick member, especially if the infant is involved [27].

CONCLUSIONS

HCV infection in pregnant patients can have an unfavorable impact on both the mother and child. Even though this viral infection causes more drastic outcomes in fetuses/children, potential complications of pregnancy must not be neglected. As stated before, HCV infection during pregnancy has be-

come a worldwide public health threat, consequently expecting women have become a population of interest in the medical field. Therefore, it is common sense to acknowledge that universal screening guidelines for identifying infected women (ideally before pregnancy, but also during the first trimester) stands for a real cornerstone in fighting this phenomenon. This and the possibility of approving antiviral treatment during pregnancy could seriously lower the risk of VT, making the goal of the United Nations, i.e. eliminating HCV in Europe by 2030, more feasible.

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