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Perinatal transmission of hepatitis C virus: an update

Mortada H.F. El-Shabrawi[1], Naglaa M. Kamal[1], Engy A. Mogahed[1], Mona A. Elhusseini[2], Mohamed F. Aljabri[3]

[1]Department of Pediatrics and Pediatric Hepatology, Faculty of Medicine, Cairo University, Egypt
[2]Department of Obstetrics and Gynecology, Red Crescent Hospital, Cairo, Egypt
[3]Department of Pediatrics and Pediatric Neurology, Alhada Armed Forces Hospital, Taif, Saudi Arabia

Corresponding author:
Naglaa M. Kamal MD
Department of Pediatrics and Pediatric Hepatology
Faculty of Medicine
Cairo University
Cairo, Egypt
Phone: +96 6565580081
E-mail: Nagla.kamal@kasralainy.edu.eg

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Abstract

Infection with hepatitis C virus (HCV) is a major health problem worldwide. A large proportion of perinatal HCV infections are silent and may present later in adulthood with long-term complications. HCV has no effective immune prophylaxis and hence appropriate follow-up of all infants born to HCV-infected mothers is necessary. Universal antenatal screening for HCV is largely debatable. Intrauterine and partum transmission of HCV are both possible and higher rates are associated with a high maternal serum viral load (> 10^6 copies per milliliter), concomitant HIV infection, prolonged or difficult delivery, and invasive fetal monitoring during delivery. Infection during pregnancy and infancy needs to be investigated more in order to design management strategies for perinatal transmission of HCV most effectively. The recently approved new-generation, oral, direct-acting antiviral drugs may open a new era in HCV therapy for pregnant women and infected infants if proved to be safe during conception and infancy.

Key words: hepatitis C virus, perinatal transmission, vertical transmission, children, direct-acting antiviral drugs.

Introduction

Hepatitis C virus (HCV) infection is a major health problem all over the world. It can cause chronic hepatitis and liver cirrhosis and represents the main risk factor of primary hepatocellular carcinoma [1]. It is estimated to chronically affect ~3% of the world's population (~170 million people), with more than one million new cases annually [1]. There is great variability in HCV prevalence rate from one country to another and even within the same country from one region to another [2]. Moreover, there are controversies between researchers as some of them suggested a decreasing trend of HCV prevalence [3] while others expected an increasing burden [4, 5].

Percutaneous inoculation is the commonest mode of HCV transmission, but sexual, household, occupational, and vertical transmission can also occur [6]. Nowadays, HCV is the main indication for adult liver transplantation [7]. Until 2011, the historically accepted standard of care therapy was pegylated interferon (Peg-IFN) and ribavirin (RBV), producing a sustained virologic response in almost half of the patients for

genotype 1 and higher rates up to 50% for other genotypes [8].

When considering the health burden and dynamics of HCV infection, pregnant women and their infants represent a group with special physiological changes which can cause a modified course of chronic HCV and subsequently needs special considerations [9].

Recently, HCV has emerged as the most important cause of chronic viral hepatitis in children in many countries. Before universal screening of blood and blood products, which started in 1992, HCV was transmitted mostly through transfusions and organ transplants [10]. Nowadays, and especially in developed countries, perinatal transmission of HCV is considered the main cause of HCV infection in children [11]. Perinatal transmission leads to acquisition of HCV very early in life – in the intrauterine period (antenatal/antepartum), during delivery (natal/intrapartum) or after delivery (postnatal/postpartum) – with the consequence of chronic liver disease and liver cancer in early adulthood [12, 13]. Seropositive children at 18 months of age or older are generally believed to have been perinatally infected with HCV. Testing for HCV-RNA is essential to differentiate those with chronic infection from those who have spontaneously cleared the virus [14]. Screening of pregnant women who do not have known risk factors for infection as a method of prevention of perinatal transmission has remained a great challenge owing to the unavailability of HCV vaccine and the lack of an approved antiviral therapy during pregnancy [15].

Some authors hypothesize that routine prenatal HCV screening to identify HCV-infected women unaware of their infection may lead to performing other interventions during labor and in the perinatal period, reducing the risk of mother-to-infant transmission [16].

Pegylated interferon and ribavirin are no longer recommended for treatment of adults [17]. The advent of the newly available treatment regimens based on very effective and well-tolerated direct-acting antiviral agents (DAAs) will probably change the whole image dramatically [15].

Epidemiology

Worldwide HCV infection prevalence in pregnant women

The general HCV infection prevalence in pregnant females in the world is around 1–8%. Perinatal transmission occurs from infected mothers to their offspring in 3–10% of cases [18–21], with 10,000–60,000 new pediatric perinatal infections per year in developed countries [9].

The European Pediatric HCV Network reported that HCV-PCR testing has low sensitivity at birth which increases to 70–85% after 1 month of age [22]. This is partially explained by the very low viral loads in the first month of life and the wide incubation period of HCV that may extend up to 6 months. Therefore, a negative PCR test at birth is not a true indicator of the infant's HCV infection status. On the other hand, a negative PCR test after 12 months of age should be confirmed with anti-HCV, which is considered the gold standard, to detect children who have achieved spontaneous viral clearance [9].

In pregnant women, the prevalence of HCV infection varies considerably from one part of the world to another, 0.5–2% in high income countries and 5–15% in developing countries [23–25] with 3–10% perinatal HCV transmission to their offspring [26–38]. Consequently, the pediatric HCV infection rate is very low in developed countries (0.05–0.36%), it increases to 1.8–5.8% in some developing countries, and is maximum in Egypt, Sub-Saharan Africa, the Amazon Basin and Mongolia. A higher seroprevalence (10–20%) has been reported among children with other risk factors of exposure such as those treated for malignancies, or undergoing hemodialysis or surgery [28–30]. The HCV prevalence among pregnant women in Europe, the Americas and Asia is shown in Table I [39–72].

HCV prevalence among pregnant women in Arab countries

HCV infection is a serious health problem in Arab countries, with very wide variability in prevalence rate from one country to another, 0.4–23% [34, 35], owing to different levels of development of health care systems and awareness, and availability of budget and resources [33] (Table I).

HCV prevalence among pregnant women in African countries

Africa is geographically divided into 5 regions (Table I) with heterogeneity in religion, culture and practices, and with a high human immune-deficiency virus (HIV) burden in sub-Saharan areas. Arab countries lie at the northern region. Most of the countries in the other four regions suffer from political conflicts, military confrontations, droughts and famines, leading to large numbers of internally and externally displaced people which might increase the prevalence of sexually transmitted diseases [73].

A systematic review and meta-analysis study published in 2015, conducted in 21 sub-Saharan African countries, found that the overall HCV prevalence among pregnant women in antenatal clinics was 3% and was 2% in the Central African region [74].

Table I. HCV prevalence among pregnant women in Arab and African countries

Country	HCV prevalence in pregnant women	Special comment
America	In the United States, the estimated prevalence of antenatal HCV infection is 1–2.5%; some studies estimate the prevalence to be as high as 4% [39, 40] In Brazil, HCV prevalence in young pregnant is 0.098% [41]	–
Europe	Variable [42] from 0.1% in Slovenia [43] to 0.8% and 0.9% in the United Kingdom and Norway respectively [44, 45]	In the general population of Serbia about one quarter of human immunodeficiency virus (HIV) infected persons also have HCV co-infection [46]
Asia	The highest prevalence of HCV is noted in Central Asia (3.8%), East Asia (3.7%), and North Africa/Middle East (3.6%) [47, 48]	–
Saudi Arabia [35, 36, 49]	0.7%	–
Yemen [37]	8.5%	–
Syria, Jordan and Lebanon [35]	No data	This reflects underestimation of the magnitude of the problem in this region [35]
Iraq [38]	3.21%	–
Egypt [50, 51]	8.6%	Egypt is one of the areas of highest prevalence of HCV among the population in general and pregnant women in particular [50, 51] with genotype 4 being predominant (90%) [52]
Sudan [53–55]	0.6%	Prevalence in pregnant women (0.6%) is lower than that of the general population (2.2–3.0%) [53–55]
Libya and Maghreb region	Lowest in Libya [56–58] (< 1%), followed by Tunisia [59–62], the Kingdom of Morocco [59, 63], Algeria [59], and Mauritania [64–66]	Genotype 4 is the most prevalent in Libya, which is the same as in Egypt, while genotype 1 [57, 61, 62, 64] is predominant in the rest of Maghreb countries, like the nearby western countries [58] HCV prevalence variation might be explained by the interaction with western countries in Maghreb countries with more open communities than in Libya [58]
Eastern Africa	2–2.9% [65] in some reports, and 0% to 2% in others [66]	Studies of HCV prevalence are scarce and controversial [65]
Southern Africa	Has not been well studied [65]	Endemicity estimates put the region in the intermediate group [65]
Central Africa	Prevalence is 4.3% among pregnant women [68–70]	One of the most heavily infected parts of the world, reaching > 13% in some countries [67]. Cameroon has the highest prevalence (13.8%), followed by Burundi (11.3%) and Gabon (9.2%) [67]
Western Africa	The prevalence among pregnant women is 3% in Nigeria [71] and 2.2% in Burkina Faso [72]	Highly endemic for HCV [71, 72]

Natural history of HCV infection in infected pregnant women

Pregnancy is considered a state of relative immunodeficiency [75], especially T-cell mediated immunity [76], with a shift in the Th1/Th2 balance toward the Th2 response, and expansion of regulatory T-cells [23], to safeguard against rejection of the newly developing embryo by the maternal immune system [77]. This alteration in the immune system directly alters the natural course of HCV infection, giving more room for the virus to replicate while suppressing its immune-mediated damage to hepatocytes, which is demonstrated by the surprising finding of increasing viral RNA load with concomitant decreasing ALT levels [23, 78, 79].

It was reported that estrogen suppresses the intra-thymic T-cell differentiation while activating the extra-thymic pathways during pregnancy [80,

81]. After delivery, the maternal immune system regains its baseline activity with the resultant decrease in viral load and increase in immune-mediated hepatocyte damage and consequently ALT level [82]. Spontaneous resolution of HCV viremia postpartum has also been reported [9].

Interestingly, greater rates of viral clearance after pregnancy were reported, compared to a non-pregnant control group, which can be attributed to the loss of pregnancy-induced physiological immunosuppression with a surge in maternal cellular immune activation with a decrease in Th2 activity and a rebound increase in Th1 activity, combined with fewer viral quasispecies, resulting in the clearance of HCV infection [83, 84]. Several reports have recommended initiating antiviral therapy at this time, augmenting the natural defense mechanism [9].

Another maternal obstetric complication of HCV is the earlier and more frequent development of cholestasis in HCV infected than non-infected women, which could be attributed to the altered transport of sulfated hormones in the liver, a failure in the transport of toxic substances, and a defect of the bile salt export pump [24, 85–87].

Natural history of HCV infection in perinatally infected children

It is believed that maternal HCV infection can affect the babies in different ways:

1. It can lead to increased incidence of intrauterine growth retardation, low birth weight, a higher neonatal intensive care admission rate and more frequent need for ventilatory support [88]. Other authors found no evidence to support that [84, 89, 90].
2. It was found by Berkley *et al.* [91] that babies born to anti-HCV positive mothers were more likely to have neonatal abstinence syndrome when adjusted for the dose of methadone used. This may be due to the poor metabolism of methadone in the HCV-infected liver; hence, a considerably higher dose is transferred transplacentally compared to women who are not infected.
3. Perinatal infection may happen as the presence of reactive neutralizing antibodies in the mother does not prevent perinatal HCV transmission or progression to chronicity in infants and children. The timing of perinatal transmission of HCV is based on the appearance of HCV-RNA positivity in the newborn [92].

Perinatal infection can lead to: i) chronicity in 80% of cases [77], moreover, the appearance of cross-reactive neutralizing antibodies during the chronic phase does not correlate with better control of viremia or with the clearance of HCV [92], ii) a wide range of variability of ALT levels in the first year of life, when high values may be found, indicating acute hepatitis [92, 93].

Biology and genetics of perinatal HCV transmission

Other authors attributed the biology of perinatal transmission of HCV to the infection of maternal peripheral blood mononuclear cells (PBMCs) by the virus and to the presence of the negative strand of HCV inside the PBMC, which is a sign of viral replicative activity [94].

It was noted that HLA antigen class II diversity between the mother and the baby induces rapid clearance of infected maternal cells through the newborn alloimmune anti-major histocompatibility complex response; this was demonstrated to be protective for perinatal transmission of HCV [95]. A biologically reasonable explanation has been provided for these apparently contradictory results involving the important role of the interaction between HLA antigen class II molecules and CD4+ T lymphocytes in the immune response and in allo-recognition [95].

With regard to single nucleotide polymorphisms of interleukin (IL)-28B that have been demonstrated to be important in determining spontaneous and treatment-induced clearance of HCV in children and in adults [96–98] recently, neither the mother's nor the children's IL-28B status was associated with an increased risk of perinatal transmission [98].

High levels of NK cells in the placenta of HCV-positive mothers were detected by some researchers [99]. These cells had greater cytotoxicity in the HCV-positive mothers. This may be an explanation for the relatively low rates of vertical transmission, though the increased cytotoxicity of the NK cells may also lead to a higher risk of preterm delivery [9].

Risk factors of HCV perinatal transmission

Although HCV perinatal transmission is lower than that of HBV and HIV [32, 100–102], it has a disadvantage, there being no currently available vaccines that can prevent or reduce its transmission [23, 103], with almost 33% of the infected children acquiring infection intrauterine and up to 50% intrapartum [104].

There are many factors that can increase or decrease the risk of HCV perinatal infection, as shown in Table II [105–124]. It has to be kept in mind that viremia per se is a risk factor for perinatal transmission independently of HCV RNA levels [17, 125]. As a consequence, each condition associated with the possible contact of HCV-infected maternal blood with the fetus or the newborn can be theoretically considered a risk factor [126].

Table II. Factors affecting the risk of HCV perinatal transmission

Factors increasing the risk of HCV perinatal transmission:
High maternal serum viral load at the time of delivery as it indicates active viremia [18–20, 105, 106]. The risk is proportionate to the increase in levels of viral load above 105 IU/ml [19, 107] and reaches a maximum at levels above 107 IU/ml [108]
High maternal serum ALT levels in the 12 months before pregnancy and/or at the time of delivery as it is considered a reflection of higher viral replication rate [23, 101] that may cause more extensive hepatic damage and subsequently elevated ALT [79, 109–111]
Rupture of membranes > 6 h [9, 23, 86, 107]
Prolonged and/or difficult deliveries [112]
Fetal sex remained the only risk factor significantly associated with HCV perinatal transmission, with girls as twice as likely to be infected as boys in one study [113] and 8 to 3 in another study [114]. This finding likely reflects hormonal or genetic differences in susceptibility or response to infection. Maternal infections increase fetal cortisol and dehydro-epiandrosterone synthesis [115]. Androgens may influence the immune response [116]; estradiol protects stimulated feline lymphocytes from apoptosis, and human male and female fetuses exhibit differences in regulation of the cytokine network [113]
Twin pregnancies discordant for transmission of HCV are another supporting factor [117]
Use of invasive procedures during pregnancy such as amniocentesis, although its impact is still debatable [23, 77]
Studies reported conflicting findings on the effect of invasive fetal monitoring [9, 18, 118]. Some authors suggested that there is higher risk of HCV exposure with the use of scalp electrodes [19]
Concomitant HIV infection: – Increases risk by 3- to 4-fold [19, 119–121] – A meta-analysis showed that HIV and HCV co-infection increases the odds of HCV perinatal transmission by 90% [121] – The incidence of HCV vertical transmission is approximately 3–5% in HCV RNA-positive mono-infected mothers, but can be as high as 19% in HIV-co-infected [9] – Even when controlling HIV, presence of HCV viremia increases the odds of vertical transmission 2.82-fold. This is thought to be attributed to the higher HCV load in immunosuppressed HCV/HIV-co-infected women than in women with HCV infection only [122]
Factors decreasing the risk of HCV perinatal transmission:
Specific HLA markers such as HLA D13 and HCV-specific CD4 reactivity decrease transmission, highlighting the potential importance of immune-mediated mechanisms in HCV spread [123, 124]
High NK cells in the placenta. These cells had greater cytotoxicity in the HCV-positive mothers. This may be an explanation for the relatively low rates of vertical transmission; however, the increased cytotoxicity of the NK cells may also lead to a higher risk of preterm delivery in HCV-positive mothers [9]

On the other hand, some factors seem to play no role in HCV perinatal transmission, such as HCV genotype [23], intrauterine device (IUD) insertion [18], and past history of liver disease, blood or blood products transfusion, and hepatitis during pregnancy. Also, no consistent relation was observed between the presence or absence of HCV infection in the first versus the second or subsequent infants [105], even in identical twins [127].

Breast feeding and HCV perinatal transmission

Although HCV-RNA is detectable in colostrums [31] and theoretical transmission may be possible through breast feeding, discouraging breast feeding in HCV-infected mothers is not recommended [9, 23, 79, 86, 128], as there is no proof of any increase in the risk of HCV transmission with breast-feeding [105]. The European Paediatric Hepatitis C Virus Network [21] noted no difference in infection rates in breast-versus formula-fed infants in a study carried out on 1,758 infants born to HCV-infected mothers.

Most researchers found that the HCV viral count in breast milk is extremely low and that it likely becomes inactivated in the digestive tract of the infants [129–133].

The risk increases if there is exposure to maternal blood with breast-feeding if the mother has cracked or bleeding nipples [9].

On the other hand, human breast milk may even have a protective antiviral role against HCV transmission. Pfaender *et al.* [134] designed an interesting study using a productive cell culture system to show that HCV infectivity is markedly decreased after incubation with human breast milk. They studied the effect of variables including HCV genotype, temperature, and milk from different species on the breast milk antiviral effect

and they found that it was independent of any of those variables. Integrity of the viral envelope was impaired and free fatty acids, likely produced by the action of milk lipase, are responsible for the reduction in viral infectivity. Lipases present in human milk (lipoprotein lipase and bile salt stimulated lipase) produce products that are incorporated into the viral envelope, destroying viral integrity and decreasing its infectivity. Thus, milk digestion products released in the stomach might be able to inactivate residual viral particles, which otherwise could be transmitted upon breastfeeding [134].

Mode of delivery and HCV perinatal transmission

The effect of the mode of delivery on HCV perinatal transmission is controversial. Some authors suggested that with vaginal delivery, there is increased risk of HCV transmission to the baby due to increased risk of exposure to virus-contaminated maternal blood. Consequently, cesarean section may hypothetically be a better option [135].

Four large studies [18, 19, 118, 129] were carried out on 2,080 mothers and their infants, comparing the HCV transmission risk with elective cesarean (group 1) versus vaginal or emergency cesarean section (group 2), where three of them [118, 129] reported higher transmission risk with group 2, which was statistically significant in only 1 one of them.

On the other hand, other studies, including the European Pediatric Hepatitis C Virus Network study on 1,758 mothers and their infants, reported that delivery mode does not appear to influence the risk of transmission [9, 18, 23, 79, 86].

Management opportunities

Treatment regimens

According to the recent 2018 ESPGHAN guidelines, Peg-IFN and RBV combination is no longer recommended for HCV treatment in children [17]. Today, DAAs are changing the image completely [15]. The ESPGHAN recommend that all treatment-naïve and treatment-experienced children with chronic HCV infection be considered for therapy [17]. Liver biopsy is not routinely indicated in children with chronic HCV infection but it should be evaluated on a case-to-case basis. Treatment is considered without delay in presence of significant fibrosis and cirrhosis, extrahepatic manifestations and co-morbidities increasing the risk of rapid evolution of liver disease (solid organ or hematopoietic stem cell transplant recipients, other patients undergoing immunosuppressive treatments) [17].

Target groups

HCV-PCR positive pregnant women

- Pregnancy and the immediate post-partum period appear to be a highly unique period in the interaction between HCV and the chronically infected host. These periods appear to force some adaptation of the virus, due to the intense physiological changes, which may offer a therapeutic window when more suitable agents come into use [9].
- Peg-IFN and ribavirin therapy: They are no longer recommended for HCV treatment in adults in general [17] and pregnant women in particular. Peg-IFN can cause major psychiatric side effects during pregnancy, especially as pregnant females have a high susceptibility to post-partum depression [9]. Moreover, the injectable solution of Peg-IFN contains benzyl alcohol, which can be transmitted via the placenta and could cause infant toxicity [72]. On the other hand, ribavirin is absolutely contraindicated not only for HCV-infected pregnant women or childbearing women but also for HCV-infected men, whose partners may become pregnant due to its significant teratogenic effect [107].
  With the era of DAAs, knowing the pregnant women's HCV status with subsequent treatment of mothers after delivery and clearing the HCV infection before subsequent pregnancies to completely eradicate HCV; vertical transmission in the future became a realistic strategy [15].

HCV-PCR positive neonates and children

Close follow-up of newborns to rule out vertical infection is essential for detection of pediatric HCV, especially after the recently reported safety of DAAs in children as young as 6 years old [136].

Treatment of infected females before pregnancy

In the new era of DAAs, treatment of infected females before pregnancy seems to be an intelligent strategy.

Preventive regimens

In our opinion, DAAs' success and safety should encourage healthcare systems' standards of care to include universal screening of HCV during pregnancy. The benefits for women and their children should outweigh the additional costs for healthcare systems.

With successful treatment of the mother, there is the potential for completely eliminating vertical HCV transmission. At present, as treatment is not yet available during pregnancy, only children born from subsequent pregnancies would be protected,

following antenatal diagnosis and treatment after delivery [15].

Conclusions

The HCV perinatal infection is an underestimated health problem which can lead to major chronic complications in later life. This necessitates intimate follow-up of all infants born to HCV-infected mothers by anti-HCV serology and PCR to apply timely management when needed. In areas with high HCV prevalence, a national screening program for HCV in females before marriage is warranted so as to start DAA treatment before marriage, which in turn can eradicate HCV vertical infection.

Understanding the modulatory effects of pregnancy on the immune response to HCV within the mother's liver as well as how HCV infects the fetal liver as it matures is necessary to allow better therapy.

The recently approved DAAs may open a new era of treatment of HCV infection during pregnancy in the near future. Universal HCV screening during pregnancy is a fair, realistic strategy which should be implemented in healthcare systems worldwide.

Conflict of interest

The authors declare no conflict of interest.

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