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REVIEW

Vertical hepatitis C virus transmission: Main questions and answers

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Abstract

Hepatitis C virus (HCV) affects about 3% of the world's population and peaks in subjects aged over 40 years. Its prevalence in pregnant women is low (1%-2%) in most western countries but drastically increases in women in developing countries or with high risk behaviors for blood-transmitted infections. Here we review clinical, prognostic and therapeutic aspects of HCV infection in pregnant women and their offspring infected through vertical transmission. Pregnancy-related immune weakness does not seem to affect the course of acute hepatitis C but can affect the progression of chronic hepatitis C. In fact, postpartum immune restoration can exacerbate hepatic inflammation, thereby worsening the liver disease, particularly in patients with liver cirrhosis. HCV infection increases the risk of gestational diabetes in patients with excessive weight gain, premature rupture of membrane and caesarean delivery. Only 3%-5% of infants born to HCV-positive mothers have been infected by intrauterine or perinatal transmission. Maternal viral load, human immunodeficiency virus coinfection, prolonged rupture of membranes, fetal exposure to maternal infected blood consequent to vaginal or perineal lacerations and invasive monitoring of fetus increase the risk of viral transmission. Cesarean delivery and breastfeeding increases the transmission risk in HCV/human immunodeficiency virus coinfected women. The consensus is not to offer antiviral therapy to HCV-infected pregnant women because it is based on ribavirin (pregnancy category X) because of its embryocidal and teratogenic effects in animal species. In vertically infected children, chronic C hepatitis is often associated with minimal or mild liver disease and progression to liver cirrhosis and hepatocarcinoma is lower than in adults. Infected children may be treated after the second year of life, given the adverse effects of current antiviral agents.

Key words: Hepatitis C infection; Pregnancy; Vertical transmission; Antiviral therapy; Prevention

Core tip: Hepatitis C virus (HCV) infection during pregnancy is an emerging problem. While not negatively affecting acute hepatitis, it may exacerbate chronic hepatitis and worsen liver function in woman with liver cirrhosis. HCV does not affect delivery outcome apart from an increased risk of premature membrane rupture and cesarean delivery. The mother-to-child HCV transmission rate is low (3%-5%) and is related to high maternal viremia, human immunodeficiency virus (HIV) coinfection, prolonged rupture of membranes, vaginal lacerations and invasive fetal monitoring. Cesarean delivery and no breastfeeding are indicated for HIV/HCV coinfected women. Antiviral therapy is not routinely offered to pregnant women and infants because of its side effects.

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INTRODUCTION

Since its discovery in 1989, hepatitis C virus (HCV) has been recognized as a global public health problem that affects about 3% of the world's population (150-200 million people)[1,2]. In the United States, almost 4 million people have been infected by the virus and more than half of these are estimated to have chronic hepatitis C[3,4]. In most European countries, the prevalence of HCV in the general population ranges between 0.5% and 2% (*i.e.*, 5 to 10 million people)[5]; the prevalence rate peaks in subjects between 40 and 59 years old[1,3].

HCV infection can cause chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). Acute HCV infection, which is asymptomatic in 50% to 90% of cases, can progress to chronic hepatitis in more than half of patients and can be associated with variable rates of fibrosis progression[1,3]. About 10% to 20% of patients with chronic C hepatitis develop cirrhosis 20-30 years after contracting the infection. Patients with liver cirrhosis have a risk of about 1% to 5% of developing HCC[1,3]. In addition, HCV can be associated with extra-hepatic complications such as lymphoma[4,6]. Notably, HCV-related liver cirrhosis is the major cause of liver transplantation in developed countries[1,3]. Unfortunately, the burden of liver cirrhosis, HCC and death related to HCV is expected to increase in the next few years[6], although the incidence of acute infection is declining[1,5].

HCV infection occurs after exposure to infected blood, through the parenteral and inapparent parenteral route[7]. Injection drug use, unsafe medical practices, high-risk sexual practices and birth to an infected mother are the most frequent routes of infection[3]. In most countries, only people with high risk behaviors are currently tested for HCV infection. However, the United States Center for Disease Control recommends HCV screening for all individuals born between 1945 and 1965 (irrespective of risk factors) because of the high prevalence of HCV infection in that birth cohort[8].

Despite research conducted in the last 20 years, an effective vaccine against HCV has not yet been developed. On the contrary, antiviral therapies are now available that guarantee viral clearance (also called "sustained virological response") in a remarkable percentage of patients affected by chronic hepatitis C.

An emerging problem is HCV infection during pregnancy. In fact, the incidence of pregnancies and deliveries has increased (four-fold and between 5% and 10%, respectively) in women over the age of 40 years in most western countries, including the United States[9,10]. Since these women are at a higher risk of HCV infection than younger women, physicians might have to treat an increasing number of HCV-infected pregnant women in the near future. The true size of the problem has not yet been defined; in fact, data related to the prevalence of HCV infection in pregnant women are largely discordant. Between 1% to 2% of pregnant women in the United States and Europe have been estimated to be anti-HCV positive[11-17] and more than 70% of them have HCV viremia[12,13]. The prevalence is reported to be higher in pregnant women with high risk behaviors for blood-transmitted infections (*i.e.*, intravenous drug use, multiple sexual partners, co-infection with human immunodeficiency virus (HIV), or who live in developing countries)[16-20]. Because HCV screening is recommended only for high risk subjects, a large number of infected women in the general population without classical risk behaviors or history of blood exposure eludes the screening strategy. Unfortunately, even in Italy, where a free-of-charge test for HCV, hepatitis B virus (HBV) and HIV is offered to all women from the 33th to the 37th week of pregnancy[21], many women remain untested until delivery.

Here we review the clinical, prognostic and therapeutic aspects of HCV infection in pregnant women, as well as aspects of HCV vertical infection. Specifically, we address the following topics: (1) Can pregnancy worsen HCV-related disease? (2) Can HCV increase obstetrical complications? (3) What is the risk of transmitting HCV infection to the newborn and how is it prevented? (4) What is the course of HCV infection in the newborn? and (5) What are the benefits and risks of antiviral therapy for the mother and her child?

HCV INFECTION AND PREGNANCY: RECIPROCAL EFFECTS

During pregnancy, the maternal immune system undergoes various modifications that enable tolerance of the paternal alloantigens, therefore preventing anti-fetal immune aggression[17,22,23]. In fact, consequent to these modifications, pregnant women experience a condition of immunological weakness that results in increased immunoglobulin production, a decreased T-cell mediated response (due to a shift in the Th1/Th2 balance toward the Th2 response) and expansion of regulatory T-cells[22]. Also, sex hormones and immunosuppressive cytokines produced by pregnant women may concur to modulate the immune response to HCV[22,23]. Pregnancy-associated immune modulation can also influence the immune response to HCV, thereby affecting both the maternal viral disease and mother-to-child transmission of the virus.

The innate immune system, through natural killer (NK) cells, also plays a role in modulating immune response to the virus. This process involves the interaction between the inhibitory NK cell receptor KIR2DL3, which belongs to the family of cell immunoglobulin-like receptors (KIR), and its human leukocyte antigen C group 1 (HLA-C1), which is an inhibitory receptor for self-MHC class I ligand. The effector functions of NK cells occur only when activating signals overcome inhibitory signals. Therefore, individuals with two copies of HLA-C1 alleles (HLA-C1C1) and homozygous for KIR2DL3 (which binds HLA-C1 with less affinity than

other inhibitory receptors) tend to resolve HCV infection. In these subjects, the weaker inhibitory receptor-ligand interaction is easily overridden by activating signals and results in a stronger activity of NK cells. This effect was demonstrated in Caucasians and African Americans with expected low infectious doses of HCV but not in those with high-dose exposure, in whom the innate immune response is likely to be overwhelmed[24].

Question 1: Impact of pregnancy on maternal HCV-related disease

Acute hepatitis C has been rarely reported during pregnancy[17,23,25]. Consequently, the data available are not sufficient to draw any conclusion about its course. The few reports available indicate that pregnant women with acute hepatitis C may have the same course and outcome as non-pregnant women, except for an increased risk of developing jaundice[17,23,25].

Various studies have been carried out on women affected by chronic hepatitis C who become pregnant. The results showed that serum aminotransferase levels (ALT) decrease and reach normal range during the second and third trimester of pregnancy[17,22,26,27]. The HCV viral load increases concomitant with the decrease in serum ALT and reaches a peak during the third trimester. These fluctuations, which are similar to those described in HBV-infected women during pregnancy[28], were not found in another study[23]. Only one study reported sustained clearance of HCV RNA during the second trimester of pregnancy[29]. After delivery, restoration of the maternal immune system results in a better control of HCV replication. In fact, exacerbation of chronic hepatitis C, including rebound of ALT levels and worsening liver histopathology (Knodell score, portal necrosis, lobular degeneration and inflammation) were reported in the postpartum period, together with a reduction in the plasma HCV load. It is feasible that the decrease in ALT levels and the increased HCV viral load observed in the third trimester of pregnancy in women chronically infected with HCV could be due to a pregnancy-associated decline in immune-mediated hepatocellular destruction. Indeed, expansion of $CD4^+$ $CD25^+$ Treg cells begins early in gestation and reaches a peak in the second trimester. $CD4^+$ $CD25^+$ T regulatory cells may affect the clinical presentations of chronic HCV infection by suppressing $CD4^+$ T cell responses. Le Campion *et al*[22] and Bolacchi *et al*[30] reported that the HCV-specific TGF-β response induced by $CD4^+$ $CD25^+$ (high) T cells was significantly greater in patients with a normal ALT level than in patients with abnormal ALT levels. This phenomenon is the hallmark of exacerbation of hepatic inflammation[17,22] which, in some patients, can worsen the course of chronic hepatitis C[31-35] but in a few cases it can be associated with viral clearance[36], suggesting that postpartum may be an optimal time to start antiviral therapy in the attempt to achieve a sustained response.

HCV-infected pregnant women seem to develop cholestasis earlier and more frequently than anti-HCV-negative women. This phenomenon has been attributed to 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[16,23,37-41], but its pathogenesis is still being debated.

Lastly, HCV-infected women with advanced liver disease seem to be at a high risk of developing liver decompensation, which results in worsening of the portal hypertension and coagulopathy[42-44]. Hence, pregnancy should be strongly discouraged in these women.

Question 2: Effect of HCV infection on pregnancy and delivery

Very few studies have investigated the impact of maternal hepatitis C infection on pregnancy outcome. Although it can be difficult to separate the role of HCV from other risk factors (*i.e.*, alcohol intake, tobacco smoking and drug abuse), the data available indicate an increased risk of gestational diabetes (reported in patients with excessive weight gain), premature membrane rupture and an increased rate of caesarean delivery in HCV-infected pregnant women than in anti-HCV-negative pregnant women[16,17,22,45-47]. In addition, various obstetrical complications have been reported in HCV-infected women, namely, higher rates of preterm delivery, placental abruption, low birth weight, prematurity, low Apgar scores at 1 min, increased neonatal jaundice, congenital malformations and newborn perinatal mortality[22,45,48]. However, these findings were not confirmed in other studies[23, 49,50].

Question 3: Risk of mother-to-child HCV transmission and preventive measures

Numerous studies have evaluated the risk of mother-to-child HCV transmission (vertical transmission) with conflicting results. In fact, the rates of transmission varied from 0% to 30%[11-20,22]. These large fluctuations are probably due to differences in study size (*e.g.*, the number of HCV-infected mothers enrolled), the study methodology (prospective or retrospective study; detection of maternal infection based on anti-HCV antibody positivity or on HCV RNA positivity) and the diagnostic criteria of neonatal HCV infection (*e.g.*, number of polymerase chain reactions performed and duration and timing of follow-up in the neonates)[14,15]. The rate of HCV transmission is estimated to be lower[14,15,17,23,51-57] than the rate of HBV and HIV transmission. However, unlike HIV-infected or HBV-infected pregnant women, no drugs or vaccines are available for HCV-infected pregnant women to reduce and/or prevent vertical transmission, which is the main cause of HCV infection in the pediatric setting[15,22,51]. Thus, when a HCV-infected pregnant woman asks "How can I avoid infecting my child?", the answer is unfortunately, "we do not know".

The pathogenesis of vertical transmission, specifically the timing and route of transmission of the virus, and the host's defense mechanisms are unknown. The timing of vertical transmission is based on the appearance of HCV RNA positivity in the newborn: if a neonate tests HCV-RNA-positive at delivery or within the first 3 d of life, he/she was probably infected *in utero* (intrauterine

Table 1 Clinical factors and risk of vertical transmission

Associated with vertical transmission
Pregnant woman:
High HCV viral load
Elevated ALT levels before pregnancy
HIV-HCV co-infection *iv* drug abuse[1]
Obstetric procedures:
Prolonged rupture of membranes vaginal and/or perineal lacerations
invasive monitoring of fetus intrauterine pressure catheter
amniocentesis (debated)
Father HCV infection[1]
Fetus gender[1]
Not associated with vertical transmission
Maternal HCV genotype
Mode of delivery[2]
Breastfeeding[2]

[1]To be confirmed; [2]Except in the presence of HIV-HCV coinfection. HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

transmission); if a neonate who tests HCV-RNA-negative in the first 3 d of life becomes positive, he/she was probably infected in the *peripartum* or *postpartum* period (perinatal transmission)[22,23]. The data available support both intrauterine[23,58,59] and perinatal transmission[22,23,53,60,61], the former accounting for 30% of cases and the latter for 40-50% of cases. Many sites of human placenta could act as HCV-receptors and/or entry cofactors (*e.g.*, claudin-1, occludin, SR-B1, LDLr or DC-SIGN)[22,23]. Consequently, they could be directly implicated in HCV infection of placental cells. However, the rate of vertical transmission (3%-5%) seems to be lower than the potential biological exposure of fetus/neonate to maternal HCV. In fact, in the case of intrauterine transmission, although maternal HCV RNA has not been detected in amniotic fluid[11], a very large amount of virus (1×10^{13} to 1×10^{14} virions) has been estimated to reach the placental bed during gestation[11]. Therefore, the fetus could be exposed to free virions or to the cell-associated virus that crosses the placenta[22] in a percentage higher than the reported transmission rate (30%)[22,62]. Also, in the case of perinatal transmission, leakage of maternal HCV-infected blood into the fetal bloodstream and/or labor trauma (which exposes the offspring to maternal HCV-infected blood)[15] occurs more frequently than vertical transmission of the virus (40%-50%)[15,22].

The reason for the low rate of vertical transmission is not known. Various biological and immunological factors could protect the fetus against HCV infection, *i.e.*, placental immune cells, fetal cellular adaptive immunity, fetal plasma inflammatory markers, maternal HLA class Ⅱ alleles and IL-28B genotype[22,60,63-65], but their role is poorly understood. Also, the suggested association with gender (girls seem to be infected twice as often as boys) could reflect biological differences in susceptibility or in the response to infection[66], although this has yet to be confirmed.

Many factors related to the status of pregnant women and delivery/obstetrical practices have been associated with an increased risk of transmission (Table 1)[11,16,17,22,23].

The first factor is the mother's viral load, especially at the time of delivery. In fact, there is evidence that HCV-RNA-negative mothers have a low risk of infecting their infant, whereas this risk increases in HCV-RNA-positive mothers parallel to increases in levels of viral load above 10^5 IU/mL[60,67] and reaches a maximum in women who have viremia levels above 10^7 IU/mL[68]. Moreover, a high maternal serum ALT level in the 12 mo before conception and/or at the time of delivery has recently been associated with a higher rate of vertical transmission. In fact, a high ALT level is a hallmark of high viral replication in both the maternal bloodstream and in mononucleated blood cells[22,54,55]. However, the effects of maternal HCV disease activity on vertical transmission are not completely understood. Lastly, HCV genotype is not considered a significant risk factor in terms of vertical HCV transmission[22].

The second factor is HIV co-infection, which can cause a three-four fold increase of the risk of mother-to-child-transmission[16,22,69]. How HIV-1 infection enhances the rate of HCV transmission is unclear. It is conceivable that HIV-1 infection facilitates HCV entry and replication in peripheral mononucleated blood cells[16,22,69].

Moreover, HIV induces immune suppression, which can result in a less effective HCV-specific innate or cell-mediated maternal immune response at the maternal/fetal interface[16,22]. On the other hand, HIV can infect trophoblasts, thereby compromising the integrity of the placenta and enhancing the passage of HCV through this barrier. HIV-associated chorioamnionitis could also induce placental microtransfusions through which HCV infection can be transmitted to the fetus[22,69]. Lastly, antiretroviral treatment of HIV/HCV co-infected pregnant women can dramatically lower the risk of HCV transmission from 19% to 8%[16]. Additional risk factors, namely, intravenous drug abuse by the mother and concomitant HCV infection of the father, have been proposed but have yet to be confirmed[16].

The main obstetrical factors associated with the risk of vertical transmission are prolonged rupture of membranes (more than 6 h before delivery), exposure of the fetus to maternal infected blood during vaginal delivery (consequent to vaginal and/or perineal lacerations) and invasive monitoring of the fetus with scalp electrodes or intrauterine pressure catheter placement[11,16,22,60]. Amniocentesis may contribute to the risk of maternal-to-fetus transmission[17,22], although its impact is still being debated[17]. On the contrary, neither the delivery mode nor breastfeeding (two main concerns for the pregnant woman) appear to influence the risk of transmission[11,16,17,22,66,70,71] in HCV-infected women. In fact, a cohort study of 1787 mother-child pairs showed that the rate of vertical HCV transmission was 6.2% and was not influenced by caesarean section[66]. The failed protective effects of cesarean delivery was confirmed in a meta-analysis study[72]. The issue of breastfeeding is more complex and needs to be discussed with the mother. In fact, although the amount of HCV in maternal milk and colostrum is very low and probably inactivated in the infant'

s digestive tract, the presence of cracked or bleeding nipples can be a contraindication to breastfeeding because it can expose the infant to contaminated milk. On the other hand, cesarean delivery must be recommended for HIV/HCV co-infected patients, associated with antiretroviral therapy to prevent or to reduce the risk of transmission of both viral agents[54]. Vaginal delivery and breastfeeding are contraindicated in HIV/HCV co-infected mothers[16,54,71,73].

Question 4: Outcome of HCV infection in the newborn

HCV infection is the most common cause of chronic hepatitis in childhood. The prevalence of pediatric infection seems to be very low in the United States and Europe (0.05%-0.36%), while it increases (1.8%-5.8%) in some developing countries and reaches its highest prevalence in Egypt, Sub-Saharan Africa, the Amazon Basin and Mongolia; the highest prevalence worldwide has been reported in Egypt (9% and up to 50% in certain rural areas)[22,74]. Vertical or perinatal transmission is the most common route of pediatric HCV infection[11] and can lead to an estimated 10000-60000 cases per year[11].

At the time of delivery and during the first year of life, the anti-HCV positivity detected in the newborn can be due to the passive transfer of maternal antibodies. Therefore, the diagnosis of HCV infection based on antibody assays in children of HCV-infected mothers before the age of 12 mo is not reliable[75]. The diagnosis can be made by testing neonates for HCV RNA, preferably 1 or 2 mo after birth[76]. Indeed, the sensitivity of PCR for HCV RNA is about 22% at birth and increases to 70%-85% 1 mo after birth. Similarly, the predictive positive value of PCR testing is 33% at birth and reaches 78% when the child is 9 mo old[77]. These findings could reflect the very low viral loads in the first month of age and/or the incubation period of HCV that ranges from 2 wk to 6 mo[11]. Notably, a negative PCR test at birth/first month of age cannot exclude HCV infection and must be confirmed by further testing.

Spontaneous clearance of HCV has been reported in up to 25%-30% of HCV-infected children[78,79] irrespective of the route of infection (vertical or parenteral transmission). However, the rate of chronicity seems to be higher in infants with perinatally acquired HCV infection than in infants infected by parenteral transmission[80-83]. Various factors are associated with HCV clearance, namely, a younger age of the child, normal ALT levels[84], the IL-28B genotype[74] and IFN-γ responses against structural and non-structural recombinant HCV antigens[85]. The clinical course of chronic HCV infection in childhood seems to differ from that in adulthood. Pediatric HCV infection is associated with minimal or mild liver disease. In fact, advanced liver damage is uncommon[86-88], although another study suggested that fibrosis can be severe in children despite the relatively short duration of infection[89]. Progression of liver damage in children depends on viral load, serum ALT levels, gender, ethnicity, obesity, toxins, environmental factors and co-morbid risk factors (hemolytic anemias, chemotherapy for malignancy, immunosuppression and concomitant HIV or HBV infection) and genetic factors such as the IL-28B genotype[90].

Differently from adults, data about the rate of progression from cirrhosis to HCC in childhood and early adolescence are scarce but it seems that HCC is rare in children with HCV infection[91] and the number of HCV-infected children requiring liver transplantation is low in developed countries[91]. Long-term studies are required to quantify the incidence of cirrhosis and HCC in adults who acquired hepatitis C infection by vertical transmission.

In childhood, membranoproliferative glomerulonephritis is one of the most frequent extra-hepatic manifestations of chronic HCV infection but, unlike adults, neither cryoglobulinemia nor lymphoma have been reported in children[91]. The involvement of the central nervous system in HCV-infected children could explain the developmental delay, learning disorders and cognitive deficits that have been reported in some cases[92,93].

Question 5: Antiviral therapy of hepatitis C in pregnant women and infants

The last, but not least, question regards the treatment of HCV infection in both the pregnant woman and the newborn. While some anti-HBV and anti-HIV drugs can be safely used to prevent or reduce the risk of vertical transmission, the two cornerstones of the standard-of-care treatment for HCV infection, namely, pegylated interferon (PEG IFN) and ribavirin (RBV), have several side effects or contraindications that limit their use during pregnancy and childhood[11,16].

The problem of therapy in HCV-infected pregnant women is not negligible. In fact, in a United States study of 45690 HCV-infected patients, pregnancy was the third most common contraindication (1.9%) to treatment, after bipolar disorders (6.5%) and anemia (5.9%). In addition, about 1.3% of women became pregnant during a median follow up of 33 mo[94]. Consequently, the concern is not only about the indication of antiviral therapy for pregnant women but also how to manage a woman who becomes pregnant during antiviral therapy. The answers to these issues are mainly based on limited clinical data. Recombinant interferon alpha is classified by the United States Food and Drug Administration in pregnancy category C. In fact, given its abortifacient effect in animals[1], it could have the same effect in humans[95,96] as PEG INF[97,98]. In fact, abortifacient effects have been observed in Macaca mulatta (rhesus monkeys) treated with interferon alpha-2b or alpha 2a during the early to middle fetal period of organogenesis (gestation day 22 to 70). Abortifacient activity was also observed in pregnant rhesus monkeys treated (500 times the human dosage) during late fetal development (days 79 to 100 of gestation). These drugs may impair fertility. In fact, in nonhuman primates, menstrual cycle irregularities, *i.e.*, prolonged or shortened menstrual periods and erratic bleeding (anovulatory cycle) have been observed and the females returned to a normal menstrual rhythm after discontinuation of therapy. Decreased serum estradiol and progesterone concentrations have been reported in

women treated with human leukocyte interferon. No mutagenic effects or toxicity has been reported. However, due to the species specificity of interferon, the effects in animals are unlikely to be predictive of those in man. Lastly, the injectable solution contains benzyl alcohol that can be transmitted *via* the placenta and could be toxic in premature infants. No effect on male fertility has been reported[95,96]. No studies on the teratogenic effect of PEG-IFN are available. Since non-pegylated interferon alpha resulted in a statistically significant increase in abortions of Macaca, PEG-IFN should also be assumed to have abortifacient potential. There are no well-controlled studies in pregnant women[97,98].

Nevertheless, in clinical practice, IFN-alpha is used to treat essential thrombocythemia in pregnant women to prevent or lower the risk of thrombocythemia-related fetal loss[99]. A systematic review of data about pregnancies exposed to IFN-alpha (60% of women had received IFN throughout pregnancy) showed that IFN did not significantly increase the risk of major malformation, miscarriage, stillbirth or preterm delivery above the rates observed in the general population[99]. Therefore, the treatment of HCV-infected pregnant women with IFN does not seem to entail a risk for the offspring. Data on PEG-IFN treatment during pregnancy are lacking. It is not known whether IFN is excreted in human milk. Given the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug based on the importance of the drug for the mother. The main concern of IFN therapy is not only the risk for the fetus, but also the risk of serious psychiatric side effects, namely exacerbation of postpartum depression[11]. Therefore, all pregnant women who are candidates for PEG-IFN must be carefully selected, also considering their psychological and psychiatric conditions.

The other drug available for HCV infection is RBV, which is classified by the USA Food and Drug Administration in pregnancy category X[100,101]. Ribavirin is absolutely contraindicated, not only for HCV-infected pregnant and childbearing women, but also for HCV-infected men whose partners may become pregnant. These subjects are recommended to take contraceptive measures during RBV therapy because of its significant embryocidal and teratogenic effects[1] in animals[100-102]. Malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract have been described in the offspring of female animals that have been directly exposed to the drug[102]. In addition, RBV caused cell toxicity, mutagenicity and a decrease in the epididymal sperm count in all the animal species studied; these sperm cell mutations are believed to cause cell death or to be associated with infertility[102].

In HCV-infected treated men, the RBV concentration was two-fold higher in seminal fluid than in serum[103]. In addition, the round cell/spermatozoa ratio (suggestive of spermatogenic abnormality) and the sperm DNA fragmentation index were significantly higher in a HCV-infected man during RBV therapy and returned to baseline levels only four and eight months, respectively, after treatment withdrawal[104]. All these data indicate the need to avoid pregnancy for longer than the recommended 6 mo after discontinuing RBV treatment in men[102].

Only a few cases of direct or indirect exposure to RBV have been reported in pregnant women and these resulted in healthy infants and no miscarriages or elective terminations[102,105-110]. However, it is difficult to quantify the true risk of direct or indirect exposure to RBV. Consequently, a Ribavirin Pregnancy Registry was established in 2003 to monitor pregnancy exposure to RBV. Between 2003 and 2009, 118 live births from mothers exposed to RBV (49 direct and 69 indirect exposures) were recorded. Birth defects were reported only in 6 cases (3 direct and 3 indirect exposures): torticollis (2 cases), hypospadias (1 case), polydactyly and a neonatal tooth (1 case), glucose-6-phosphate dehydrogenase deficiency (1 case), ventricular septal defect, and cyst of the 4th ventricle of the brain (1 case). Although these preliminary results did not indicate that RBV exerts a teratogenic effect, it is not possible to draw conclusions about the risk of direct or indirect prenatal exposure to the drug in humans[102].

More recently, new therapeutic approaches targeting essential components of the HCV life cycle have been developed, including the protease inhibitors (boceprevir, telaprevir) and polymerase inhibitor (sofosbuvir), indicated mainly for the treatment of chronic hepatitis C patients infected by genotype 1 virus.

Boceprevir and telaprevir are classified by the United States Food and Drug Administration in the Pregnancy Category B[111,112]. In fact, although no adequate and well-controlled studies are available in humans, the absence of negative effects on fetal development in animals (mice, rats and rabbits) seems to indicate *"no evidence of risk in humans"*[2], although the chance of fetal harm still remains possible. Boceprevir did not cause genotoxicity in *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosomal aberration in human peripheral blood lymphocytes and mouse micronucleus assays[111]. Nevertheless, reversible effects on fertility and early embryonic development in female rats have been reported, as well as decreased fertility in male rats, most likely due to testicular degeneration. No effects on fetal development have been observed in rats or rabbits exposed to boceprevir at doses higher than the recommended dosage in humans[111]. A clinical study showed the absence of testicular toxicity in humans[107] at the recommended clinical dose, while a decrease in percent motile sperm and an increase in non-motile sperm count occurred in rats at exposures 0.3-fold the human recommended clinical dose[111]. Telaprevir did not result in fetal harm in mice or rats. The effects on fertility parameters in rats (*e.g.*, decreased percent motile sperm and increased non-motile sperm count) may be associated with testicular toxicity in male animals. Telaprevir did not affect the birth body weight of rat offspring[112].

Since these drugs cannot be used as monotherapy but have to be associated with PEG-IFN and RBV (triple therapy), their use is contraindicated during pregnancy

and childbearing females have to take adequate contraceptive measures. Similarly, the excretion of protease inhibitors into human breast milk is not known yet; in lactating rats, the levels of both boceprevir (or its metabolites) and telaprevir in the milk were slightly higher than levels observed in maternal blood[111,112]. Because of the potential adverse reactions in infants, nursing must be discontinued prior to starting the treatment[111,112].

The last licensed polymerase inhibitor (sofosbuvir[1]) is classified by the United States Food and Drug Administration in the pregnancy category B. In this case also, adequate and well-controlled studies with the drug in pregnant women are missing but no effects on fetal development have been observed in rats and rabbits at the highest doses tested[113]. Similarly, no data are available on the excretion of sofosbuvir and/or its metabolites in human breast milk; no data are available for the pediatric setting[113]. When used in triple therapy (associated with PEG IFN and RBV), sofosbuvir is contraindicated as well as the protease inhibitors; when used in regimen IFN and RBV-free, it could be a promising option in the treatment for the pregnant women.

The therapy of HCV-infected infants is still being debated in the absence of a consensus on when or how to optimally treat. Because of the low rates of vertical transmission (overall between 3% and 5%) and the favorable course of hepatitis C (relatively high rate of spontaneous resolution of HCV infection, the lack of symptoms, *etc.*) in the first class of age, the rationale is to only treat the child with chronic hepatitis C at high risk of progression[11]. A previous meta-analysis showed that children had a higher SVR and tolerated IFN alpha monotherapy better than adults[114]. In contrast, there are few pediatric trials on the standard of care therapy; a systematic review of 4 randomized controlled trials and 31 non-randomized studies showed that children had an SVR similar to adults[115]. The standard of care therapy seemed to be well tolerated in the large majority of children; the main adverse effects (*i.e.*, flu-like symptoms and neutropenia) were mild or moderate. The rate of treatment discontinuation was low but half of the children required a reduction of PEG-IFN dosage[115].

The decision of when to start antiviral therapy in the early ages must be based on several factors: the estimated/known duration of infection, HCV genotype, presence/degree of fibrosis, co-morbidities, predicted parents' compliance with the therapy, expected adverse events and possible interference with home life or school activities and the IL-28 genotype[111]. Injectable solutions of IFN contain benzyl alcohol and are not indicated for use in neonates or infants because of reports of death in neonates and infants exposed to excessive doses of benzyl alcohol[91-94].

It has been suggested that treatment with weight-adjusted doses of PEG-IFN and RBV should be offered to HCV-infected children over 2 years old and with significant hepatic fibrosis (detected by liver biopsy or transient elastography), irrespective of HCV genotype[116]. Moreover, such treatment should be avoided in children under 2 years of age because of the risk of PEG-IFN-related neurotoxicity[115] and growth suppression described in older children[11,116]. In fact, PEG IFN-a-2a has an inhibitory effect[1] on children's growth. A study of 31 Japanese children showed that the Z-scores of height and body weight decreased during treatment and, although they improved after withdrawal, they were significantly lower than pre-treatment scores. This growth inhibitory effect was smaller in children aged 10 years and older[116].

Antiviral therapy for hepatitis C can be routinely offered to all HCV-infected newborns only when new drugs with a well demonstrated long-term safety profile become available[11], but at the moment both the safety and effectiveness of protease or polymerase inhibitors in pediatric patients have not been established.

CONCLUSION

The problem of HCV infection in pregnancy is still a matter of concern. The first concern is the possible impact of HCV infection on the mother's health during pregnancy and in the postpartum period due to the intense physiological changes and the virus/host interaction that characterize this period. Pregnancy-associated immune modulation affects the immune response against HCV because it leads to immune tolerance during pregnancy and immune restoration immediately after delivery. This phenomenon does not seem to impact negatively on liver disease in most pregnant women but may worsen liver function in some cases. Differently, childbearing women with HCV-related liver cirrhosis are at high risk of liver decompensation during pregnancy.

The second concern is the impact of HCV on delivery outcome. HCV-infected women may have an increased risk for premature membrane rupture and for cesarean delivery but there is no evident risk for complications for offspring.

The main concern is that HCV-infected women may transmit the infection to their offspring during pregnancy, upon delivery or during breastfeeding. The overall rate of vertical transmission is low (3%-5%) but the risk is higher for women with high viremia or HIV co-infection and in the case of exposure of the neonate to infected blood (*i.e.*, during prolonged rupture of membranes or vaginal lacerations and consequent to invasive monitoring of the fetus during pregnancy). Cesarean delivery, which limits the exposure to vaginal/perineal lacerations, was formerly suggested to avoid this risk of transmission.

However, it is currently recommended only for HIV/HCV coinfected women. The problem of breastfeeding is complex and must be discussed with the woman. In fact, the risk is not due to milk or colostrum (which contain a very low amount of virus and can be inactivated in the infant's digestive tract) but to contamination by infected blood through damaged or cracked nipples. HIV/HCV co-infected pregnant women are recommended to avoid vaginal delivery and breastfeeding because of the high risk of infecting their offspring.

The last concern is antiviral therapy. Currently, the

consensus is not to routinely offer antiviral therapy to all HCV-infected pregnant women and HCV-infected offspring. Given the side effects of the drugs available in these settings, candidates for therapy must be carefully selected based on the benefits of therapy and the severity of the disease. The ideal solution would be to encourage young women infected with HCV to start and complete therapy before pregnancy in order to lower or clear the virus and so reduce the risk of vertical transmission. Another strategy would be to start treatment postpartum and to avoid breastfeeding.

In the childhood setting, the standard of care therapy should be started only after the second year of life, except in cases that require immediate treatment to avoid rapid progression of liver disease.

The recently approved new generation drugs (protease and polymerase inhibitors) for the treatment of HCV infection have opened a new perspective in HCV therapy for pregnant women and infected infants since one of these agents, *i.e.*, sofosbuvir, has been reported to also be effective in IFN-free and RBV-free regimens.

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