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Hepatitis C Virus Infection in Pregnancy

An Update

ABSTRACT

Parenteral transmission is the major route of hepatitis C virus transmission in adults; however, vertical transmission is most common in children. There are several factors that have been shown to be associated with vertical transmission of hepatitis C virus, including hepatitis C virus RNA, human immunodeficiency virus coinfection, and peripheral blood mononuclear cell infection. As there is no effective vaccine to prevent hepatitis C virus infection, and there are no human data describing the safety of the new direct acting antiviral agents in pregnancy, the only preventive strategy for vertical transmission is to treat the hepatitis C virus infection before becoming pregnant. Direct acting antiviral agents are interferon-free, and many are also ribavirin-free. Based on animal studies, sofosbuvir plus ledipasvir may be the best safety profile during pregnancy for now; however, it is too early to recommend treating hepatitis C virus-infected pregnant women with these direct acting antiviral agents currently.

Chronic infection with the hepatitis C virus (HCV) is a global health problem, with an estimated 3% of the world population exposed to HCV (>185 million people) (Mohd Hanafiah, Groeger, Flaxman, & Wiersma, 2013) and between 0.9% and 2.1% chronically infected worldwide (Baser, Kariburyo, Altinbas, & Baser, 2014; Bruggmann et al., 2014; Gower, Estes, Blach, Razavi-Shearer, & Razavi, 2014; Hope, Eramova, Capurro, & Donoghoe, 2014; Yildirim et al., 2009). The majority (75%–85%) of those who develop acute HCV infection progress to chronic HCV infection, with only a small proportion of patients spontaneously clearing virus (Di Bisceglie, 2000). However, the true incidence and prevalence are likely under-represented, as many patients with chronic hepatitis C (CHC) are unaware of their diagnosis owing to the asymptomatic nature of HCV infection and limited screening of at-risk individuals (Linas, Hu, Barter, & Horberg, 2014).

Background

The main routes of HCV transmission are through intravenous (IV) drug use and receipt of contaminated blood products. Even a single episode of (IV) drug use in the distant past is recognized to be a risk factor for HCV infection (http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm). It is estimated that 0.5%–40% of HCV-infected patients are actively involved in injecting practices, and more than 90% of persons who inject drugs are HCV-positive (Patrick, Buxton, Bigham, & Mathias, 2000; Razavi et al., 2014).

Although the implementation of blood product screening from the early 1990s has dramatically reduced the risk of transfusion-associated CHC, blood product screening is not universal worldwide; those receiving blood products in developing countries remain at risk. In addition, up to 26% of HCV-infected persons reported a history of receiving blood products during their lifetime (Razavi et al., 2014).

Other potential risk factors include nosocomial transmission through inadequately sterilized medical equipment, incarceration, hemodialysis, cultural practices such as acupuncture or cupping, occupational

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exposure (mucosal splashes and needlestick injuries), unsterile tattooing and piercing, high-risk sexual practices, human immunodeficiency virus (HIV) or hepatitis B virus (HBV) infection due to shared transmission routes, and transmission from household contacts (including individuals born to HCV-positive mothers). No risk factor is identified in 10% of HCV-infected patients (Flamm, Parker, & Chopra, 1998). As a result, most countries recommend HCV screening in individuals with the aforementioned risk factors (Benova, Mohamoud, Calvert, & Abu-Raddad, 2014; Karaca et al., 2006; Tahan et al., 2005) (Table 1). In addition, birth cohort screening in the "baby boomer" population born in the years 1945–1965 is recommended in the United States (U.S.), as this age group represents 70% of the HCV-positive population in U.S. Vertical transmission, defined as HCV transmission from mother to infant during pregnancy, at the time of delivery, or during the first 28 days after birth, occurs in around 5% of children born to HCV-positive mothers (Benova et al. 2014).

Despite the implementation of needle exchange programs and education regarding safe injecting practices, IV drug use remains the main risk factor for HCV transmission in adults nowadays. In contrast, owing to the implementation of blood product screening in many countries, the predominant route of transmission of HCV in children nowadays is vertical transmission (Arshad, El-Kamary, & Jhaveri, 2011). This represents an important route of HCV transmission, as HCV screening is not routinely performed during pregnancy in many countries and the previous standard of care therapy (interferon [IFN] and ribavirin [RBV]) was contraindicated during pregnancy. Interferon (designated Category C in pregnancy) has been shown to have abortifacient effects on developing animal fetuses, and RBV (designated Category X in pregnancy) has been associated with significant teratogenic and/or embryocidal effects in all animal species examined.

TABLE 1. Risk Factors for HCV Acquisition

1. Intravenous or intranasal drug use (current or prior)
2. Recipient of blood products including clotting factor concentrates and immunoglobulin prior to 1992
3. Solid organ transplantation prior to 1992
4. Occupational exposure
5. Born between 1945 and 1965
6. Coinfection with HIV
7. Multiple sexual partners or high-risk sexual practices
8. Born to HCV-positive mothers
9. Living in high-prevalence developing countries
10. Undergoing hemodialysis
11. Incarceration
12. Received unsterile tattoos or piercings

Note. HCV = hepatitis C virus; HIV = human immunodeficiency virus.

Until recently, the mainstay of treatment of HCV infection has been IFN combined with RBV. Despite the low cure rates (overall cure rate 54%–56%) and significant toxicity, this remained the only successful therapy for the better part of two decades owing to the lack of experimental models for drug development. Therefore, many patients were unable or unwilling to tolerate or were ineligible for IFN/RBV therapy. This, combined with the aging HCV-infected population, has contributed to a sharp increase in the number of patients with complications from CHC infection, with a tripling of the number of patients with cirrhosis, decompensated liver disease, and hepatocellular carcinoma over the past 15 years.

Almost 350,000 HCV-related deaths each year are directly attributed to CHC worldwide (Gower et al., 2014; Hope et al., 2014), and all-cause mortality is almost 2.4 times higher in HCV-infected individuals compared with HCV-uninfected persons (El-Kamary, Jhaveri, & Shardell, 2011). These estimates are expected to continue to rise to 60%–110% by the year 2030 if there are no changes in the update and efficacy of HCV therapy (Bruggmann et al., 2014).

The development of the replicon model system for HCV, together with the crystallization of the nonstructural HCV proteins and characterization of the HCV life cycle, has led to the development of direct acting antiviral agents (DAAs) that directly target steps in the HCV replication life cycle. These agents have revolutionized the treatment landscape of HCV infection, with cure rates in excess of 90% for all genotypes with minimal toxicity. These agents are now approved and are available in many countries around the world for adult patients with CHC. As these regimens are IFN- and potentially RBV-free, there is a hope that these new IFN-free and RBV-free DAA combination regimens may be safe for use during pregnancy and therefore may have a role in preventing vertical transmission of HCV (Kanninen, Dieterich, & Asciutti, 2015).

However, this remains to be proven, as data regarding the safety of DAAs during pregnancy and lactation are currently limited to animal studies and there are no data regarding the efficacy of prevention of perinatal transmission of HCV with these new agents. In this review article, we summarize the existing data about HCV in pregnancy and the natural history of perinatally acquired HCV, as well as HCV treatment options

in pregnancy, with a specific focus on safety of the DAAs during pregnancy and lactation in the animal studies.

Results

Prevalence of HCV Infection Among Pregnant Women

The frequency of anti-HCV antibodies in pregnant women ranged between 0.1% and 3.6% and varied according to geographic region (Altinbas, Erdogan, & Danisman, 2010; Arshad et al., 2011; Baldo et al., 2000; Benova et al., 2014; Blasig et al., 2011; Bruggmann et al., 2014). The proportion of pregnant women with active HCV infection, as determine by HCV RNA positivity in the presence of anti-HCV antibodies, varied from 45% to 72% (El-Kamary et al., 2015; Floreani, 2013). However, these data must be interpreted with caution, as they may not reflect the true prevalence of HCV in pregnant women. This is due to the lack of universal HCV screening for all pregnant women during the antenatal period, the asymptomatic nature of HCV infection, and the fact that HCV screening may only be undertaken in pregnant women with risk factors for HCV infection (Prasad & Honegger, 2013).

This is supported by a study that found that 40%–73% of HCV-infected pregnant women may be missed when HCV screening is performed solely based upon risk factor-based screening policies (Conte, Fraquelli, Prati, Colucci, & Minola, 2000; Ward et al., 2000). Several studies reported that the number of pregnancies per woman may be a risk factor for HCV infection itself (2.0- or 3.2-fold increased risk for HCV infection with five or more pregnancies compared with nulligravida women, after adjustment for age at time of pregnancy) (Khan, Janjua, Akhtar, & Hatcher, 2008; Murphy et al., 2010; Stoszek et al., 2006). These data may support the cumulative iatrogenic spread of HCV infection either through exposure to unsterile medical equipment or receipt of unscreened blood products during each subsequent pregnancy.

Vertical Transmission of HCV

Overall Transmission Rate

The rate of vertical transmission of HCV varies considerably among different global populations of pregnant HCV-positive women. In a review of 77 studies, Yeung, King, and Roberts (2001) calculated that the overall crude rate of vertical transmission of HCV is 5.6% among HCV-positive viremic pregnant women, irrespective of HCV RNA levels. When adjusted for the inverse of the variance, the weighted rate was calculated at 1.7%. Another meta-analysis of 20 studies reporting vertical transmission of HCV calculated the pooled transmission rate was 5.8% in HCV viremic women, with increased HCV vertical transmission in particular subgroups, namely, HCV/HIV-coinfected women, where transmission rates were 19.4% (Benova et al., 2014).

Known Risk Factors for Vertical Transmission of HCV

HCV RNA Levels. Mother-to-infant transmission of HCV should occur only in the setting of active HCV infection, as demonstrated by HCV viremia in the mother; however, there are several reports of vertical HCV transmission occurring in the context of anti-HCV antibody positivity but negative HCV RNA levels (Benova et al., 2014; Granovsky et al., 1998; Marine-Barjoan et al., 2007; Yeung et al., 2001). Ordinarily, this would represent past HCV infection and therefore HCV transmission should not be allowed to occur as there is no active HCV replication. However, it should be noted that in these isolated cases, HCV RNA testing was not always mandatory or HCV RNA quantification was performed using the old and insensitive first- and second-generation HCV RNA assays, where the lower limit of detection was as high as 31,746 IU/ml. Therefore, it is conceivable that these insensitive assays were unable to detect lower level HCV viremia in these women. In addition, HCV levels can fluctuate significantly and therefore testing at a single time point does not preclude the same women returning a positive HCV RNA level later during pregnancy. When limited to HCV viremic pregnant women, the crude mother-to-infant HCV transmission rate was higher at 8.1%, with a weighted rate of 4.3% (Yeung et al., 2001).

Many studies have reported an association between the actual level of HCV viremia and vertical transmission of HCV, although not all studies have demonstrated this association (Conte et al., 2000; Resti et al., 1998). However, the cutoff level to define increased risk in these studies varies considerably. The majority of studies have demonstrated that HCV RNA levels greater than 10^5 to 10^6 copies/ml correlate with a greater likelihood of mother-to-infant HCV transmission (Baroncelli et al., 2016; Elrazek et al., 2017; Marine-Barjoan et al., 2007; Roberts & Yeung, 2002).

In HCV-positive mothers with HCV RNA levels less than 6 $\log_{10}$ IU/ml, the maternal-to-child HCV transmission rate was 1.7% and increased to 17.4% in mothers who had HCV RNA levels 6 $\log_{10}$ IU/ml or more (Marine-Barjoan et al., 2007). Similarly, in another study, the mean HCV RNA level was 9×10^6 copies/ml in pregnant women who subsequently transmitted HCV compared with 2×10^6 copies/ml in women who did not transmit virus (Mast et al., 2005).

In a prospective cohort of 3,000 pregnant women followed during their pregnancy who received HCV testing during the third trimester, data mining analysis demonstrated that a polymerase chain reaction (PCR) titer of more than 3,000,000 IU/ml was associated with a high risk for vertical transmission of HCV (Baroncelli et al., 2016; Elrazek et al., 2017; Marine-Barjoan et al., 2007; Roberts & Yeung, 2002). In addition, a PCR titer between 975,000 and 3,000,000 IU/mL was still identified as a considerable risk factor for mother-to-infant HCV transmission.

HIV Coinfection. Another well-described risk factor for maternal-to-child transmission of HCV is HIV coinfection (Benova et al., 2014; Okamoto et al., 2000; Valladares, Chacaltana, & Sjogren, 2010). In a multicenter review of children born to HCV-positive mothers, transmission was threefold higher in HCV/HIV-coinfected women compared with monoinfected women (Marine-Barjoan et al., 2007). In women with lower viral loads, defined as an HCV RNA less than 6 $\log_{10}$ IU/ml, the odds ratio for vertical transmission was 8.3 in HCV/HIV-coinfected women (12.5%) compared with 1.0 in HCV-monoinfected women with similarly low HCV RNA levels (1.7%). The rate of mother-to-child transmission was similar in HCV/HIV-coinfected and HCV-monoinfected women with higher HCV RNA levels, suggesting that HIV itself represents a greater risk factor for vertical transmission than HCV RNA in the context of HCV/HIV coinfection (Marine-Barjoan et al., 2007) (Table 2).

In a meta-analysis of vertical transmission in pregnancy, children born to HCV/HIV-coinfected mothers had approximately double the vertical rate of HCV transmission compared with HCV-monoinfected mothers (10.8% vs. 5.8%, respectively), and in an adjusted regression meta-regression model, HIV coinfection was identified as the most important determinant of mother-to-infant HCV transmission, with an odds ratio of 2.56 (Benova et al., 2014; Okamoto et al., 2000; Valladares et al., 2010).

The immunosuppressive effect of HIV has been shown to increase HCV viral loads in HCV/HIV-coinfected individuals compared with HCV-infected individuals without HIV (Baroncelli et al., 2016; Elrazek et al., 2017; Marine-Barjoan et al., 2007; Matthews-Greer et al., 2001; Roberts & Yeung, 2002). Therefore, it is unclear whether the presence of HIV itself in HCV/HIV-coinfected mothers confers an increased risk of vertical transmission of HCV or whether the higher transmission is a consequence of higher HCV RNA levels that occur in HCV/HIV-coinfected individuals leading to greater HCV transmission. In another study of HCV/HIV-coinfected mothers on antiretroviral therapy, HCV RNA levels were similar to HCV-monoinfected mothers and none were found to transmit HCV to their child, also supporting the importance of HIV-related immunosuppression. This also highlights the importance of HIV testing and adequate management of HIV during pregnancy.

Peripheral Blood Mononuclear Cell Infection. Another factor that has been associated with increased vertical transmission of HCV is HCV infection in peripheral blood mononuclear cells (PBMCs) (Azzari et al., 2008, 2000). In a study of 170 HCV-positive mothers, HCV PBMC infection and maternal IV drug use were found to be associated with vertical transmission (Azzari et al., 2008). Multivariate analysis revealed that maternal HCV PBMC infection was associated with vertical transmission, however, maternal IV drug use was not associated, suggesting that the previously observed link between mothers who inject drugs and mother-to-child transmission is, in fact, due to HCV infection of PBMCs rather than IV drug use.

TABLE 2. Risk Factors for Vertical Transmission of HCV Infection

Risk Association	Risk Factors
Established	HCV RNA levels HIV coinfection
Possible	Early membrane rupture (>6 hr before delivery) Internal fetal monitoring in viremic mothers Emergency cesarean section
Not associated	Mode of delivery Breastfeeding in the absence of nipple trauma

Note. HCV = hepatitis C virus; HIV = human immunodeficiency virus.

Factors Not Associated With HCV Vertical Transmission

Mode of Delivery: Vaginal Delivery Versus Elective Cesarean Section. Several large meta-analyses have demonstrated that vertical transmission of HCV is not influenced by the mode of delivery in women without HIV coinfection (Durmaz, 2012; Gibb et al., 2000; Marine-Barjoan et al., 2007; McIntyre, Tosh, & McGuire, 2006; Tahan et al., 2005). Therefore, vaginal delivery should not be discouraged and elective cesarean section (C/S) is not recommended over vaginal delivery unless there is an alternative indication.

In contrast, in HIV-positive women with HCV coinfection, there are older data suggesting that elective C/S may reduce the risk of vertical transmission of HCV (Baroncelli et al., 2016; European Paediatric Hepatitis C

Virus Network, 2001, 2005; Snijdewind et al., 2015). In a large study from the European Paediatric Hepatitis C Virus Network (2001), mother-to-child transmission of HCV was significantly lower in women who had an elective C/S (odd ratio = 0.4). However, in the era of widespread availability of highly active antiretroviral therapy (HAART) for HIV, the benefit of C/S was not observed in women who demonstrated HIV suppression with HAART. Hence, recommendations regarding mode of delivery in HCV/HIV-coinfected pregnant women should be made on the basis of the status of the HIV infection.

Breastfeeding. Although HCV can be detected in colostrum of HCV-positive asymptomatic mothers at much lower levels than serum, vertical transmission of HCV from breast milk has not been documented (Lin et al., 1995). In addition, testing of mature breast milk from 73 HCV-positive mothers failed to detect the presence of HCV RNA in and of the samples despite the presence of HCV RNA in the serum of 60% of the women (Polywka, Schröter, Feucht, Zöllner, & Laufs, 1999). Several larger systematic reviews and prospective studies have confirmed a lack of HCV transmission through breastfeeding (Cottrell, Chou, Wasson, Rahman, & Guise, 2013; Rest et al., 1998; Thomas, Newell, Peckham, Ades, & Hall, 1998).

However, in a small prospective study, including five symptomatic HCV-positive mothers, three of the infants developed symptomatic hepatitis (Kumar & Shahul, 1998). All three infants were born via elective C/S, were breastfed, and no other risk factors for transmission were identified. None of the mothers reported overt nipple trauma, a potential source of HCV transmission ("ACOG Committee opinion," 1999; "Recommendations for Prevention," 1998). On the basis of these data, breastfeeding is recommended except in the setting of nipple trauma or in HIV coinfection, where HIV transmission also can occur.

Potential Risk Factors and Prevention of Vertical Transmission of HCV

Despite best efforts, there is currently no effective vaccine to prevent against HCV infection; therefore, the only strategy to prevent vertical transmission is to treat HCV before becoming pregnant. This, however, requires diagnosis of HCV in the first instance (a well-established barrier to accessing therapy and was not a practical option for women in the IFN/RBV era due to the long duration of therapy and subsequent 6-month washout period) (Thomas et al., 1998). Furthermore, this therapy was only effective in around half of the patients and was associated with significant toxicity, making many ineligible for and intolerant to therapy. The advent of short, highly efficacious IFN- and RBV-free treatment options provides an opportunity for global HCV eradication, including in women of childbearing age, that will not only have a positive impact upon the worldwide HCV incidence, prevalence, and vertical transmission rates over the coming decades but also reduce the burden of end-stage liver disease resulting from CHC infection (Vandijck et al., 2014; Wedemeyer et al., 2014).

Natural History of HCV Infection in Infants With Vertically Transmitted HCV

As observed in adult HCV infection, HCV infection may also resolve spontaneously in children with vertically transmitted HCV, where spontaneous resolution occurred in 25% by the end of 7 years of follow-up (Yeung, To, King, & Roberts, 2007). The route of childhood HCV transmission in this study was heterogeneous, but spontaneous clearance rates were similar in children with transfusion-associated HCV infection and all other routes of transmission. More specific to vertical transmission of HCV, Ceci et al. (2001) found that spontaneous clearance rates may approach 75% among infants with vertically acquired HCV by 24 months of age.

Treatment of HCV During Pregnancy and Lactation

For the past two decades, IFN plus RBV for up to 12 months' duration has been the mainstay of therapy for HCV infection. In addition to suboptimal responses rates (54%–56% overall cure rate), therapy was associated with significant toxicity that resulted in up to 14% discontinuing therapy due to adverse events in the registration trials (Fried et al., 2002; Hadziyannis et al., 2004; McHutchison et al., 1998). Because of the significant toxicities, many individuals were either ineligible or intolerant to therapy. Furthermore, this combination therapy was contraindicated in pregnant and lactating women, with IFN designated Category C and RBV Category X in pregnancy by the Food and Drug Administration (FDA) (Durmaz, 2012; Floreani, 2013; Gurol, Saban, Oral, Cigdem, & Armagan, 2006; Karaca et al., 2006; Martin et al., 2013; Okamoto et al., 2000; Tahan et al., 2005; Valladares et al., 2010) (Table 3).

The development of the replicon system for HCV and subsequent delineation of the HCV life cycle (Bartenschlager, 2002), and the crystallization of the nonstructural HCV proteins (Lesburg et al., 1999; Yao, Reichert, Taremi, Prosise, & Weber, 1999), led to the development of new DAAs. Combinations of DAAs have allowed the development of IFN- and also RBV-free regimens for the treatment of HCV infection, and several combinations have been licensed for the first-line therapy for HCV infection in many countries. These regimens range from 8 to 24 weeks' duration and have the advantages of superior efficacy (>95% cure rates)

TABLE 3. The Safety Categories of the Drugs Throughout Pregnancy

Category A	No harmful effect on fetus in the first trimester based on controlled studies
Category B	No harmful effect on fetus based on animal studies (no controlled studies in human being)
Category C	Harmful effect on fetus based on animal studies (no controlled studies in human being)
Category D	Harmful effect on fetus based on investigational or postmarketing studies
Category X	Clear harmful effect on fetus based on human and animal studies

and minimal toxicities (Holmes & Thompson, 2015). The registration of clinical trials of these agents specifically excluded pregnant and lactating women, and owing to the recent development of these agents, there are no real-world data regarding safety in pregnancy.

Animal Studies of DAAs in Pregnancy

The animal studies revealed that most of the DAAs cross the placenta; however, teratogenicity was seen with simeprevir and daclatasvir usage individually (Spera, Eldin, Tosone, & Orlando, 2016; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/206843s006lbl.pdf). Because of the favorable pharmacokinetic profiles and nonteratogenic features coming from animal studies, the combination of sofosbuvir and ledipasvir looks like the best option for HCV infection treatment in pregnancy so far (Spera et al., 2016).

Currently, a clinical trial (NCT02683005) is being conducted to assess the safety and efficacy profile of sofosbuvir and ledipasvir combination during the second and third trimesters of pregnancy. According to the instruction booklets of ombitasvir, paritaprevir/ritonavir and dasabuvir, velpatasvir, glecaprevir, pibrentasvir, elbasvir, and grazoprevir, the animal studies have shown no adverse effects on embryo–fetal or prepostnatal development (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619lbl.pdf, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208341s000lbl.pdf, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209394s000lbl.pdf, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208261Orig1s000lbl.pdf).

Because RBV-related sperm toxicity reversed 4–8 months after the drug cessation, male patients are also advised to take all precautions for the risk of pregnancy for their female partners (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021511s023lbl.pdf). The impact of new DAAs on spermatogenesis is still not clear.

FDA Recommendations for DAA Use in Pregnant and Lactating Women

The first approved DAAs were the first-generation protease inhibitors telaprevir and boceprevir. However, these agents were used with an IFN plus RBV backbone and were not approved as monotherapy for HCV infection (Feeney & Chung, 2014; Tahan et al., 2005). Therefore, these agents were also contraindicated in pregnancy and in breastfeeding women.

Owing to the lack of teratogenicity in limited animal studies, the FDA has given DAAs a classification of Category B in pregnancy for sofosbuvir, ledipasvir, daclatasvir, asunaprevir, paritaprevir, ombitasvir, and dasabuvir, representing the currently approved IFN-free regimens (Kanninen et al., 2015). Simeprevir has been given a Category C in pregnancy (Spera et al., 2016). However, there are no human data regarding their safety in pregnancy and lactation; therefore, in the clinical setting, these agents have not been widely recommended for use in women who are pregnant, those who are breastfeeding, or in women planning to become pregnant.

Because the animal studies (in rats) determined that sofusbuvir and ledipasvir have no harmful effect on nursing pups, the FDA recommends that the benefits of breastfeeding during sofosbuvir and ledipasvir treatment need to be evaluated along with the mother's clinical need for the drugs and the potential harm on the child (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205834s010lbl.pdf).

Several regimens also still include RBV. These combinations remain contraindicated in pregnant women and breastfeeding women. Moreover, owing to the long half-life of RBV (steady state is reached after 4 weeks), women are advised against becoming pregnant for 6 months after completing RBV-based therapy.

Clinical Scenarios

Scenario 1: Chronic HCV-Infected Patients Become Pregnant. The natural course of HCV infection may depend on the status of the underlying liver disease. The risk of hepatic decompensation is high in cirrhotic patients and therefore these patients are discouraged from becoming pregnant (Tahan et al., 2005; Valladares et al., 2010). In addition, fertility is decreased in cirrhotic women. On the contrary, if HCV-related liver destruction is limited, most pregnancies may be completed without any HCV infection-induced problem.

Frequently, because of pregnancy-associated immunomodulation, the decline in HCV viral load and the normalization of transaminase levels have been reported at the same time (Floreani, 2013; Fontaine, Nalpas, Carnot, Bréchot, & Pol, 2000; Gervais et al., 2000; Paternoster et al., 2001). These changes might be related to endogenous IFN release, hemodilution, and

an altered immune system. However, these mild changes do not lead to viral clearance (Fontaine et al., 2000; Paternoster et al., 2001). As is widely accepted, HCV viral load usually increases toward the third trimester. In contrast, Baroncelli et al. (2016) showed a stable HCV viral load from the first to third trimesters. With immune restoration even after delivery, the risk of HCV exacerbation increases (Gervais et al., 2000; Oketani, Shibatou, Yamashita, Arima, & Arima, 2002; Paternoster et al., 2001). So, even though there is no consensus, close monitoring of patients transaminases and HCV viral load levels should not be overlooked during pregnancy or after delivery. Spontaneous HCV clearance was noted only in a few cases (Baroncelli et al., 2016; Zein, Abu-Lebdeh, & Zein, 2001).

In the past, this follow-up was recommended only to define liver deterioration earlier. On the contrary, the new DAAs may be an option for use at the beginning of the third trimester as is being done in HBV infection in the near future. This alternative can decrease HCV viral load toward delivery to protect the mother from the HCV rebound seen after delivery and the child from HCV transmission by preventing vertical transmission. Of course, these suggestions need to be supported by clinical trials and it is too premature to suggest using these agents during pregnancy.

Conversely, the effect of CHC infection on pregnancy is a dilemma. Higher intrahepatic cholestasis seen in HCV-infected pregnant women has been supported by several studies and none in the opposite direction (Marschall, Wikström Shemer, Ludvigsson, & Stephansson, 2013; Paternoster et al., 2001). However, low birth weights, premature rupture of membranes, neonatal jaundice, and increased necessity of intensive care unit use for newborns are controversial (Pergam et al., 2008). On the contrary, increased C/S rates in HCV-positive patients are not due to obstetric indications, but they were mostly aimed to decrease the rate of HCV transmission by preferring C/S rather than vaginal delivery, even though it is not an evidence-based approach (Floreani, 2013; Jabeen et al., 2000).

Scenario 2: Acute HCV Infection in Pregnant Women. Acute HCV infection usually presents silently and ends with chronic infection in almost 75% of patients. Among them, 20% develop cirrhosis after 20–30 years of infection (Di Bisceglie, 2000). Faster progression of HCV infection-related liver disease may be seen in older patients, posttransplant patients, or those with HIV and/or HBV coinfection or alcohol abuse. However, a minority of patients are symptomatic, and these patients have a chance to clear the HCV infection. Therefore, to start medication against HCV infection is commonly advised in asymptomatic patients who fail to eradicate HCV at the end of the sixth week of infection whereas it is at 12 weeks in symptomatic patients.

Probably, the course of acute HCV infection in pregnancy is similar to that in nonpregnant women (Floreani, 2013). Data about acute HCV infection during pregnancy are limited and come from just a few case reports (Gonzalez et al., 2006; Kogure et al., 2006; Ozaslan, Yilmaz, Simsek, & Tatar, 2002). We should note that only severe liver injuries related to HCV infection were reported. Therefore, it is difficult to build a specific guideline for acute HCV infection in pregnancy. Because of the rarity of acute HCV infection in pregnancy, and that the natural course of HCV infection is under-reported, we do not know exactly which patients should be treated to prevent severe liver injury or vertical transmission of HCV. If none of the acute HCV infections result in severe liver injury or increased vertical transmission rate, therapy becomes useless.

Conclusion

The global burden of HCV-related liver disease remains a significant health issue. Parenteral transmission is the major route of HCV transmission in adults; however, vertical transmission is most common in children. Therefore, universal HCV screening, particularly among pregnant women, is needed to fight against HCV infection. There are several factors that have been shown to be associated with vertical transmission of HCV, including HCV RNA, HIV coinfection, and PBMC infection. Mode of delivery and breastfeeding have not been associated with transmission. Infants born to HCV-positive mothers should be followed up and have HCV testing, and it should be noted that maternal anti-HCV antibodies may persist in the infant for up to 18 months. Therefore, HCV nucleic acid testing should be used in combination with anti-HCV antibody testing to diagnose HCV infection. As there is no effective vaccine to prevent HCV infection, and no human data describing the safety of the new DAAs in pregnancy, the only preventive strategy for vertical transmission is to treat the HCV infection before becoming pregnant.

Although the DAAs are IFN-free and many are also RBV-free, the lack of human safety data in the light of limited animal data has meant that these agents have been given a Category B or C classification in pregnancy. Data from animal studies suggest that the combination of sofosbuvir plus ledipasvir may have the best safety profile during pregnancy; however, it is too early to recommend treating HCV-infected pregnant women with these DAAs currently and therefore they are not routinely recommended in clinical practice. Furthermore, the majority of the approved combination DAA therapies are only 12 weeks' duration and hence pregnancy may be able to be deferred until

completion of DAA therapy. These agents are likely to have a significant impact upon the incidence/prevalence and natural history of HCV, reducing the burden of HCV-related liver disease. ✪

REFERENCES

ACOG committee opinion. Breastfeeding and the risk of hepatitis C virus transmission. Number 220, August 1999. Committee on Obstetric Practice. American College of Obstetricians and Gynecologists. (1999). *International Journal of Gynaecology and Obstetrics, 66*(3), 307–308.

Altinbas, S., Erdogan, M., & Danişman, N. (2010). The seroprevalences of HBs Ag and anti-HCV in pregnant women in Ankara. *Archives of Gynecology and Obstetrics*, *281*(2), 371.

Arshad, M., El-Kamary, S. S., & Jhaveri, R. (2011). Hepatitis C virus infection during pregnancy and the newborn period—Are they opportunities for treatment? *Journal of Viral Hepatitis, 18*(4), 229–236.

Azzari, C., Moriondo, M., Indolfi, G., Betti, L., Gambineri, E., de Martino, M., & Resti, M. (2008). Higher risk of hepatitis C virus perinatal transmission from drug user mothers is mediated by peripheral blood mononuclear cell infection. *Journal of Medical Virology*, *80*(1), 65–71.

Azzari, C., Resti, M., Moriondo, M., Ferrari, R., Lionetti, P., & Vierucci, A. (2000). Vertical transmission of HCV is related to maternal peripheral blood mononuclear cell infection. *Blood*, *96*(6), 2045–2048.

Baldo, V., Floreani, A., Menegon, T., Grella, P., Paternoster, D. M., & Trivello, R. (2000). Hepatitis C virus, hepatitis B virus and human immunodeficiency virus infection in pregnant women in North-East Italy: A seroepidemiological study. *European Journal of Epidemiology, 16*(1), 87–91.

Baroncelli, S., Pirillo, M. F., Amici, R., Tamburrini, E., Genovese, O., Ravizza, M., ... Floridia, M. (2016). HCV-HIV coinfected pregnant women: Data from a multicentre study in Italy. *Infection, 44*(2), 235–242.

Bartenschlager, R. (2002). Hepatitis C virus replicons: Potential role for drug development. *Nature Reviews, Drug Discovery*, *1*(11), 911–916.

Baser, O., Kariburyo, M. F., Altinbas, A., & Baser, E. (2014). Economic burden and complications of hepatitis C virus patients with and without peginterferon and ribavirin treatment in Turkey. *Value in Health*, *17*(7), A672. doi:10.1016/j.jval.2014.08.2490

Benova, L., Mohamoud, Y. A., Calvert, C., & Abu-Raddad, L. J. (2014). Vertical transmission of hepatitis C virus: Systematic review and meta-analysis. *Clinical Infectious Diseases*, *59*(6), 765–773.

Blasig, A., Wagner, E. C., Pi, D., Bigham, M., Remple, V. P., Craib, K. J., … BC HCV Vertical Transmission Study Group. (2011). Hepatitis C infection among pregnant women in British Columbia: Reported prevalence and critical appraisal of current prenatal screening methods. *Canadian Journal of Public Health,102*(2), 98–102.

Bruggmann, P., Berg, T., Øvrehus, A. L., Moreno, C., Brandão Mello, C. E., Roudot-Thoraval, F., ... Hindman, S. J. (2014). Historical epidemiology of hepatitis C virus (HCV) in selected countries. *Journal of Viral Hepatitis, 21* (Suppl. 1), 5–33.

Ceci, O., Margiotta, M., Marello, F., Francavilla, R., Loizzi, P., Francavilla, A., ... Selvaggi, L. (2001). Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: A 24-month prospective study. *Journal of Pediatric Gastroenterology and Nutrition, 33*(5), 570–575.

Conte, D., Fraquelli, M., Prati, D., Colucci, A., & Minola, E. (2000). Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology*, *31*(3), 751–755.

Cottrell, E. B., Chou, R., Wasson, N., Rahman, B., & Guise, J. M. (2013). Reducing risk for mother-to-infant transmission of hepatitis C virus: A systematic review for the U.S. Preventive Services Task Force. *Annals of Internal Medical*, *158*(2), 109–113.

Di Bisceglie, A. M. (2000). Natural history of hepatitis C: Its impact on clinical management. *Hepatology, 31*(4), 1014–1018.

Durmaz, O. (2012). Hepatitis C infection in childhood. *Clinics and Research in Hepatology and Gastroenterology, 36*(3), 294–296.

El-Kamary, S. S., Hashem, M., Saleh, D. A., Ehab, M., Sharaf, S. A., El-Mougy, F., ... El-Ghazaly, H. (2015). Reliability of risk-based screening for hepatitis C virus infection among pregnant women in Egypt. *Journal of Infection, 70*(5), 512–519.

El-Kamary, S. S., Jhaveri, R., & Shardell, M. D. (2011). All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. *Clinical Infectious Diseases, 53*(2), 150–157.

Elrazek, A. E., Amer, M., El-Hawary, B., Salah, A., Bhagavathula, A. S., Alboraie, M., & Saab, S. (2017). Prediction of HCV vertical transmission: What are factors should be optimized using data mining computational analysis. *Liver International*, *37*(4), 529–533.

European Paediatric Hepatitis C Virus Network. (2001). Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. European Paediatric Hepatitis C Virus Network. *BJOG, 108*(4), 371–377.

European Paediatric Hepatitis C Virus Network. (2005). A significant sex—but not elective cesarean section—effect on mother-to-child transmission of hepatitis C virus infection. *The Journal of Infectious Diseases*, *192*(11), 1872–1879.

Feeney, E. R., & Chung, R. T. (2014). Antiviral treatment of hepatitis C. *BMJ*, *348*, g3308.

Flamm, S. L., Parker, R. A., & Chopra, S. (1998). Risk factors associated with chronic hepatitis C virus infection: Limited frequency of an unidentified source of transmission. *The American Journal of Gastroenterology*, *93*(4), 597–600.

Floreani, A. (2013). Hepatitis C and pregnancy. *World Journal of Gastroenterology*, *19*(40), 6714–6720.

Fontaine, H., Nalpas, B., Carnot, F., Bréchot, C., & Pol, S. (2000). Effect of pregnancy on chronic hepatitis C: A case–control study. *The Lancet*, *356*(9238), 1328–1329.

Fried, M. W., Shiffman, M. L., Reddy, K. R., Smith, C., Marinos, G., Gonçales, F. L., Jr., ... Yu, J. (2002). Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *The New England Journal of Medical*, *347*(13), 975–982.

Gervais, A., Bacq, Y., Bernuau, J., Martinot, M., Auperin, A., Boyer, N., ... Marcellin, P. (2000). Decrease in serum ALT and increase in serum HCV RNA during pregnancy in women with chronic hepatitis C. *Journal of Hepatology*, *32*(2), 293–299.

Gibb, D. M., Goodall, R. L., Dunn, D. T., Healy, M., Neave, P., Cafferkey, M., & Butler, K. (2000). Mother-to-child transmission of hepatitis C virus: Evidence for preventable peripartum transmission. *The Lancet*, *356*(9233), 904–907.

Gonzalez, F., Medam-Djomo, M. A., Lucidarme, D., Decoster, A., Houze de l'Aulnoit, D., & Filoche, B. (2006). Acute hepatitis C

during the third trimester of pregnancy. *Gastroenterologie Clinique et Biologique*, *30*(5), 786–789.

Gower, E., Estes, C., Blach, S., Razavi-Shearer, K., & Razavi, H. (2014). Global epidemiology and genotype distribution of the hepatitis C virus infection. *Journal of Hepatology*, *61*(1, Suppl.), S45–S57.

Granovsky, M. O., Minkoff, H. L., Tess, B. H., Waters, D., Hatzakis, A., Devoid, D. E., ... Goedert, J. J. (1998). Hepatitis C virus infection in the mothers and infants cohort study. *Pediatrics, 102*(2, Pt. 1), 355–359.

Gurol, E., Saban, C., Oral, O., Cigdem, A., & Armagan, A. (2006). Trends in hepatitis B and hepatitis C virus among blood donors over 16 years in Turkey. *European Journal of Epidemiology, 21*(4), 299–305.

Hadziyannis, S. J., Sette, H., Jr., Morgan, T. R., Balan, V., Diago, M., Marcellin, P., … PEGASYS International Study Group. (2004, March 2). Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: A randomized study of treatment duration and ribavirin dose. *Annals of Internal Medical, 140*(5), 346–355.

Holmes, J. A., & Thompson, A. J. (2015). Interferon-free combination therapies for the treatment of hepatitis C: Current insights. *Hepatic Medicine*, *7*, 51–70. doi:10.2147/HMER.S55864

Hope, V. D., Eramova, I., Capurro, D., & Donoghoe, M. C. (2014). Prevalence and estimation of hepatitis B and C infections in the WHO European Region: A review of data focusing on the countries outside the European Union and the European Free Trade Association. *Epidemiology and Infection*, *142*(2), 270–286.

Jabeen, T., Cannon, B., Hogan, J., Crowley, M., Devereux, C., Fanning, L., ... Whelton, M. J. (2000). Pregnancy and pregnancy outcome in hepatitis C Type 1b. *QJM*, *93*(9), 597–601.

Kanninen, T. T., Dieterich, D., & Asciutti, S. (2015). HCV vertical transmission in pregnancy: New horizons in the era of DAAs. *Hepatology*, *62*(6), 1656–1658.

Karaca, C., Cakaloğlu, Y., Demir, K., Ozdil, S., Kaymakoğlu, S., Badur, S., & Okten, A. (2006). Risk factors for the transmission of hepatitis C virus infection in the Turkish population. *Digestive Diseases and Sciences, 51*(2), 365–369.

Khan, U. R., Janjua, N. Z., Akhtar, S., & Hatcher, J. (2008). Case–control study of risk factors associated with hepatitis C virus infection among pregnant women in hospitals of Karachi-Pakistan. *Tropical Medicine & International Health*, *13*(6), 754–761.

Kogure, T., Ueno, Y., Kanno, N., Fukushima, K., Yamagiwa, Y., Nagasaki, F., ... Shimosegawa, T. (2006). Sustained viral response of a case of acute hepatitis C virus infection via needle-stick injury. *World Journal of Gastroenterology, 12*(29), 4757–4760.

Kumar, R. M., & Shahul, S. (1998). Role of breast-feeding in transmission of hepatitis C virus to infants of HCV-infected mothers. *Journal of Hepatology, 29*(2), 191–197.

Lesburg, C. A., Cable, M. B., Ferrari, E., Hong, Z., Mannarino, A. F., & Weber, P. C. (1999). Crystal structure of the RNA-dependent RNA polymerase from hepatitis C virus reveals a fully encircled active site. *Nature Structural Biology, 6*(10), 937–943.

Lin, H. H., Kao, J. H., Hsu, H. Y., Ni, Y. H., Chang, M. H., Huang, S. C., ... Chen, D. S. (1995). Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. *Journal of Pediatrics, 126*(4), 589–591.

Linas, B. P., Hu, H., Barter, D. M., & Horberg, M. (2014). Hepatitis C screening trends in a large integrated health system. *The American Journal of Medicine*, *127*(5), 398–405.

Marine-Barjoan, E., Berrébi, A., Giordanengo, V., Favre, S. F., Haas, H., Moreigne, M., ... Bongain, A. (2007). HCV/HIV co-infection, HCV viral load and mode of delivery: Risk factors for mother-to-child transmission of hepatitis C virus? *AIDS*, *21*(13), 1811–1815.

Marschall, H. U., Wikström Shemer, E., Ludvigsson, J. F., & Stephansson, O. (2013). Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: A population-based cohort study. *Hepatology*, *58*(4), 1385–1391.

Martin, N. K., Vickerman, P., Grebely, J., Hellard, M., Hutchinson, S. J., Lima, V. D., ... Hickman, M. (2013). Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology*, *58*(5), 1598–1609.

Mast, E. E., Hwang, L. Y., Seto, D. S., Nolte, F. S., Nainan, O. V., Wurtzel, H., & Alter, M. J. (2005). Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *The Journal of Infectious Diseases*, *192*(11), 1880–1889.

Matthews-Greer, J. M., Caldito, G. C., Adley, S. D., Willis, R., Mire, A. C., Jamison, R. M., ... Chang, W. L. (2001). Comparison of hepatitis C viral loads in patients with or without human immunodeficiency virus. *Clinical and Diagnostic Laboratory Immunology, 8*(4), 690–694.

McHutchison, J. G., Gordon, S. C., Schiff, E. R., Shiffman, M. L., Lee, W. M., Rustgi, V. K., ... Albrecht, J. K. (1998). Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *The New England Journal of Medicine*, *339*(21), 1485–1492.

McIntyre, P. G., Tosh, K., & McGuire, W. (2006). Caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission. *Cochrane Database of Systematic Reviews*, (4), CD005546.

Mohd Hanafiah, K., Groeger, J., Flaxman, A. D., & Wiersma, S. T. (2013). Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. *Hepatology, 57*(4), 1333–1342.

Murphy, E. L., Fang, J., Tu, Y., Cable, R., Hillyer, C. D., Sacher, R., … Retrovirus Epidemiology Donor Study. (2010). Hepatitis C virus prevalence and clearance among US blood donors, 2006–2007: Associations with birth cohort, multiple pregnancies, and body mass index. *The Journal of Infectious Diseases, 202*(4), 576–584.

Okamoto, M., Nagata, I., Murakami, J., Kaji, S., Iitsuka, T., Hoshika, T., ... Hino, S. (2000). Prospective reevaluation of risk factors in mother-to-child transmission of hepatitis C virus: High virus load, vaginal delivery, and negative anti-NS4 antibody. *The Journal of Infectious Diseases*, *182*(5), 1511–1514.

Oketani, M., Shibatou, T., Yamashita, K., Arima, T., & Arima, T. (2002). Postpartum acute exacerbation of chronic hepatitis C with complete response to interferon-alpha. *Journal of Gastroenterology*, *37*(8), 658–662.

Ozaslan, E., Yilmaz, R., Simsek, H., & Tatar, G. (2002). Interferon therapy for acute hepatitis C during pregnancy. *Annals of Pharmacotherapy, 36*(11), 1715–1718.

Paternoster, D. M., Santarossa, C., Grella, P., Palù, G., Baldo, V., Boccagni, P., & Floreani, A. (2001). Viral load in HCV RNA-positive pregnant women. *The American Journal of Gastroenterology*, *96*(9), 2751–2754.

Patrick, D. M., Buxton, J. A., Bigham, M., & Mathias, R. G. (2000). Public health and hepatitis C. *Canadian Journal of Public Health*, *91*(Suppl. 1), S18–S21, S19–S23.

Pergam, S. A., Wang, C. C., Gardella, C. M., Sandison, T. G., Phipps, W. T., & Hawes, S. E. (2008). Pregnancy complications associated with hepatitis C: Data from a 2003–2005 Washington State birth cohort. *American Journal of Obstetrics and Gynecology, 199*(1), 38.e31–38.e39.

Polywka, S., Schröter, M., Feucht, H. H., Zöllner, B., & Laufs, R. (1999). Low risk of vertical transmission of hepatitis C virus by breast milk. *Clinical Infectious Diseases, 29*(5), 1327–1329.

Prasad, M. R., & Honegger, J. R. (2013). Hepatitis C virus in pregnancy. *American Journal of Perinatology*, *30*(2), 149–159.

Razavi, H., Waked, I., Sarrazin, C., Myers, R. P., Idilman, R., Calinas, F., ... Estes, C. (2014). The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. *Journal of Viral Hepatitis, 21*(Suppl. 1), 34–59.

Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. (1998). *MMWR Recommendations and Reports*, *47*(RR-19), 1–39.

Resti, M., Azzari, C., Mannelli, F., Moriondo, M., Novembre, E., de Martino, M., & Vierucci, A. (1998). Mother to child transmission of hepatitis C virus: Prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany Study Group on Hepatitis C Virus Infection. *BMJ*, *317*(7156), 437–441.

Roberts, E. A., & Yeung, L. (2002). Maternal–infant transmission of hepatitis C virus infection. *Hepatology*, *36*(5, Suppl. 1), S106–S113.

Snijdewind, I. J., Smit, C., Schutten, M., Nellen, F. J., Kroon, F. P., Reiss, P., & van der Ende, M. E. (2015). Low mother-to-child-transmission rate of hepatitis C virus in cART treated HIV-1 infected mothers. *Journal of Clinical Virology*, *68*, 11–15.

Spera, A. M., Eldin, T. K., Tosone, G., & Orlando, R. (2016). Antiviral therapy for hepatitis C: Has anything changed for pregnant/lactating women? *World Journal of Hepatology*, *8*(12), 557–565.

Stoszek, S. K., Abdel-Hamid, M., Narooz, S., El Daly, M., Saleh, D. A., Mikhail, N., ... Strickland, G. T. (2006). Prevalence of and risk factors for hepatitis C in rural pregnant Egyptian women. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *100*(2), 102–107.

Tahan, V., Karaca, C., Yildirim, B., Bozbas, A., Ozaras, R., Demir, K., ... Tozun, N. (2005). Sexual transmission of HCV between spouses. *The American Journal of Gastroenterology, 100*(4), 821–824.

Thomas, S. L., Newell, M. L., Peckham, C. S., Ades, A. E., & Hall, A. J. (1998). A review of hepatitis C virus (HCV) vertical transmission: Risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection. *International Journal of Epidemiology*, *27*(1), 108–117.

Ugbebor, O., Aigbirior, M., Osazuwa, F., Enabudoso, E., & Zabayo, O. (2011). The prevalence of hepatitis B and C viral infections among pregnant women. *North American Journal of Medical Sciences*, *3*(5), 238–241.

Valladares, G., Chacaltana, A., & Sjogren, M. H. (2010). The management of HCV-infected pregnant women. *Annals of Hepatology, 9*(Suppl.), 92–97.

Vandijck, D., Moreno, C., Stärkel, P., Van Damme, P., Van Vlierberghe, H., Hindman, S. J., ... Laleman, W. (2014). Current and future health and economic impact of hepatitis C in Belgium. *Acta Gastro-enterologica Belgica*, *77*(2), 285–290.

Ward, C., Tudor-Williams, G., Cotzias, T., Hargreaves, S., Regan, L., & Foster, G. R. (2000). Prevalence of hepatitis C among pregnant women attending an inner London obstetric department: Uptake and acceptability of named antenatal testing. *Gut, 47*(2), 277–280.

Wedemeyer, H., Duberg, A. S., Buti, M., Rosenberg, W. M., Frankova, S., Esmat, G., ... Gower, E. (2014). Strategies to manage hepatitis C virus (HCV) disease burden. *Journal of Viral Hepatitis, 21*(Suppl. 1), 60–89.

Yao, N., Reichert, P., Taremi, S. S., Prosise, W. W., & Weber, P. C. (1999). Molecular views of viral polyprotein processing revealed by the crystal structure of the hepatitis C virus bifunctional protease-helicase. *Structure*, *7*(11), 1353–1363.

Yeung, L. T., King, S. M., & Roberts, E. A. (2001). Mother-to-infant transmission of hepatitis C virus. *Hepatology*, *34*(2), 223–229.

Yeung, L. T., To, T., King, S. M., & Roberts, E. A. (2007). Spontaneous clearance of childhood hepatitis C virus infection. *Journal of Viral Hepatitis*, *14*(11), 797–805.

Yildirim, B., Barut, S., Bulut, Y., Yenişehirli, G., Ozdemir, M., Cetin, I., ... Sahin, S. (2009). Seroprevalence of hepatitis B and C viruses in the province of Tokat in the Black Sea region of Turkey: A population-based study. *The Turkish Journal of Gastroenterology*, *20*(1), 27–30.

Zein, C. O., Abu-Lebdeh, H., & Zein, N. N. (2001). Spontaneous clearance of chronic hepatitis C during pregnancy. *The American Journal of Gastroenterology*, *96*(10), 3044–3045.

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