World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i40.6714

World J Gastroenterol 2013 October 28; 19(40): 6714-6720
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (2): Hepatitis C virus

Hepatitis C and pregnancy

Annarosa Floreani

Annarosa Floreani, Department of Surgery, Oncology and Gastroenterology, University of Padova, 35128 Padova, Italy
Author contributions: Floreani A designed and wrote the review.
Correspondence to: Annarosa Floreani, MD, Department of Surgery, Oncology and Gastroenterology, University of Padova, Via Giustiniani 2, 35128 Padova, Italy.annarosa.floreani@unipd.it
Telephone: +39-49-8212894 Fax: +39-49-8760820
Received: July 11, 2013 Revised: August 22, 2013
Accepted: September 4, 2013
Published online: October 28, 2013

Abstract

Acute hepatitis C is a rare event in pregnancy. The most common scenario is chronic hepatitis C virus (HCV) infection in pregnancy. During pregnancy in women with chronic HCV infection a significant reduction in mean alanine aminotransferase levels has been reported, with a rebound during the postpartum period. In few cases exacerbation of chronic hepatitis C has been reported in pregnancy. A cofactor that might play a role in the reduction of liver damage is the release of endogenous interferon from the placenta. Observations regarding serum HCV-RNA concentration have been variable. In some women HCV-RNA levels rise toward the end of pregnancy. In general, pregnancy does not have a negative effect on HCV infection. Conversely, chronic hepatitis does not appear to have an adverse effect on the course of pregnancy, or the birth weight of the newborn infant. The role of spontaneous abortion is approximately the same as in the general population. The overall rate of mother-to-child transmission for HCV is 3%-5% if the mother is known to be anti-HCV positive. Co-infection with human immunodeficiency virus (HIV) increases the rate of mother-to-child transmission up to 19.4%. Numerous risk factors for vertical transmission have been studied. In general, high viral load defined as at least 2.5 × 10^6 viral RNA copies/mL, HIV co-infection, and invasive procedures are the most important factors. Both interferon and ribavirin are contraindicated during pregnancy. Viral clearance prior to pregnancy increases the likelihood that a woman remains non-viremic in pregnancy with a consequent reduced risk of vertical transmission.

Key words: Hepatitis C virus; Pregnancy; Virus transmission; Liver damage; Viral RNA

Core tip: In general, pregnancy does not have a negative effect on hepatitis C virus (HCV) infection. Conversely, chronic hepatitis does not appear to have an adverse effect on the course of pregnancy, or the birth weight of the newborn infant. The overall rate of mother-to-child transmission for HCV is 3%-5% if the mother is known to be anti-HCV positive. Co-infection with HIV increases the rate of mother-to-child transmission up to 19.4%.

Floreani A. Hepatitis C and pregnancy. *World J Gastroenterol* 2013; 19(40): 6714-6720 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i40/6714.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i40.6714

INTRODUCTION

The global prevalence of hepatitis C virus (HCV) infection is 2%-3%, with 130-170 million HCV-positive people - most of them chronically infected[1]. The epidemiology of HCV is varies among countries and the reported prevalence of HCV in pregnant women has not been extensively studied, due to the lack of preventative screening of infection and the lack of preventative measures of mother-to-child transmission. The pathogenesis of HCV infection during pregnancy remains poorly understood. During pregnancy, the maternal immune system must at the same time develop tolerance to paternal alloantigens to prevent maternal immune aggression against the fetus

Table 1 Prevalence of serum anti-hepatitis C virus and hepatitis C virus RNA in in studies examining ⩾ 3000 pregnant mothers

Ref.	No. screened	Anti-HCV$^+$	HCV RNA$^+$
Hillemanns *et al*[3]	3712	0.94%	57%
Conte *et al*[4]	15250	2.40%	72%
Ward *et al*[5]	4729	0.80%	72%
Baldo *et al*[6]	4008	1.70%	42.50%
Goldberg *et al*[7]	3548	0.60%	NA
Kumar *et al*[8]	8130	1.03%	NA
Sami *et al*[9]	5902	1.80%	NA
Ohto *et al*[10]	22664	0.50%	54%
Seisdedos *et al*[11]	474539	0.15%	NA
Ugbebor *et al*[12]	5760	3.60%	NA
Pinto *et al*[13]	115386	0.10%	NA
Urbanus *et al*[14]	4563	0.30%	NA
Mean		1.16%	59.75%

HCV: Hepatitis C virus; NA: Not available.

and maintain active immunity against HCV to protect both mother and fetus from infection[2]. Moreover, it is important to define the effect of pregnancy on HCV and vice versa. Finally, understanding the transmission of HCV to infants and the risk factors correlated with transmission will provide information for counseling and management of HCV infection during puerperium.

EPIDEMIOLOGY OF HCV IN PREGNANCY

The current prevalence of HCV in pregnant mothers is difficult to be estimated, because of the lack of selective screening in a large proportion of this population. The prevalence of serum HCV antibody in cohorts of ⩾ 3000 pregnant mothers ranges between 0.1% and 3.6% with a mean of 1.16%, and the prevalence of HCV RNA ranges between 42.5% and 72%[3-14] (Table 1). It is particularly interesting that in Egyptian rural villages the prevalence of anti-HCV reaches a mean of 15.5%, with a 30% rate in women aged > 35 years[15]. The epidemiological risk factors explaining this dramatic high prevalence include: previous delivery attended by a traditional birth assistant; circumcision by a traditional birth assistant or a "healthy barber"; and injection therapy for schistosomiasis.

In all series the main route of acquiring HCV in pregnant mothers is intravenous drug use, whereas a previous blood transfusion is a risk factor in up to 11% of cases[4,6,16-22] (Table 2).

It is should be noted that a large study in Japan has demonstrated a significant decline in HCV prevalence in pregnant women[10]. In a cohort studied between May 1990 and November 2004, a total of 22664 consecutive serum samples were screened for anti-HCV. Among women known to be transfused, rates fell from 14.8% to 3.1% with the implementation of HCV screening. In non-transfused women rates fell from 1.8% to 0.3%. This reduction has been mainly explained by the hygienic improvements including needles for medical injections and single-use acupuncture needles. The prevalence of HCV infection has been found to be lower in recent years compared to the 1990s and 2000s, even in Upper Egypt[23]. The lower prevalence rates may be due to the amelioration of standard care and to the hepatitis B virus (HBV) vaccination of all newborns, together with the mandatory testing of blood donors and blood products and careful preoperative measures.

Table 2 Proportion of intravenous drug use or blood transfusio risk factors in pregnant hepatitis C virus-positive mothers

Ref.	No. screened	IVDU	BT
Paccagnini *et al*[16]	70	79.00%	9.00%
Zanetti *et al*[17]	94	17.00%	13.00%
Granovski *et al*[18]	147	79.00%	NA
Hillemanns *et al*[19]	35	20.00%	11.00%
Resti *et al*[20]	403	25.00%	4.50%
Gervais *et al*[21]	26	35.00%	19.00%
Conte *et al*[4]	370	32.00%	18.00%
Baldo *et al*[6]	40	45.00%	2.50%
Mast *et al*[22]	242	52.30%	19.80%
Mean		42.60%	12.10%

IVDU: Intravenous drug use; BT: Blood transfusion.

ACUTE HEPATITIS C

Acute hepatitis C during pregnancy has been rarely reported in pregnancy, and limited to high-risk groups, such as intravenous drug users, whereas the risk in the general population is negligible. Flichman *et al*[24] described a case in a 16-year-old pregnant woman who developed icteric acute hepatitis. She was a chronic HIV carrier and was diagnosed with HCV superinfection. HCV infection interfered with HIV replication, because the HIV levels were undetectable during the course of acute HCV infection. Another case of acute hepatitis C was described in a 26-year-old woman at week 16 of pregnancy, who was treated with a short course of interferon[25]. Although the therapy was discontinued due to adverse effects, a complete biochemical and virological response was obtained. Premature labor occurred and healthy twin infants were born transvaginally; they did not acquire HCV infection. A case with acute hepatitis C and premature delivery, but no vertical transmission has also been reported[26]. Finally, acute hepatitis C was reported in a 29-year-old Japanese woman who developed fatigue, jaundice and ascites after a needle-stick injury[27]. When these symptoms were presented, the patient became pregnant by artificial insemination. She was treated with interferon-β following eradication of HCV infection without severe side effects. In general, however, it should be said that acute hepatitis C is a rare event in pregnancy and that there is also a publication bias, due to reporting only severe cases[28].

From the epidemiological point of view, however, acute hepatitis C is not a relevant problem in pregnancy[29,30].

The differential diagnosis of acute hepatitis C requires us to rule out hepatitis caused by other hepatotropic viruses (hepatitis A, B, D and E) and liver disorders unique to pregnancy. Hepatitis A is transmitted by the oral-fecal

route. The whole Mediterranean area is endemic for this infection. Acute hepatitis A virus infection in pregnancy has been described only in anecdotal cases, and virtually in 100% of cases it has a favorable outcome[31]. To date, acute episodes of HBV infection in Italy have been rare, because HBV vaccination in newborns and adolescents has been compulsory since 1991. However, acute infections in pregnancy can occur in immigrants from developing countries or in high-risk groups, such as intravenous drug users. The clinical course of acute hepatitis B in pregnancy is benign, and the risk of fulminant cases is similar in pregnant and non-pregnant women. Acute infection with hepatitis D virus (HDV) does not represent a relevant risk for death in pregnancy. However, HDV epidemiology has dramatically changed over the past 20 years. Only sporadic cases are recorded in the Mediterranean countries, whereas, it is still a problem in some South American areas (especially in the Amazon Basin) and India[32]. Hepatitis E virus (HEV) is endemic in many tropical and subtropical countries, including Central Asia and India[33]. Sporadic cases in immigrants from these countries might be seen in developed countries. Generally, symptoms of acute illness including jaundice develop in 80% of cases. The reported risk for fulminant hepatic failure in pregnancy was up to 20% in previous studies[34]. Even in mothers who recover from acute hepatitis, an increased frequency of abortion and fetal complications have been reported. Moreover, the severity of acute hepatitis E in pregnant women seems directly correlated with viral load[35]. However, the results from recent studies in India and elsewhere indicate that the severity of viral hepatitis during pregnancy is similar to that in non-pregnant women[36].

Acute viral hepatitis in pregnancy requires differential diagnosis from liver disorders unique to pregnancy, in particular the HELLP syndrome, intrahepatic cholestasis of pregnancy (ICP), and acute fatty liver of pregnancy[37,38]. The HELLP syndrome is a variant of pre-eclampsia/eclampsia and is characterized by elevated liver enzymes, low platelet count and hemolysis. Its onset is generally in the second trimester of pregnancy, and patients may show initially elevated blood pressure, edema and proteinuria[39]. The intrahepatic cholestasis of pregnancy most frequently occurs in the third trimester of pregnancy with pruritus and elevated serum transaminases and bile salts; jaundice is rare and synthetic function of the liver is conserved[40]. Acute fatty liver of pregnancy is a severe condition that usually occurs in the third trimester with symptoms of encephalopathy and liver failure[41]. Early diagnosis is essential because treatment of acute hepatitis is generally conservative, whereas acute fatty liver of pregnancy and often HELLP syndrome require immediate delivery.

CHRONIC HEPATITIS C

The most important studies of HCV in pregnancy have dealt with chronically infected women, and the natural history of the liver disease in pregnant mothers and their offspring is not fully understood.

EFFECT OF PREGNANCY ON HCV

During pregnancy in chronic HCV infection a significant reduction in the mean alanine aminotransferase (ALT) levels has been reported[4,42,43], with rebound during the postpartum period. However, when we consider a cohort of pregnant women with HCV infection and persistently high aspartate aminotransferase/ALT levels, this trend is not confirmed[43]. The release of endogenous interferon from the placenta during pregnancy might partly explain changes in liver enzymes, but does not interfere with viral clearance[44]. Other factors, such as hemodilution or immune tolerance, may account for the decrease in serum transaminases during pregnancy. Sex hormones, and possibly immunosuppressive cytokines synthesized during pregnancy, might result in modulation of the immune response against HCV.

Observations regarding serum HCV-RNA concentration have been variable. Gervais *et al*[21] investigated a small number of pregnant women tested for viral load at regular intervals, and found that HCV RNA increased toward the end of pregnancy in some women. In our own study of 65 pregnant women tested during all three trimesters, we failed to show significant changes in viral load during and after pregnancy, although there was a trend toward an increase in the third trimester[43]. However, monitoring of viral load by monthly testing showed that HCV RNA is relatively stable over time in HCV chronic carriers without biochemical activity of the disease, whereas a low number of viremic flares can occur over a year in patients with biochemical activity of liver disease[45].

Spontaneous clearance of HCV has been described in a single pregnant woman[46]. Only two reports describe significant worsening of histological disease consequent to pregnancy[47,48]. The study by Fontaine *et al*[48] included 12 cases with chronic hepatitis C and 12 controls without HCV infection. The first biopsy was done 1.6 years after delivery and the second at 4.3 years after the first biopsy. The overall Knodell score at initial biopsy was 4.8 in HCV-positive cases *vs* 5.3 in the controls. The Knodell score in the final biopsy was unchanged in controls, and was 8.4 in HCV-positive cases ($P = 0.016$). The necroinflammation score showed 83% deterioration in cases and 25% in controls ($P = 0.02$). The fibrosis score showed 41.6% deterioration in cases and 8.3% in controls ($P > 0.05$). These findings in a small group of subjects, however, did not allow for any definite conclusion to be drawn.

Effect of HCV on course of pregnancy

There is no unfavorable effect of HCV on pregnancy. In particular, three studies have addressed this question[18,49,50] (Table 3). The study from Jabeen *et al*[49] is particularly interesting, because it included a large cohort of rhesus-negative women in Ireland who became in-

Table 3 Effect of hepatitis C virus on the course of pregnancy

	Hillemanns *et al*[19]	Jabeen *et al*[49]	Floreani *et al*[50]
Miscarriages	NA	12.4% *vs* 22.2%	-
Typical obstetric complications	-	-	-
Preterm delivery	29% *vs* 19%	4.5% *vs* 3.2%	NA
Rate of cesarean section	42% *vs* 21% (P = 0.004)	5.6% *vs* 12.7%	41.50%
Fetal outcome	Good	Good	Good

NA: Not available.

fected with HCV following exposure to contaminated anti-D immunoglobulin in 1977-1978. Thirty-six women who had been infected after their first pregnancy were compared to an age- and parity-matched control group of rhesus-positive women. Comparison with the control group showed no increase in spontaneous miscarriage rate, and no significant difference in obstetric complications. Taken together, these three studies have documented a good fetal outcome. The rate of cesarean section was significantly higher in the study by Hilleman *et al*[19] compared to controls (42% *vs* 21%, P = 0.004) and was similar to that observed in the Italian study[50]. The high rate of cesarean section in our study was due to the local protocol used in the past decade for reducing the rate of transmission of HCV in HCV-positive mothers, rather than peculiar obstetric indications for cesarean section.

In a population-based cohort study using Washington state birth records from 2003 to 2005, including 506 HCV-positive mothers, 2022 randomly selected HCV-negative mothers, and 1439 drug-using HCV-negative mothers, it was shown that infants born to HCV-positive women were more likely to have low birth weight, be small for gestational age, be admitted to the intensive care unit, or require assisted ventilation[51].

In a more recent study using birth certificate records of 1670369 pregnancies, it was found that women with HCV were more likely to have infants born preterm, with low birth weight and congenital anomalies[52]. However, that study had several limitations, in particular, its retrospective design and the lack of association with several variables, such as use of tobacco, alcohol or drugs. Indeed, there is no explanation for prematurity and low birth weight in HCV-negative mothers, although increased cytotoxicity of placental natural killer T cells could be hypothesized possibility[53].

It has also been reported that in pregnant women involved in a methadone treatment program, HCV reactivity was associated with an increased risk of neonatal withdrawal regardless of maternal methadone use[54].

Risk factors for the development of ICP in HCV-positive mothers have been described. The first retrospective study reported a highly significant incidence of ICP in HCV-positive pregnant women compared with HCV-negative women[55]. Subsequently, another prospective Italian study confirmed these results and suggested the need to investigate the HCV status in women with ICP[56]. In a study population of 21008 women with ICP identified from the Finnish Hospital Discharge Register during 1972-2000, hepatitis C was found to have a significantly higher incidence than in the controls[57]. More recently, a study of women with births between 1973 and 2009, registered in the Swedish Medical Birth Registry, confirmed a strong positive association between ICP and hepatitis C both before and after ICP diagnosis[58]. The link between ICP and HCV has not been completely explained so far, although several hypotheses can be suggested, including a defect in the transport of sulfated pregnancy hormones in the liver. It has been suggested that HCV downregulates the expression of the ABC transporter multi-drug resistance protein 2 (MRP2) in the liver, thus inducing failure in the transport of various toxic substances[59]. Furthermore, another link may be with a defect in the *ABCB11* gene encoding the bile salt export pump[60].

Vertical transmission of HCV

The overall rate of mother-to-child transmission of HCV from HCV-infected, HIV-negative mothers has been estimated at 3%-5%[61-66]. However, in an overview of 77 prospective cohort studies with at least 10 mother-infant pairs, the overall rate was 1.7% if the mother was known to be anti-HCV positive. If the mother was known to be viremic, that is HCV-RNA-positive, the rate was 4.3%[67]. At least one-third of infants acquire HCV infection during the intrauterine period; the perinatal transmission is estimated to be as high as 40%-50%, whereas postpartum transmission is rare[30,68]. The detection of HCV RNA in the serum of infants in the first 24 h of life suggests that early intrauterine infection may be possible[68]. The diagnosis of perinatal transmission should be considered in children born to HCV-positive mothers when: HCV RNA is detected in at least two serum samples at least 3 mo apart during the first year of life; and/or when testing of antibodies against HCV is positive after 18 mo of age[69].

There is an interesting observation reported by the European Paediatric Hepatitis C Virus Network from a multicenter prospective study of HCV-infected pregnant women and their infants[69]. In that study girls were twice as likely to be infected as boys. This sex association is an intriguing finding that probably reflects biological differences in susceptibility or response to infection.

Co-infection with HIV increases the rate of mother-to-child transmission up to 19.4%[67]. The weighted rate of transmission is 8.6% in mothers who are anti-HCV positive and injecting drug users, compared with 3.4% in anti-HCV-positive mothers without known injecting drug use. A meta-analysis including 2382 infants estimated that the risk of HCV vertical transmission was 2.82 from anti-HCV^+/HIV^+ co-infected mothers compared with anti-HCV^+/HIV mothers[70]. Vertical transmission of HIV and HCV separately is most likely from HIV/HCV-co-infected mothers; however, transmission of both infections is less frequent[71].

Numerous risk factors for vertical transmission have been studied. In general, high viral load defined as at least

2.5×10^6 viral RNA copies/mL, HIV co-infection, and invasive procedures are the most important factors[22]. In general, maternal peripheral blood mononuclear cell infection by HCV, membrane rupture > 6 h before delivery, and procedures exposing the infant to maternal blood infected with HCV during vaginal delivery are associated with an increased risk of transmission[69]. Abnormal ALT levels in mothers in the year before pregnancy may reflect a more severe liver disease and may help in identifying mothers with an increased risk of vertical transmission[72]. Finally, a Japanese study suggested that maternal liver dysfunction, large blood loss at delivery, and vaginal delivery were potential novel risk factors for mother-to-child transmission of HCV[66].

ANTIVIRAL THERAPY FOR CHRONIC HCV INFECTION

Antiviral therapy for HCV is contraindicated in pregnancy. Pegylated interferon would be problematic because of its psychiatric side effects in these women, who have a high background rate of postpartum depression[73]. Ribavirin carries the risk of teratogenicity for up to 7 mo after cessation of treatment. Treatment options should be offered before pregnancy in HCV-infected women. In fact, delay in initiation of antiviral therapy likely to be much longer than 9 mo, taking into account the postpartum recovery, breastfeeding and infant care. The benefits of considering treatment first and pregnancy second are superior to the drawbacks, including eliminating the risk of transmission of HCV to infants and reducing the risk of liver progression in mothers. Furthermore, improved efficacy of new drug regimens will require reassessment of the utility of universal screening for HCV in pregnant women[74].

MANAGEMENT OF HCV-INFECTED WOMEN

All women should receive antenatal screening for hepatitis B surface antigen and anti-HCV; HCV should tested for in those found to be HCV positive, immigrants from developing countries, and in those with high-risk behavior (*e.g.*, multiple sexual partners and intravenous drug use)[75]. A consensus for management of HCV-infected pregnant women and their children by the European Paediatric Network has been recently published[76]. The conclusions of this panel of experts indicate that although several risk factors for vertical transmission have been identified, none are modifiable and there are currently no interventions available to prevent such transmission. Based on the current evidence, it would be prudent to avoid amniocentesis, instrumented vaginal delivery, and prolonged rupture of membranes. A recent meta-analysis including 641 mother-infant pairs showed that cesarean section does not decrease perinatal HCV transmission from HCV-RNA$^+$/HIV mothers to infants[77]. Thus elective cesarean delivery should not be offered, and breastfeeding should not be discouraged. HCV/HIV co-infected women should be offered elective cesarean section to prevent HIV transmission and avoid breastfeeding where safe alternative are available[78].

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ISSN 1007-9327