

REVIEW

Hepatitis C in pregnancy

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At the end of the second millennium, chronic hepatitis C virus (HCV) infection is recognised as a major public health problem. The global prevalence of chronic HCV infection is estimated to be approaching 3% (over 170 million HCV infected people) with considerable geographical variation, ranging from 0.01–0.1% in the United Kingdom and Scandinavia to 17–26% in Egypt.¹ At present, the infection rate peaks among adults aged 30–49 and declines sharply in those older than 50 years, suggesting acquisition of HCV within the past 10–30 years.¹ In the United States, the estimated anti-HCV prevalence in 6–11 year old children is 0.2%, and among adolescents aged 12–19 it is 0.4%.^{2,3} HCV induced end stage chronic liver disease is a leading indication for transplantation in the adult population of the United States.^{1,2} Anti-HCV screening of blood products introduced during the early 1990s has minimised this mode of HCV acquisition, leaving vertical transmission from infected mothers as the predominant mode of infection in children. Theoretically, vertical transmission of HCV may occur at conception, in utero, perinatally, or during lactation. However, its mechanisms, including timing, remain largely unknown.

HCV and conception

Any significant chronic liver disease may render both women and men subfertile through a combination of pathogenic mechanisms. Most female patients with chronic HCV, however, will not develop end stage chronic liver disease during their fertile period. A recent study from Ireland followed up a group of 36 rhesus negative women infected with HCV type 1b following postnatal exposure to contaminated anti-D immunoglobulin.⁴ Over 20 years, despite the presence of biochemical abnormalities in 55% and liver fibrosis in 42%, there were a total of 100 pregnancies, with no difference in the incidence of spontaneous miscarriages, premature deliveries, and obstetric interventions compared with controls. None of the 53 HCV RNA positive women in a large Italian study,⁵ from whom biopsy specimens were taken either before or after pregnancy, was cirrhotic. Mild fibrosis was found in most of the patients, and bridging fibrosis was more commonly the result of HCV genotype 3a infection.⁵

Following reports that HCV can be found in the semen⁶ and that the infection can be

acquired during artificial insemination,⁷ suggestions have been made to introduce tighter anti-infectious control measures in reproductive medicine. This may include compulsory HCV testing of donors of genetic material, to eliminate the risk of transmission from HCV infected sperm/egg donors.

HCV and pregnancy

Results from several small studies have shown variations in anti-HCV prevalence in pregnancy from 0.6% in Japan⁸ to 4.5% in the United States.⁹ In the largest study performed so far, investigating more than 15 000 pregnant women from northern Italy over four years, a prevalence of 2.4% was found.⁵ The principal risk factors were history of intravenous drug abuse (32%) and exposure to blood products (24%). Some 40% of the women, however, had no risk factors for HCV infection. In the same study, 4% and 2.1% of the patients were found to be anti-HIV and HBsAg positive respectively. A recent UK study of multiethnic pregnant HIV negative women from inner city areas, who volunteered for testing, showed an anti-HCV prevalence of 0.8%, with 75% of the patients also being HCV RNA positive.¹⁰ It was noteworthy that 69% of the pregnant women were newly diagnosed and 73% had no identifiable risk factors for hepatitis C.

HCV virions can be detected in amniotic fluid,¹¹ but their presence may not be relevant to vertical transmission. In a cohort of 22 anti-HCV positive pregnant women who had an amniocentesis for obstetric reasons at four months of pregnancy, Delamare *et al*¹¹ identified only one viraemic patient, whose amniotic fluid was positive for HCV RNA (230 copies per ml). The virions could not be detected in the amniotic fluid of the remaining 21 women, 15 of whom were HCV RNA seropositive. The offspring of the mother with HCV infected amniotic fluid had negative HCV RNA shortly after birth and appears to have escaped the infection. Follow up, however, was limited to four days, and only nine of the remaining 21 babies were tested for HCV RNA and found to be negative.

Several studies have shown improvement in biochemical markers of liver damage in HCV positive women during pregnancy.^{5,12} This may be partially explained by haemodilution, secondary to a relative increase in circulating blood volume in the final trimester of pregnancy, because the transaminase levels appear

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to return to levels found before pregnancy shortly after delivery.⁵ It may be possible, however, that the changes in immune response during pregnancy play a role in the host-HCV interaction. Several papers have shown a linear increase in HCV viraemia throughout pregnancy,^{5 12} which may be compatible with impaired immune reactivity. In pregnancy, maternal immune responses against foreign, including fetal, antigens, are downregulated by incompletely understood mechanisms. HCV specific immune response involves activation of antigen specific helper (Th) and CD8+ cytotoxic T cells. After HCV infection, activated T cells display a Th1 cytokine profile, with a predominance of interferon γ .¹³ It has been suggested that increases in serum oestrogen concentration during pregnancy may alter the process of T cell differentiation.¹⁴ On the other hand, the placenta is a site of interferon α synthesis,¹⁵ which may assist HCV control by the pregnant host. A recent case report has only added to the conundrum surrounding the immune mechanisms of HCV control in pregnancy.¹⁶ Severe haemolytic disease of the fetus was treated by repeated intrauterine red blood cell transfusions between 19 and 31 weeks of gestation, including blood from a donor who HCV seroconverted four months after the last donation. The pregnant woman, but not her offspring, became infected. The authors speculate that a difference in immune reactivity between the mother and the fetus against the virus may have been responsible for the different outcomes.

Overall, there is no apparent deleterious effect of pregnancy on the course of HCV infection. Conversely, there is also no evidence to suggest a shorter duration, increased number of congenital anomalies and obstetric complications, or lower birth weights in children born to HCV infected women.^{5 17 18} One retrospective single centre study noted a twofold increase in the rate of obstetric indications for caesarean section in anti-HCV positive women (42%),¹⁹ probably due to limited intrapartum fetal surveillance in an attempt to minimise the risk of vertical transmission by avoiding fetal scalp blood sampling.

Vertical transmission of HCV

A Japanese study was the first to show the presence of the same HCV genotype with > 95% homology in three generations of the same family.²⁰ Some 44% of Italian children diagnosed with HCV infection since the introduction of mandatory anti-HCV screening of blood products are vertically infected.²¹ However, blood products may still represent a potential source of infection because of manufacturing incidents or a seroconversion window in blood donors.^{4 16}

Timing of vertical HCV infection remains unknown. Silverman *et al*²² found that 19% of cord blood samples from 47 anti-HCV positive women were HCV RNA positive. However, Conte *et al*²³ showed a low predictive value of cord blood HCV RNA testing for vertical transmission. In their study, 16 of 18 newborns

who were HCV RNA positive at birth became negative, while six who were HCV RNA negative were found to be positive by the fourth month of life. On the basis of these results, the authors suggest that, to identify vertically infected infants, polymerase chain reaction on HCV RNA should be performed at 4 months of age. A few smaller studies have shown “negativisation” of HCV RNA later in infancy after positive tests in the neonatal period.^{23–26} These observations suggest either the presence of a genuine transient postnatal viraemia or possible problems with the standardisation of HCV RNA PCR assays. The presence of passively acquired maternal antibodies, which can persist in infants until 15–18 months of age, renders anti-HCV detection of limited value for the diagnosis of infection. At our centre we are investigating vertical transmission by testing HCV RNA PCR at birth, 6, 18, and 24 months of age.

There is no geographical variation in the reported risk of vertical HCV transmission, which is about 5%.^{5 17 27–29} HIV co-infection and high HCV and HIV viral loads increase the risks of vertical transmission severalfold.^{17 27} Resti *et al*²⁸ found that the rate of HCV vertical transmission in HIV negative women who were intravenous drug users or blood product recipients was 12%, as opposed to 2% in women with no risk factors. In a retrospective study from the United Kingdom, none of the infants born by elective caesarean section were infected, whereas the HCV transmission rate was 7.7% for vaginal delivery and 5.9% for emergency caesarean section.²³ Vaginal delivery and female sex of the offspring were found by one study to increase the risks of vertical HCV transmission.¹⁷ These findings were not confirmed by other larger studies.^{5 27} A recent prospective study from northern Italy showed a lack of neutralising anti-C100 antibodies, tested by recombinant immunoblot assay, in the mothers who would eventually transmit the virus.²⁹ The viral genotype seems not to play a major role in vertical transmission.^{30 31} The risk of transmission does not appear to be increased in subsequent pregnancies of HCV positive women who infected their offspring during previous pregnancies.³²

Vertical HCV transmission and breast feeding

HCV virions can be detected in colostrum and breast milk of about 20% of viraemic women.²⁴ A number of large epidemiological studies of vertical transmission failed to document a role for breast feeding (reviewed by Hunt *et al*³³). However, Kumar and Shahul³⁴ showed HCV infection in infants who were HCV RNA negative at birth and exclusively breast fed by viraemic mothers. A recent small study from Spain showed a significantly increased rate of vertical transmission in breast fed infants of HCV positive/HIV negative women.²⁴ In this study there was a positive correlation between maternal serum HCV RNA levels and presence of HCV in breast milk.

Although the numerous retrospective studies could not document an increased risk of vertical transmission in breast fed infants,^{5 27 33} the fact that HCV may be present in colostrum and breast milk²⁴ and may be involved in late transmission³⁴ should not be overlooked. When counselling on the preferable mode of delivery and breast feeding in HCV positive women, a prudent view may be a tailor made one, based on recognised risk factors such as viral load during pregnancy and HIV/HBV co-infection. An individualised approach should also include assessment of socioeconomic circumstances because the general benefits of breast feeding in developing countries outweigh the slightly increased risk of HCV vertical transmission.

Natural history of vertically acquired HCV infection

The natural history of chronic HCV infection, including a vertically acquired one, is not well defined. Most children have mild biochemical and histological abnormalities and would not develop significant liver complications during childhood.^{35 36}

In a study preceding the discovery of HCV, Tong *et al*³⁷ found that six infants born to women who developed non-A-non-B hepatitis during the last trimester of pregnancy had abnormal serum alanine aminotransferase levels at 4–8 weeks of age. In contrast, three infants born to women who became symptomatic in the second trimester had no biochemical abnormalities. A few small studies investigating the progression of vertically acquired HCV infection have shown abnormal liver function tests and histology in a significant percentage of patients over a relatively short period.^{36 38} Bortolotti *et al*³⁶ found abnormal transaminases in all 14 HIV negative children with vertical HCV infection during the first year of life. In a separate report, the same group found that over a six year period none of the vertically infected children had cleared HCV, with very little variation in HCV RNA levels.³⁹ Similar to suggestions from studies in adults, they found no correlation between HCV RNA levels, biochemical markers, and histological activity of the disease. In another Italian study, seven children with vertically acquired HCV were followed up over a mean period of 5.5 years: abnormality of transaminase levels was seen in all, and chronic persistent hepatitis was found in all five children who had a liver biopsy.³⁸ In contrast, a recent large German study assessing children who acquired HCV from blood transfusions during open heart surgery showed a 45% rate of spontaneous viral clearance over 20 years. Only mild histological changes were found in biopsy specimens from 16 out of 17 patients who remained viraemic with biochemical evidence of liver injury.⁴⁰ Whether different modes of HCV acquisition have diverse natural histories remains unclear at present.

Prevention of vertical transmission: is HCV screening in pregnancy indicated?

At present, there is no uniform pan-European policy for prevention of vertical transmission of

Table 1 Women for whom anti-HCV testing should be performed in pregnancy

- Women with history of exposure to blood products
- Women with history of intravenous drug abuse
- Patients and staff members involved in chronic dialysis programmes
- Women with HIV or HBV infection
- Sexual partners of people with HIV, HBV or HCV infection
- Women with history of body piercing and tattooing
- Recipients of organ transplants before 1992
- Women with unexplained hypertransaminasaemia
- Participants in *in vitro* fertilisation programmes from anonymous donors

HCV, Hepatitis c virus; HBV, hepatitis B virus.

HCV. The recommendations vary significantly with respect to selective testing during pregnancy, elective caesarean section, and risks associated with breast feeding.⁴¹ Current international guidelines do not suggest avoidance of vaginal delivery and breast feeding to minimise the risk of vertical HCV transmission.^{42 43}

On the basis of an estimated HCV prevalence of 1–2% and a vertical transmission rate of 5%, to identify a single case of infantile hepatitis C, it would be necessary to screen 5000–10 000 pregnant women. Given the lack of measures to prevent transmission and to treat the infection efficiently, universal screening in pregnancy has been considered to be not justified in geographical areas with relatively low HCV prevalence.⁴⁴ However, I strongly believe that at least certain high risk categories should be offered anti-HCV testing during pregnancy (table 1). Selective HCV screening during pregnancy may not only help to identify children at risk of acquiring HCV, but should also detect at an early stage asymptomatic adults, probably highly motivated because of prospective parenthood, who would benefit from education and treatment. As a consequence they may modify their alcohol intake, sexual behaviour, and views on tissue and organ donation, with overall benefits for the individual natural history and global epidemiology of HCV. In a pilot study in the United Kingdom, most pregnant women did not hesitate to accept the offer of HCV testing.¹⁰ Theoretically, if experience from the large studies in adults could be extrapolated to children, earlier treatment of a mild HCV related disease should result in higher HCV clearance rates. It should be borne in mind that interferon treatment is contraindicated in children younger than 2 years, and treatment with a combination of interferon and ribavirin, currently under investigation, is not recommended in children younger than 3 years.

Infants with suspected HCV infection should be tested for HCV RNA by PCR on two separate occasions. Children older than 18 months should be assessed for the presence of antibodies against HCV. Once the diagnosis is confirmed, HCV infected children should be followed at tertiary centres and possible treatments discussed with the family. Mothers and children with chronic hepatitis C should be immunised against hepatitis A and B because superinfection may have a more severe course in HCV positive people.⁴⁵

I believe that the current general attitude to diagnosis of HCV infection in pregnancy and

infancy needs to be modified. HCV testing is undoubtedly justified for the selected categories of pregnant women with risk factors. However, we need to be aware that this approach may miss more than half of HCV positive pregnant women.⁵⁻¹⁰ It is to be hoped that the continuing dynamic research on methods of HCV treatment for both children and adults will result in improved management. This would strengthen the case for the eventual introduction of universal HCV screening in pregnancy, which is not indicated at present.

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