Update on hepatitis C and implications for pregnancy

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Abstract

Mother-to-child transmission of hepatitis C virus infection occurs in a significant minority of cases and the diagnosis, treatment and cure of hepatitis C virus infection with direct acting antivirals prior to pregnancy can eliminate this risk in almost all cases. Women with hepatitis C virus infection have increased risks of adverse events in pregnancy and poor perinatal outcomes for their children, although the contribution of hepatitis C virus per se is difficult to determine. Altering the mode of delivery does not reduce mother to child transmission of hepatitis C virus infection, although avoidance of fetal scalp electrodes and other potential high risk procedures is recommended during pregnancy and delivery. Breast feeding has not been demonstrated to be a risk for mother-to-child transmission and avoidance of breast feeding is not recommended, although breast feeding with cracked or bleeding nipples is generally avoided. Safety of the currently available hepatitis C virus antivirals in pregnancy and breastfeeding has not yet been established.

Keywords

Hepatitis C, pregnancy, mother-to-child transmission, antiviral therapy

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Epidemiology and effects of the virus

The hepatitis C virus (HCV) is a common viral pathogen, infecting more than 184 million people worldwide.¹ The main transmission routes are via blood-to-blood transmission and adult women are predominantly infected via non-sterile needle use though drug injection, tattooing or medical procedures. Mother-to-child transmission is an uncommon transmission route.

The infection causes chronic hepatitis in up to 75% of cases with the potential subsequent development of complications such as cirrhosis and liver cancer with associated mortality. Women are up to twice as likely as men to clear the infection during the acute phase and have a lower rate of progression to end stage liver disease, at least in the pre-menopausal period, with a 10 year difference in the median time to progression to cirrhosis between the sexes.²

Timing of HCV diagnosis in relation to pregnancy

The prevalence of HCV infection in pregnant women varies according to the underlying local prevalence and risk factors in the population studied. There is debate about whether universal HCV testing (screening) in pregnancy or a risk factor based approach is advisable for the diagnosis of HCV infection in pregnancy.

Some studies have found acceptable cost effectiveness of a universal screening strategy and some that did not find cost effectiveness anticipate cost effectiveness of such a strategy in the future with anticipated reductions in the cost of HCV antiviral therapy.^{3,4} Some national guidelines recommend routine screening and some authors have recommended against national screening where the prevalence in pregnant women was found to be low.^{5,6}

It is clear that a risk factor based-approach will not detect a proportion of cases when compared to universal testing in a range of settings, probably due to reluctance to disclose HCV-associated transmission risks.^{7–9} Single centre studies have documented that risk factor-based assessment missed cases in 2.5–10% of subjects and in another study, a risk factor questionnaire had a sensitivity of 85%.^{7–9} The diagnosis of HCV infection in pregnancy allows for follow-up of the infant for HCV infection and treatment of the woman before any subsequent pregnancy. A qualitative HCV RNA PCR test is needed to confirm the presence of chronic infection in

women with a positive serological test as a significant proportion (25–50%) of women clear the infection and remain seropositive.

If possible, the diagnosis of HCV infection should be made prior to pregnancy to ensure that treatment can be completed before conception.

Natural history of HCV infection in pregnancy

The natural history of acute HCV infection in pregnancy is not known. In women with chronic HCV infection, the viral load generally increases and the hepatic transaminase levels decline in the second and third trimesters, with normalization of hepatic transaminase levels in 77% of women.¹⁰ Approximately two-thirds of women experience an increase in HCV viral load and reduction in hepatic enzymes in the post-partum period.¹¹ HCV clearance has been reported in pregnancy.¹²

Effects of HCV infection on fertility and pregnancy

HCV is not thought to directly affect fertility and the outcomes of fertility interventions in 218 serodiscordant couples appeared to be similar to couples without HCV infection.^{13,14}

Intrahepatic cholestasis in pregnancy is 20 times more likely in women with HCV infection.¹⁵ An increased risk of gestational diabetes mellitus has also been identified in studies using administrative datasets, which may represent the known diabetogenic effects of infection with HCV.^{16,17} One study identified an adjusted odds ratio of 1.6 for gestational diabetes, but could not control for some factors potentially associated with gestational diabetes such as family history and weight

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changes.¹⁶ Another study did examine changes in weight during pregnancy and found those women with HCV infection and excess weight gain in pregnancy were 2.5 times more likely to have gestational diabetes.¹⁷ Again, family history of diabetes was not able to be assessed. Those without excess weight gain did not have an increased risk, suggesting that multiple mechanisms may be involved.

There appear to be differences in pregnancy outcomes in women with HCV infection that are independent of the route of transmission or other risk factors for adverse pregnancy outcomes. A meta-analysis of cohort and case control studies found that preterm birth was approximately 60% more frequent in women with HCV infection and appeared to be unrelated to route of HCV acquisition or other factors associated with preterm birth such as age, parity, tobacco and alcohol use.¹⁸ Preterm birth and other adverse perinatal outcomes may relate to effects of HCV on trophoblasts leading to placental changes.¹⁹ One US cohort study identified that infants of HCV-infected mothers had higher rates of low birthweight, small for gestational age, need for assisted ventilation and neonatal intensive care (NICU) admission.¹⁷ However, after comparison with an HCV-uninfected cohort of people who inject drugs (PWID), only the need for assisted ventilation and NICU admission remained significant, suggesting that some of the associations were related to drug use or other factors. The persistent differences may relate to unmeasured confounders within drug using populations, such as duration of drug use or frequency of drug injection, which are risk factors for HCV infection. Further, the pregnancy outcomes in a cohort of women infected with HCV genotype 1b via contaminated anti-D immunoglobulin (as opposed to PWID) were similar to controls, raising the possibility that HCV itself may not fully mediate the adverse outcomes seen in some studies.²⁰ Perinatal mortality may also be increased in infants born to women with chronic viral hepatitis, with similar caveats on the available data.²¹

Mother-to-child transmission of HCV infection

A recent meta-analysis identified a mother-to-child transmission rate of 5.8% in viraemic women, and 10.8% in HIV co-infected women.²² This analysis could not compare people taking treatment for HIV infection with those not taking treatment and it did not stratify subjects by HIV viral load. A smaller, more recent study found that in women with HIV/HCV co-infection who were taking combination antiretroviral therapy in pregnancy, the transmission rate was closer to the HCV mono-infection transmission rate.²³ Another recent study of HIV co-infected women found a transmission rate of 9% but only 47.7% of the women in this study had an undetectable HIV viral load in the third trimester, which is not the current standard of care.²⁴

The transmission of HCV appears related to HCV viral load although transmission may occur at increased rates in people with HIV co-infection with similar levels of viral load.^{24–27} Maternal injecting drug use may be a risk factor for HCV transmission.²⁸ Additional data on women with controlled HIV replication throughout pregnancy would assist in understanding the true risk of HCV transmission in the current HIV treatment era.

There is no evidence that Caesarean section as a mode of delivery reduces HCV transmission. Prolonged rupture of membranes for more than 6 h and the use of invasive fetal monitoring may increase the risk of transmission, but the available studies have had inconsistent findings.^{26,27,29} Episiotomy may represent a risk for transmission.²⁶ Most of the data are from single centre studies, some with retrospective case ascertainment and many have small sample sizes, creating some uncertainty around these findings. Large series of cases with amniocentesis in HCV are not available to reliably assess the transmission risk. Breast feeding has not been demonstrated to be a risk for mother-to-child transmission and avoidance of breast feeding is not recommended, although breast feeding with cracked or bleeding nipples is generally avoided.²⁶ Case series suggest that the vertical transmission of HCV to twins may be discordant.³⁰

The children born to HCV viraemic women should be followed to determine their infection status. Options include a qualitative HCV RNA PCR test after 3 months of age (earlier testing may be falsely negative) or serum HCV antibody testing to establish loss of maternal antibodies after 18 months of age. As these recommendations are not always followed, and if 18-month follow-up is unlikely, an HCV RNA PCR test after two months of age should be considered.³¹

Treatment of HCV infection

The development of highly effective direct acting antivirals for HCV infection has altered the prospects of curative therapy for people with HCV infection, with cure rates of 90–100% reported with the currently available agents. A number of agents, used in combination, have been developed that target different enzymes or proteins involved in the replication cycle of the virus. Older regimens of pegylated interferon alpha and ribavirin are no longer used. Most of the regimens have few, if any drug-drug interactions, but there are reports of elevations of alanine aminotransferase when the combination of paritaprevir, ritonavir, ombitasvir and dasabuvir is co-administered with ethinyls-tradiol.³² This combination appeared to be safe with progestin-based contraceptives. Clinicians should always check for drug-drug interactions before prescribing therapy in people taking HCV antivirals.³³

With the currently available therapies, a small number of people will need to be treated with ribavirin, although most will be cured with other combination drug regimens. Ribavirin is teratogenic and embryocidal in animal species and also causes sperm abnormalities including DNA packaging abnormalities.³⁴ The plasma elimination half-life is 12 days, but may persist in non-plasma compartments (e.g., red blood cells) for as long as six months. The limited human pregnancy experience has not reported developmental toxicity attributable to ribavirin and there is no evidence of embryo-fetal harm when men were treated with ribavirin before fathering an infant. Although the data are very limited, this argues against a mutagenic effect of the drug and/or the transfer of clinically significant amounts of ribavirin in sperm. However, there remain concerns about human effects leading to a Centre for Disease Control (CDC, 1988) recommendation against the use of ribavirin during pregnancy and a manufacturer's recommendation that men using ribavirin with female partners of reproductive age should use effective contraception (two reliable forms) during and for six months after completion of therapy. An interim report from a ribavirin exposure registry published a series of cases with 49 live births with direct ribavirin exposure and 69 with indirect exposure revealed a small number of defects.³⁵ Two cases had torticollis, one had hypospadias, one had polydactyly and a neonatal tooth, one had G6PD deficiency, one had a ventricular septal defect and 4th ventricular cysts. These preliminary findings have not detected a signal indicating human teratogenicity. The authors aim to enrol 131 direct and 131 indirect ribavirin exposures, so it will be prudent to await further information about ribavirin to reassess the risk of unplanned ribavirin exposure.

The other recently developed HCV antiviral drugs have not been studied in pregnant women but in-utero exposures to these drugs are likely to be reported in the next few years as treatment uptake becomes more widespread. Their use in pregnancy and lactation cannot currently be recommended.

A diagnosis of HCV in pregnancy allows for the planning of curative HCV treatment after delivery and before any subsequent pregnancy is considered to reduce the risk of subsequent mother-to-child transmission. It is important to assess for the possibility of cirrhosis. This will allow screening for oesophageal varices and hepatocellular carcinoma and assist antiviral treatment planning to determine the urgency of treatment and it may alter the regimen or duration selected, depending on the agents available in the local context. In general, treatment should be planned after completion of breast feeding and given that treatment duration may be as little as 8–12 weeks, with 12 weeks follow-up to assess for cure (sustained virological response to

therapy after 12 weeks), the whole assessment, treatment and follow-up may be completed within 6 months after completion of breast feeding.

Substantial changes in the efficacy and tolerability of HCV treatment allow for cure of HCV infection in a majority of women, therefore diagnosing and treating HCV infection may best be undertaken in the pregnancy planning period to reduce the subsequent risk of mother-to-child transmission.

Case study

A 32-year-old woman presents with positive anti-HCV antibodies following routine screening. She is negative for other blood borne viruses, notably HIV and hepatitis B virus infections. She reluctantly discloses a brief period of drug injection in her early 20s. She has a healthy two-year-old son who was delivered vaginally at another institution. She reports that she was asked about drug use in her previous pregnancy but did not feel that she could disclose this to the team and was not tested for HCV infection as she had no apparent risk.

HCV RNA testing and subsequent genotyping confirms chronic infection with genotype 1a. She has no splenomegaly, jaundice, ascites or hepatic flap. The platelet count and coagulation studies do not suggest cirrhosis although the albumin is low, consistent with pregnancy. She asks about the most appropriate mode of delivery and treatment for HCV infection and you advise her to defer antiviral therapy until after completion of breast feeding and advise that the pregnancy and delivery management should be as normal apart from avoidance of invasive procedures during delivery. She is encouraged to breast feed with the proviso she interrupts breastfeeding if she develops cracked or bleeding nipples.

You advise testing of her son and his HCV antibody test is negative, consistent with clearance of maternal antibody and absence of infection. She is informed that there is approximately a 6% risk of infection to the fetus/newborn in her current pregnancy. She has an uncomplicated delivery and the child is tested for HCV RNA at three months of age and is found to be negative.

After pregnancy she undergoes transient elastography (Fibroscan) which is consistent with minimal hepatic fibrosis and no cirrhosis. After completion of breast feeding, she undergoes HCV treatment with sofosbuvir and ledipasvir and has a sustained virological response 12 weeks after completion of treatment, which is equivalent to cure. After reassurance that she has cleared HCV infection, she starts to plan the timing of her next pregnancy.

Conclusion

As the treatment for HCV infection has become more effective with a less burdensome toxicity profile, the diagnosis and elimination of HCV infection in women before pregnancy are feasible and preferable as there are no other proven methods to reduce mother-to-child transmission. As more women of pregnancy potential are treated for HCV with the newer antiviral drugs, surveillance of the safety of these agents in pregnancy will be important to inform future treatment decisions.

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