Pregnancy and Hepatitis C Virus

Tatyana Kushner, MD
Associate Professor of Medicine
Division of Liver Diseases
Department of Obstetrics, Gynecology, and Reproductive Sciences
Icahn School of Medicine at Mount Sinai
New York, New York

What is the prevalence of hepatitis C virus in pregnant women, and why has it been increasing recently in the United States?

A number of studies, including several international systematic reviews and meta-analyses, have examined the prevalence of hepatitis C virus (HCV) in pregnant women and found that it varied worldwide. Dr Nancy S. Reau and I reviewed different international prevalence studies in a recent manuscript in the Journal of Hepatology. One meta-analysis reported that the prevalence of HCV in pregnant women in Europe ranged from 0.1% to 0.9%, whereas a meta-analysis pooling data from studies in Africa found that the estimated prevalence of HCV in pregnant women in those studies was 3.4% overall.

There have also been a number of studies recently looking at the prevalence of HCV in the United States in both pregnant women and women of childbearing age. Notably, there has been a significant increase in HCV in both of these groups recently in the United States. This increase is largely related to the rise of injection drug use that has occurred nationally, particularly in rural settings, among non-Hispanic White individuals. For example, a study recently examined birth records from the National Center for Health Statistics, which looks at all births nationally, and found a significant increase in HCV from 1.8 cases to 4.7 cases per 1000 live births in the United States. These findings suggest that there is a significant problem of HCV among women of childbearing age and those who are pregnant that is potentially becoming worse because injection drug use is increasing among young people, which includes both of these groups of women.

What is the impact of HCV on pregnancy outcomes as well as neonatal outcomes?

Several studies have evaluated how having HCV during pregnancy can increase the risk of adverse pregnancy outcomes. My colleagues and I have conducted one such study using the ICES cohort, which comes from a large database in Ontario, Canada that includes linkage between maternal and infant data, and our findings were published last year in the Journal of Hepatology. We specifically wanted to understand how having HCV with active viremia is independently associated with pregnancy outcomes. Among pregnant women who had active HCV, we found a significantly increased risk of preterm delivery as well as elevated risks of intrahepatic cholestasis of pregnancy and postpartum hemorrhage. These findings demonstrate that HCV viremia itself (as opposed to potential confounding factors associated with HCV antibody-positive status) increases adverse outcomes in pregnancy.

As for neonatal outcomes, we did not see a significant impact on outcomes such as being small for gestational age or large for gestational age among neonates, other than possibly an association with neonatal jaundice.

What are the effects of pregnancy on the disease course of HCV?

This is an interesting issue. With hepatitis B virus (HBV), it is known that there is a risk of HBV flare in the context of pregnancy owing to immune changes that occur during and after pregnancy. With HCV, that is not necessarily the case. An increase in HCV viral activity has
not necessarily been seen, for example, during pregnancy or postpartum. On the other hand, several interesting reports have suggested that there may be an increased likelihood of spontaneous HCV clearance, particularly in the postpartum period. However, I have not seen that occur commonly in my clinical practice. It is possible that perhaps there is a slightly increased likelihood of spontaneous HCV clearance in the postpartum period, but I am not certain of how clinically significant the magnitude of this difference is.

**G&H** What is the risk of vertical transmission of HCV, and can it be reduced?

**TK** A large systematic review and meta-analysis looked at vertical transmission, or transmission from mother to child, of HCV and reported a risk of approximately 5.8% overall. However, if the mother is infected with HIV as well as HCV, the risk nearly doubles. Subsequent studies have reported estimates ranging from as low as approximately 2% to as high as 20%. Thus, the risk differs depending upon the study. Generally speaking, I tell my patients that the risk of transmission from mother to child in mothers with HCV is approximately 6%.

To date, no specific measures are available that can reduce this risk. With HBV, immunoprophylaxis can be offered to infants born to mothers with HBV. In addition, there are clear guidelines for situations in which antiviral therapy should be used in mothers with HBV to reduce the risk of vertical transmission further. However, with HCV, there are no clear recommendations regarding the role of direct-acting antiviral (DAA) treatment in the context of pregnancy.

On the other hand, it is well known that, similar to HBV, a higher viral load of HCV increases the risk of vertical transmission. This was seen in our study using the ICES database. A recent meta-analysis has also shown that a viral load of at least 6.0 log IU/mL is associated with an increased risk of vertical transmission. In addition, as previously mentioned, being coinfected with HIV increases the risk of HCV transmission.

**G&H** Is universal HCV screening of pregnant women recommended and cost-effective, and is rescreening necessary?

**TK** All the major societies in the United States now support the recommendation for universal HCV screening in pregnant women. These include the American Association for the Study of Liver Diseases, Infectious Diseases Society of America, Centers for Disease Control and Prevention (CDC), and US Preventive Services Task Force. Most recently, the American College of Obstetricians and Gynecologists has also endorsed the recommendation that all pregnant women should be screened. At least 2 studies have demonstrated that screening for HCV universally during pregnancy is cost-effective, which helped to support the guidance that all women should be screened during pregnancy.

It is also recommended that patients be rescreened during every pregnancy. My colleagues and I conducted a study and found that HCV rescreening with every subsequent pregnancy is cost-effective. It has also been questioned whether 1-time screening during pregnancy is sufficient. The guidance is not very clear on this issue; however, in general, if patients have ongoing risk factors for HCV during pregnancy, doctors may consider screening them again later on during pregnancy.

**G&H** Should pregnant women with HCV be treated with DAA agents? What research is currently available on such treatment?

**TK** This is an evolving topic with a good deal of current interest in the field in terms of delineating what should be done regarding the timing of DAA treatment in pregnant women. Clearly, it is ideal to treat women with HCV before they become pregnant; the challenge is that it is not always possible to do that because many patients only present initially for care when they are already pregnant. The question then becomes whether to treat patients during pregnancy. There is a need for good safety data demonstrating that treatment during pregnancy is safe; fortunately, evaluations of the use of DAA agents during pregnancy are beginning to accumulate supporting their use. Some doctors believe that there should not be a rush to treat during pregnancy when it is possible to treat the mother later and the child starting at 3 years of age; however, many women lose health insurance or are lost to follow-up postpartum, making it difficult to ensure that treatment occurs.

In terms of the research that is currently available, Chappell and colleagues conducted a phase 1 study of ledipasvir/sofosbuvir (Harvoni, Gilead) treatment during pregnancy. Nine patients were treated during the second and third trimesters of pregnancy. The patients did well overall and had good response to treatment; no significant adverse events were noted. In addition, the TiP-HepC registry was recently established by the CDC's Coalition for Global Hepatitis Elimination to collect information about real-world exposure to DAA treatment during pregnancy. The hope is that compiling real-world experiences will provide the safety and efficacy data needed to consider treatment during pregnancy. Finally, a larger open study is currently evaluating sofosbuvir/velpatasvir (Epclusa, Gilead) treatment in pregnant women in the United States.
This multicenter study is open to recruitment with the goal of treating more individuals during pregnancy and collecting data that can eventually inform practice and help providers and patients alike feel comfortable with the idea of treatment during pregnancy.

**TK** My advice is to screen all pregnant women for HCV. Even though that is the recommendation, it is still not done across health care settings. Thus, it is necessary to emphasize the importance of screening for HCV during pregnancy. If a patient is found to be HCV-positive during pregnancy, it is vital to have a clear plan regarding the timing of treatment. Even if treatment is not offered during pregnancy or the immediate postpartum period, it is important to make sure that linkage to care occurs after pregnancy so that treatment does happen. Finally, an important piece of management involves the infants. Doctors should make sure that infants who are exposed to HCV are also tested and, if positive, linked to care.

**G&H** How should infants exposed to HCV be managed?

The current recommendation is that infants exposed to HCV should undergo HCV antibody testing at 18 months of age; however, there has also been an interest in encouraging earlier testing of infants at 2 to 6 months of age with HCV RNA testing. In fact, the CDC is currently discussing a potential plan to change its recommendation to encourage earlier testing. If infants are tested earlier, there is hopefully increased linkage to care and infants are not lost to follow-up without testing.

**G&H** Are there any misconceptions or preconceived notions involving pregnancy and HCV?

There is still a large element of stigma, particularly in women who are pregnant and may have HCV, as HCV has a potential association with a history of injection drug use, generally substance use. That stigma needs to be combated to treat patients and make sure that it does not interfere with appropriate screening, treatment, and linkage to care. There is also a fear of medication in the context of pregnancy, which has slowed research and the ability to provide treatment to pregnant women. Clearly, safety is of the utmost importance, but it is also necessary to make sure that pregnant women are not being excluded from the potential benefits of HCV cure.

**G&H** What are the priorities of research in this area?

We need further research regarding the use of DAA treatment during pregnancy as well as breastfeeding; more safety and efficacy data are needed in these settings. More work is also needed to develop interventions that can improve screening rates and enhance linkage to care of pregnant women with HCV. Also needed is more research to evaluate strategies to make sure that infants born to mothers with HCV are screened and linked to care; there is a care continuum from pregnancy to delivery and then follow-up of both the mother and infant. We need to do better to make sure that screening, treatment, and linkage to care occurs for HCV in these important patient groups.

**Disclosures**

Dr Kushner has served as an advisor for Bausch, Gilead, AbbVie, GSK, and Eiger, and has received research support from Gilead.

**Suggested Reading**


