Mother-to-Child HCV Transmission

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Hepatitis C specialists usually reassure HCV-positive women that the risk of mother-to-child HCV transmission during pregnancy or birth is quite low. Most research indicates that perinatal or vertical transmission occurs about 5% of the time. As is true for sexual transmission, however, high HCV viral load and coinfection with HIV appear to increase the chances of mother-to-child HCV transmission. For both types of transmission, recent data are conflicting, and the issue continues to generate controversy.

Numerous researchers have observed mother-to-child HCV transmission rates ranging from 0% to 10%. S.L. Thomas and colleagues conducted a systematic review of published and unpublished HCV vertical transmission studies. Analyzing data from 976 infants in 28 studies, they found that overall transmission rates were less than 10% in eight out of 12 studies of HIV-negative mothers with HCV. Rates were higher, however, in most of the seven studies in which at least half the mothers were HIV/HCV coinfected.

A recent report from the European Paediatric Hepatitis C Virus Network, however, suggests that vertical HCV transmission may be more common than previously believed. J. Mok and colleagues conducted a prospective study of 54 HCV-infected children who were first given PCR tests for HCV RNA within three days of birth. Seventeen children (31%) were found to have detectable HCV RNA on the first test. Among the 37 children who had negative PCR tests at three days, 27 had detectable HCV RNA when tested again at three months, and nine more received their first positive HCV PCR result after three months. These data, the authors concluded, "suggest that at least one-third and up to half of [HCV-] infected children acquired infection in utero." However, this study was small, and further research is needed to verify its results.

As noted above, two key factors appear to substantially increase the risk of HCV transmission from mothers to babies: high HCV viral load and coinfection with HIV. Research indicates that HCV transmission is most likely to occur when mothers have HCV viral loads above 1,000,000 copies, and very uncommon when they have undetectable HCV RNA. In the studies reviewed by Thomas, just eight instances of HCV transmission were observed from mothers who had undetectable HCV RNA.

Among HIV/HCV coinfected women, some studies have detected vertical transmission rates in the range of 15-40%. A meta-analysis by B.L. Pappalardo and colleagues of 1,010 infants in nine studies revealed that the overall risk of vertical HCV transmission was 3.5-fold higher among infants born to coinfected mothers compared to those born to mothers with HCV alone. When considering only women with detectable HCV, coinfected mothers were still 2.2 times more likely to transmit HCV. However, not all data support this finding. In Mok's study, a higher proportion of infants who tested positive for HCV RNA within three days were born to coinfected mothers, but this association did not reach statistical significance. D. Conte and colleagues, too, reported that HIV coinfection was not associated with a higher HCV transmission rate.

Besides HCV viral load and HIV/HCV coinfection, other risk factors have not been consistently linked to perinatal HCV transmission. For example, Mok's team found that women with genotype 1 HCV were more likely to pass on the virus, but Conte's team did not see the same association.

The method and timing of HCV transmission during gestation or during delivery remain uncertain. J. Rakela and colleagues found that HCV may be passed from mothers to infants by means of HCV-infected peripheral blood mononuclear cells (PBMCs; a type of white blood cell), although this does not appear to be the sole means of transmission. Mok's team suggested that more than one mechanism may be involved. They hypothesized that the infants in their study who had detectable HCV RNA at three days were probably infected in the womb, while those who tested PCR negative at birth but PCR positive more than three months later were likely infected during the birth process.

Some studies suggest that elective (planned) Cesarean section (C-section) may reduce the risk of perinatal HCV transmission. For example, in a study by D.M. Gibb and colleagues, none of the 31 infants of HCV-positive mothers delivered by elective C-section contracted HCV, compared with 5.9% of the 54

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babies born by emergency C-section and 7.7% of the 339 infants delivered vaginally. In the studies by Mok and Conte, however, C-section did not appear to protect infants from contracting HCV. Since the risk-to-benefit ratio remains unclear, most experts (including the U.S. Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists) do not recommend routine C-section for HCV-positive women.

Research on perinatal HCV transmission must be interpreted with caution. In particular, studies that test infants for HCV antibodies cannot easily be compared with studies that use PCR technology to measure HCV RNA. For one thing, newborn infants still carry their mothers' antibodies, and may not truly be infected themselves; the usual recommendation is that babies should be tested for HCV antibodies after 12-18 months. On the other hand, in Rakela's study, only about half (seven out of 13) of babies with detectable HCV RNA developed HCV antibodies by one year of age. Thus, perinatal transmission studies that look only at early HCV antibody positivity may either be overestimating or underestimating true infection rates.

In addition, it is not known what having detectable HCV RNA means for babies. Compared to adults, infants are more likely to spontaneously clear HCV, but the likelihood of this occuring remains uncertain; spontaneous clearance rates ranging from 20% to 75% have been reported in various studies. In a study of 28 babies born to HCV-infected mothers, S. Della Bella and colleagues found that 20 (71%) showed evidence of HCV-specific CD4 cell activity, which the researchers suggested might help explain the low vertical HCV transmission rates typically observed.

To date, there has been little research on the natural history of hepatitis C in individuals with vertical infection. In one such study, the European Paediatric Hepatitis C Virus Network team prospectively followed 266 children with vertically acquired HCV (10% of whom also had HIV) from birth for up to 16 years (average follow-up about four years). About one-quarter appeared to have cleared HCV (indicated by two negative HCV PCR tests, normal ALT, and no clinical signs), at a median age of 15 months. One-half had chronic asymptomatic infection and about one-third had chronic active infection (detectable HCV RNA). The only clinical sign of liver disease was hepatomegaly (enlarged liver), observed in 10% of the children. Although this study "confirm[ed] the low prevalence of HCV-related clinical signs and symptoms among vertically infected children in the first 10-15 years of life," the longer-term consequences of chronic HCV infection remain a concern, especially in the light of a recent study by R. D'Souza and colleagues showing that 71% of Asian patients infected with HCV for more than 60 years developed cirrhosis.

Lowering HCV viral load clearly reduces the risk of mother-to-child HCV transmission, but standard treatment with pegylated interferon plus ribavirin is contraindicated in pregnant women because ribavirin has been linked to birth defects. In the future, new anti-HCV medications may prove safe for pregnant women and their developing babies, and may be used as is the case with anti-HIV therapy to reduce the risk of perinatal transmission. Until that time, HCV-positive women should discuss their individual risk factors with their healthcare providers if they learn they are pregnant or are thinking about becoming pregnant.

References:

Conte, D. et al. 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. Hepatol 31(3): 751-5, March 2000.

Della Bella, S. et al. Hepatitis C virus-specific reactivity of CD4 + -lymphocytes in children born from HCV-infected women. J Hepatol 43(3):394-402, September 2005.

D'Souza, R. et al. Prevalence of hepatitis C-related cirrhosis in elderly Asian patients infected in childhood. J Clin Gastroenterol & Hepatol 3(9): 910-917, September 2005.

European Paediatric Hepatitis C Virus Network. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. Clin Infect Dis 41(1): 45-51, July 2005.

Gibb, D.M. et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. Lancet 356(9233): 904-907, September 9, 2000.

Mok, J. et al. When does mother to child transmission of hepatitis C virus occur? Arch Dis Child Fetal Neonatal Ed 90(2): F156-160, March 2005. Also: Obstet Gynecol Surv 60(9): 572-574, September 2005.

Pappalardo, B.L. et al. Effect of maternal HIV co-infection on vertical transmission of hepatitis C virus (HCV): a meta-analysis. XIV International AIDS Conference, Barcelona, July 7-12, 2002. Abstract C7503.

Rakela, J. et al. Perinatal transmission of HCV from HCV/HIV coinfected mothers to infants: likely role of extrahepatic replication and delayed/absent seroconversion in children. 54th AASLD Meeting, Boston, October 24-28, 2003. Abstract 397.

Thomas, S.L. et al. 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. Intl J Epidemiol 27 (1): 108-117, February 1998.