

Maternal-Infant Transmission of Hepatitis C Virus Infection

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Mother-to-infant transmission of hepatitis C virus (HCV) is comparatively uncommon. The prevalence of antibody to HCV (anti-HCV) in pregnant women is 0.1% to 2.4%, although in some endemic areas it is much higher. The proportion of women with anti-HCV who have active infection with viremia is 60% to 70%. Transmission of HCV occurs only when serum HCV RNA is detectable and may be related to higher levels (above 10^6 copies per mL). The rate of mother-to-infant transmission is 4% to 7% per pregnancy in women with HCV viremia. Co-infection with human immunodeficiency virus (HIV) increases the rate of transmission 4 to 5 fold. The actual time and mode of transmission are not known. Elective Cesarean section is not recommended for women with chronic HCV infection alone. The role of treatment to prevent transmission is limited by the fetal toxicity of currently available medications for hepatitis C. Breast feeding poses no important risk of HCV transmission if nipples are not traumatized and maternal hepatitis C is quiescent. Pregnant women at high risk for HCV infection should be screened for anti-HCV, and HCV RNA testing should be performed if anti-HCV is positive. Infants of women with hepatitis C should be tested for HCV RNA on two occasions, between the ages of 2 and 6 months and again at 18 to 24 months, along with serum anti-HCV. The natural history of mother-to-infant hepatitis C remains uncertain, especially the course in the first year of life when some infants appear to have spontaneous resolution. (HEPATOLOGY 2002;36:S106-S113.)

Maternal and child health issues relating to hepatitis C virus (HCV) infection have recently assumed greater importance than ever before. From the pediatric perspective, the availability of effective screening methods for HCV has virtually eliminated new cases of transfusion-associated hepatitis C in children. Consequently, childhood acquisition of HCV infection through maternal-infant transmission has become the most important mode of spread.¹ Vertical, or more precisely, mother-to-infant hepatitis C will likely be the ma-

ior type of childhood chronic hepatitis C within the next 6 to 8 years. It has been difficult to determine the rate of mother-to-infant transmission, partly because reports of mother-to-infant transmission of HCV have been based on small numbers of patients, with differing disease definitions, followed with different study designs and using different virological assays. These reports tended to be heterogeneous and conflicting. Moreover, factors that promote mother-to-infant transmission and the outcome of chronic HCV infection acquired by this route still require clarification. Likewise, for women of child-bearing age who acquired chronic hepatitis C in childhood or in early adulthood, there are important issues relating to pregnancy itself, such as its effect on the disease course of chronic hepatitis C.

Prevalence of Hepatitis C Among Pregnant Women

Numerous studies have examined the prevalence of hepatitis C among pregnant women (Table 1). The studies vary considerably in terms of the size of the study, geographic variables, and adequacy of laboratory testing. In general, the prevalence of detectable antibody to HCV (anti-HCV) is approximately 1% overall (range, 0.1% to 2.4%), based on the studies that included at least 3,000 subjects. The mean

Abbreviations: HCV, hepatitis C virus; anti-HCV, antibody to HCV; ALT, alanine aminotransferase; HIV, human immunodeficiency virus.

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Table 1. Prevalence of Serum Anti-HCV Positivity and HCV RNA (Measured by RT-PCR) in Pregnant Women, in Studies Examining at Least 3,000 Subjects

Study	No. Screened	Anti-HCV Positive (%)	HCV RNA Positive (%)
Boxall, 1994 ⁶⁶	3,522	0.14	N/A
Ohto, 1994 ³⁰	7,698	0.68	58
Marranconi, 1994 ⁶⁷	5,672	0.7	N/A
Moriya, 1995 ³¹	16,714	0.98	53
Zanetti, 1995 ³⁶	21,516	1.2	55
Manzini, 1995 ⁶⁸	5,000	0.7	~70%
Resti, 1998 ²⁷	25,654	1.5	66
Hillemanns, 2000 ¹⁵	3,712	0.94	57
Okamoto, 1999 ⁶⁹	21,791	0.58	66
Conte, 2000 ²⁸	15,250	2.4	72
Ward, 2000 ⁷⁰	4,729	0.8	75
Goldberg, 2001 ⁷¹	3,548	0.6	N/A
Mean		0.94	~64%

prevalence of anti-HCV in the 6 studies consisting of greater than 10,000 women was 1.26%, with approximately 60% of these women having detectable HCV RNA. Early smaller studies from the United States found prevalence of anti-HCV between 4% to 5%.^{2,3} Small studies from Egypt reported a very high prevalence, between 10% to 20%.^{4,5} A single study from Kinshasa (Democratic Republic of Congo) contrasted the prevalence of anti-HCV in commercial sex workers with other pregnant women and found 6.6% and 4.3%, respectively.⁶

From these data it appears that the prevalence of anti-HCV antibodies among pregnant women is no different from that in the general age-matched population. Of the women with anti-HCV, approximately two thirds may be expected to have active infection with detectable serum HCV RNA. The available studies do not address the broader question of prevalence of hepatitis C in women of child-bearing age, that is, all women in the 15- to 45-year-old age bracket. Whether the fertility of women with chronic hepatitis C is identical to that of women without this chronic infection is also not established.

Issues Relating to Pregnancy and Chronic Hepatitis C

There are few reports regarding the effect of pregnancy on the clinical course of chronic hepatitis C, and the numbers of patients observed are generally small. In several series, a trend toward markedly lower or normal serum alanine aminotransferase (ALT) levels in the third trimester has been noted, with a return to pre-pregnancy levels in the first 3 to 6 months postpartum.^{7,8} At the same time, a rise in serum HCV RNA levels has been detected.^{9,10} The improvement in serum ALT levels may be caused by physiologic changes associated with pregnancy including

expansion in plasma volume, high plasma concentrations of estrogen, and changes in immune reactivity. The extent of the reduction in serum ALT levels makes simple hemodilution an unlikely explanation (and a concomitant rise in HCV RNA levels is inconsistent). In a single case report, ALT levels normalized during pregnancy and serum HCV RNA concentration also dropped such that postpartum HCV RNA was undetectable in serum on 2 separate occasions 2 weeks apart: this was interpreted as spontaneous clearance of HCV infection.¹¹ In some women with chronic hepatitis C, the liver disease appears to worsen with pregnancy. In one case, serum ALT levels normalized during pregnancy and HCV RNA levels dropped significantly in the third trimester; however, the patient experienced an acute flare of hepatitis with abrupt elevation of HCV RNA levels 1 month postpartum. Similar exacerbation of chronic hepatitis C has been reported among women from the United Arab Emirates.¹² In a small case-control study, liver histology was compared from before and after pregnancy in HCV-positive/human immunodeficiency virus (HIV)-negative women, and both increased inflammation and fibrosis were found.¹³ Clearly, currently available data are inadequate to formulate general patterns of chronic hepatitis C disease course with pregnancy, but it is likely that individual variations in immune reactivity before and during pregnancy have an important role in determining the overall clinical course in the individual patient.

Observations regarding serum HCV RNA concentrations have also been highly variable. In some women, HCV RNA levels rise toward the end of pregnancy.^{7,9,10} The rise appears to be on the order of 50% above baseline. However, a few patients in one study were found to have undetectable serum HCV RNA during pregnancy, becoming positive for HCV RNA again in the postpartum period,⁷ and in another small study HCV RNA levels fluctuated during pregnancy and became lower or undetectable in the postpartum period.¹⁴ If elevated viral levels are a risk factor for mother-to-infant transmission, then levels should be measured in the third trimester, because the measured concentrations of HCV RNA at the onset of pregnancy may be neither representative nor predictive of the HCV RNA concentration at the time of delivery.

Conversely, chronic hepatitis does not appear to have an adverse effect on the course of pregnancy or the birth weight of the newborn infant.¹⁵⁻¹⁷ The rate of spontaneous abortion was approximately the same as in the normal population. There was no increase in typical obstetric complications such as gestational diabetes and hypertension. In one study, pre-term delivery was quantitatively higher among anti-HCV positive women, but the difference was not statistically significant.¹⁵ In the same series,

the rate of Cesarean section was twice as high among anti-HCV positive women compared with the anti-HCV negative control group (statistically significant difference, $P = .004$), and this higher rate was attributed in part to the policy of the investigators not to use fetal scalp blood sampling for fetal surveillance when fetal heart rate is abnormal in anti-HCV positive women.

Definition of Mother-to-Infant Transmission

Many infants of mothers chronically infected with HCV are found to have detectable anti-HCV in their blood, which they have acquired through passive transplacental transfer of the IgG-antibody. This passively acquired antibody continues to be detectable in the infant for the first 12 to 15 months of life, occasionally as long as the first 18 months. Possible criteria for a more rigorous definition of mother-to-infant transmission of HCV infection include: (1) detectable anti-HCV in an infant who is more than 18 months old; (2) detection of HCV RNA in an infant who is 3 to 6 months old; (3) detection of HCV RNA in the infant on at least 2 occasions; (4) finding elevated serum aminotransferase levels in the child; or (5) confirming identical genotype between mother and child. A reasonable definition for clinical assessment and diagnosis in the infant is detectable serum HCV RNA on two occasions 3 to 4 months apart after the infant is 2 months old and/or anti-HCV detected after the infant is 18 months old. This definition, however, may not be strictly applicable for critical review of the literature or for meta-analysis because of study design limitations inherent in published reports.

Risk of Spread of HCV Infection From Mother-to-Child

Reports detailing mother-to-infant transmission of HCV have been reviewed from time to time.^{18,19} We carried out a critical review of the world literature published between 1992 and 2001.²⁰ For inclusion, each study was required to have at least 10 mother-infant pairs. Language restrictions were entirely avoided. Criteria used for identifying mother-to-infant transmission of infection were (1) anti-HCV detected in an infant after the age of 1 year or (2) HCV RNA detected at least once in an infant 18 months old or less. Studies using first generation enzyme immunoassays or recombinant immunoblot assay techniques without confirmatory polymerase chain reaction testing were excluded. A weighted rate of incidence was used to adjust for sample size and variance. Seventy-seven studies were included for review, almost all of which were prospective cohort studies. The number of mother-infant pairs in each study ranged from 10 to 1,338. Taken altogether, 383 cases of mother-to-infant hepatitis C were

Table 2. Overview of Reported Mother-to-Infant Transmission of Hepatitis C Virus Infection in 77 Prospective Cohort Studies of at Least 10 Mother-Infant Pairs, Worldwide, January 1990-December 2000 (Weighted Rate; Subsets Examined for Some Specialized Parameters)

	Weighted Rate of Transmission
All studies	
Anti-HCV positive	1.7%
Viremic (HCV RNA positive)	4.3%
By geographic area	
Italian studies—viremic	5.6%
Japanese studies—viremic	6.9%
Other studies—viremic	3.1%
Rigor for defining "viremic"	
Two or more positive HCV RNA tests	7.1%
One or more positive tests	3.9%
No requirement for a positive test	0.6%
HIV co-infection	
HIV positive	19.4%
HIV negative	3.5%
Injection drug use	
Anti-HCV positive plus injection drug use	8.6%
Anti-HCV positive without injection drug use	3.4%

identified (Table 2). If the mother was known to be anti-HCV positive only, the weighted rate of mother-to-infant transmission was 1.7% (compared with a crude rate of number positive/number at risk of 5.6%). If the mother was known to be viremic, that is, HCV RNA positive, the weighted rate of mother-to-infant transmission was 4.3% (crude rate, 8.1%). Geographic variations were apparent from these studies. In Italian studies with viremic mothers, the mother-to-infant transmission rate (weighted) was 5.6%; in similar Japanese studies the rate was 6.9%, and in studies with viremic mothers from elsewhere the rate was 3.1%. Co-infection with HIV greatly increased the rate of mother-to-infant transmission of HCV: the weighted rate for mother-to-infant transmission of HCV in studies examining this issue was 19.4% for HIV-positive mothers, compared with 3.5% for HIV-negative mothers. In 6 studies examining the importance of previous or ongoing injection drug use, a subset of anti-HCV positive mothers (where maternal viremia was not reported) at higher risk for transmission of HCV was identified. The weighted rate of transmission was 8.6% in mothers who were anti-HCV positive and injection drug users, compared with 3.4% in anti-HCV positive mothers without known injection drug use.

Other extensive reviews of the literature have been published in which different analytical approaches have been used. Dore et al²¹ examined published reports from 1992 to 1996 in which HCV RNA data were available. They found 903 infants born to mothers with viremia, indicated by detectable HCV RNA, in the literature and

determined the overall rate of mother-to-infant transmission of HCV to be 6.2% (95% CI: 4.6% to 7.8%) and essentially 0% in mothers without demonstrated viremia. They further categorized the rate of transmission as 15.8% (95% CI: 11.8% to 19.8%) for mothers co-infected with HIV and 1.9% (95% CI: 1.2% to 2.6%) for mothers known to be negative for HIV or of indeterminate status for HIV. Thomas et al.¹⁹ reviewed 116 published reports and other unpublished reports. They applied strict diagnostic criteria and excluded studies with brief follow-up of the at-risk infants; they identified 976 infants in 28 studies who could be evaluated. They found that the rate of mother-to-infant transmission of HCV was less than 10% in HIV-negative women in most unselected populations, higher in the presence of HIV co-infection, and almost always associated with HCV viremia. They identified 8 instances of HCV transmission with apparent absence of HCV viremia in the mother, although they could not exclude technical factors leading to viral RNA degradation before analysis.

Findings from the most recent prospective studies have been similar. In a study from Ireland of 314 infants born to 296 anti-HCV-positive women,²² the rate of mother-to-infant transmission was 3.5% (minimum rate) to 6.4% (based on observed cases). No significant differences were found with spontaneous rupture of membranes, duration of membrane rupture, vaginal delivery or Cesarean section, or evident fetal distress. Infants tended to be small for gestational age, but this could not be attributed solely to maternal chronic hepatitis C. In a study of 2,447 HIV-negative pregnant women from Italy,²³ 78 women were identified as anti-HCV positive and these mother-child pairs were monitored for 2 years; 60 women were found to be HCV RNA positive. Eight infants were identified as infected with HCV. Thus, the mother-to-infant transmission rate was 13.3%. At 2 years old, however, only 2 infants were still positive for HCV RNA, and therefore, the overall mother-to-infant transmission rate was stated to be 3.3%. Mother-to-infant transmission correlated with high maternal viral levels. In a large retrospective analysis of prospectively collected data on 1,655 mother-child pairs from 24 centers in Europe (specifically Italy, Spain, Germany, Ireland, Scotland, Belgium, and Sweden), 9.2% of evaluable infants were infected with HCV.²⁴ Mother-to-infant transmission of HCV was more likely to occur if the mother was co-infected with HIV, but mode of delivery and breast-feeding did not affect HCV transmission in women with only chronic hepatitis C. In a recent prospective multicenter study from Italy, the rate of mother-to-infant HCV transmission was examined in 1,372 consecutive, unselected mother-infant pairs. The rate was 7.1% (95% CI: 2.2%

to 7.2%). All but 1 infant were born to women with detectable serum HCV RNA, and in this study maternal injection drug use, not maternal HIV positivity, was most closely associated with HCV transmission.²⁵ Rate of HCV transmission was not statistically different in women having Cesarean section as opposed to vaginal delivery; however, the rate of elective Cesarean in women not co-infected with HIV was very low.

Whether the risk of transmission of HCV is independent for each pregnancy has been examined formally in one study.²⁶ No increased risk for mother-to-infant transmission of HCV was found in subsequent pregnancies.

Factors Correlating With Mother-to-Infant Transmission of HCV

Viral Levels. Numerous, but by no means all,^{27,28} studies indicate that the higher the concentration of serum HCV RNA the more likely mother-to-infant transmission.^{23,29-33} In one study, a high viral level was defined as at least 2.5×10^6 viral RNA copies per mL,³³ but in general, studies showing a correlation of HCV transmission with maternal viral load exhibited the effect at 10^5 to 10^6 copies per mL. Differences in when during the course of pregnancy maternal viral levels are tested may explain some of the conflicting observations on this point.

HIV Co-Infection. Co-infection with HIV has consistently been associated with greater likelihood of transmitting HCV to the newborn infant.^{24,30,34-38} There was no increased rate of transmission of HCV to infants of HIV co-infected women in the large cohort reported by Conte et al,²⁸ but all of these mothers had received antiretroviral treatment during pregnancy, an observation which suggests that HIV infection in HIV/HCV co-infected women should be treated aggressively to reduce the risk of mother-to-infant HCV infection.

HCV Genotype. Maternal-infant transmission occurs with all known genotypes. To date, no obvious correlation between HCV genotype and rate of mother-to-infant transmission of HCV has been shown.^{39,40}

Disease Activity. There have been few observations relating disease activity in the mother and likelihood of transmission of HCV infection to the infant. In general, hepatic inflammation appears to decrease during pregnancy, as shown by a decrease in serum ALT levels in the third trimester. A single report has shown that mother-to-infant transmission correlates with peripheral blood mononuclear cell infection by HCV.⁴¹

Invasive Procedures. Some evidence is available to show that amniocentesis is a potential risk for spreading infection to the infant⁴²; however, HCV was found in amniotic fluid from only 1 of 16 viremic patients studied

prospectively in the fourth month of pregnancy.⁴³ On reasonable, common sense grounds, the use of fetal blood monitoring via scalp vein catheter has been discouraged in the presence of maternal HCV infection, and some obstetrical units prohibit this intervention altogether. However, firm data to indicate that fetal monitoring places the infant at risk for acquiring HCV infection are difficult to ascertain. One recent large study found 11.8% of 93 infants who had fetal scalp vein blood monitoring during delivery developed mother-to-infant HCV infection, whereas 9.2% of 631 infants not monitored developed HCV infection, but it was not clear whether the monitored infants had any other known risk factors for acquiring infection.²⁴

Complications of Delivery. Women with chronic hepatitis C may be at risk for complications of pregnancy and delivery for reasons independent of the HCV infection. Some observations suggest that prolonged rupture of the membranes (*i.e.*, for more than 6 hours) is associated with a higher rate of mother-to-infant transmission of HCV,⁴⁴ but other studies have not shown this association.²²

Type of Delivery. Some studies suggest that mother-to-infant transmission of HCV is more likely to occur with vaginal delivery.^{33-35,38} Other studies do not confirm this finding.^{15,27,28,30} Moreover, in some of the studies indicating increased risk with vaginal delivery, the difference fell short of statistical significance, including a large European study where mode of delivery was known for 1,400 infants.²⁴ Elective Cesarean section may confer some protection, but emergency Cesarean section does not.³⁸ In 11 studies with at least 10 mother-infant pairs for evaluation, the rates of mother-to-infant HCV were similar for vaginal delivery and Cesarean section. The weighted rate was 4.3% for vaginal delivery and 3.0% for Cesarean section.²⁰ Currently available data, therefore, do not argue cogently for the routine use of Cesarean section for women with chronic hepatitis C unless there is HIV co-infection.

Time/Mode of Mother-to-Infant Transmission of HCV Infection

When or how mother-to-infant transmission of HCV occurs remains unknown. Hepatitis C virus RNA is occasionally detectable in amniotic fluid,^{42,43} and although this finding raises the possibility of *in utero* infection, it does not equate with *in utero* infection. Cord blood positivity for HCV RNA is extremely difficult to interpret as an indication of *in utero* infection because minute contamination with maternal blood cannot be excluded. In one study, cord blood positivity for HCV RNA was not predictive of subsequent infection in the infant.²⁸ The possible effect of elective Cesarean section to diminish

risk of mother-to-infant transmission argues for infection at or around the time of vaginal delivery.^{33,38} Finding HCV RNA in the serum of the newborn infant in the first few days of life is consistent with infection occurring either *in utero* or at the time of delivery; however, finding HCV RNA in the serum of the newborn infant within 24 hours of birth would likely favor *in utero* infection. There could, of course, be more than one time or mode of infection in different patients. In the recent European multicenter study, 11 of 203 children in whom HCV RNA testing was obtained in the first 3 days of life were subsequently shown to have mother-to-infant transmission of hepatitis C; however, only 3 of the 11 had HCV RNA detectable within the first 3 days of life.²⁴

Patterns of HCV quasispecies expression in mother-to-infant HCV infection provide some clues to the time/mode of infection. Thus, infants infected with HCV appear to have one or very few quasispecies of HCV initially.⁴⁵⁻⁴⁸ The major quasispecies infecting the infant is not necessarily the dominant form in the mother. The mechanism for this apparent selectivity is not known, but it is possible that interferons generated in the placenta may play a role.⁴⁹

Breast-Feeding and Transmission of Hepatitis C

Hepatitis C virus can be detected in breast milk or colostrum.^{18,50} Nevertheless, breast-feeding is generally not considered to be a risk factor for mother-to-infant transmission of HCV.^{8,44,51,52} In published studies, the rate of transmission is nearly identical in breast- or bottle-fed infants.²⁰ Whether these studies are adequate is open to question because duration and exclusivity of breast-feeding are not routinely described in detail. The safety of breast-feeding operates on the assumption that traumatized, cracked, or bleeding nipples are not present. A single study from United Arab Emirates attributed disease acquisition (characterized as acute hepatitis C) in 3 infants, born by Cesarean section, to exposure by breast-feeding; however, the mothers of these children had unusually severe clinical disease with elevations in serum ALT and bilirubin levels in the immediate postpartum period.¹² Although these observations may not be easily generalized to others, breast feeding during a postpartum flare of hepatitis may pose a risk of HCV transmission to the infant.

Issues Relating to Anti-Viral Treatment for Chronic Hepatitis C in Pregnancy

Treatment with the most efficacious therapy (alpha interferon combined with ribavirin) cannot be used during pregnancy or immediately before pregnancy, primar-

Table 3. Criteria for Screening for Serum Anti-HCV in Pregnancy

Known HIV positivity
Previous or current use of injection drugs
Current or previous sexual partners known to use or have used injection drugs
From a geographic area of high endemicity
History of blood/blood products transfusion or organ transplant before 1992
Current or previous hemodialysis
Involved in <i>in vitro</i> fertilization from anonymous donors
History of body piercing or tattooing
History of incarceration
Elevated serum aminotransferase levels

ily because ribavirin poses an important risk of teratogenicity.⁵³ Scattered case reports have been published suggesting that the potential risk associated with ribavirin is overestimated, but these data are too limited to be convincing.^{54,55} Alpha interferon is generally regarded as contraindicated in pregnancy. There is some experience with administration of alpha interferon to pregnant women who have idiopathic thrombocytopenia, chronic myelogenous leukemia, or other hematologic malignancies. No adverse outcomes were found in the babies except for transient thrombocytopenia in one.⁵⁶ Alpha interferon is contraindicated in infants under 2 years of age because of severe neurotoxicity,^{57,58} and thus a risk of fetal neurotoxicity may also exist. Whether these drugs impair fertility is not known.

Screening of Prospective Mothers

The role of screening for hepatitis C among prospective mothers depends largely on the value of knowing that the mother has HCV infection. It can be argued that such information has no direct implications for either the mother's or infant's treatment or for technical aspects of the delivery and is, therefore, not worth collecting. Indeed at the present time it is difficult, if not impossible, to justify universal screening of pregnant women for hepatitis C. However, a selective screening strategy may have merits. Pregnant women with any of the following characteristics should be screened for anti-HCV (and subsequently for HCV RNA, if found to be anti-HCV positive): known HIV positivity; previous or current use of injection drugs; current or previous sexual partners known to use or have used injection drugs; living in or from a geographic area of high endemicity; history of blood/blood products transfusion or organ transplant before 1992. A broader set of criteria might be applied (Table 3). Other criteria to be considered include testing positive for present or past hepatitis B virus infection, older age (above 30 years old), sexual partner(s) with risk for hepatitis, and history of any sexually transmitted disease.⁵⁹ Selective screening inherently risks missing some

women with chronic hepatitis C. Ideally, screening for anti-HCV would be offered as an option to all pregnant women. Apart from being inherently fair, an optional inclusive approach may show chronic hepatitis C in women without known risk factors or who deny risk factors. Furthermore, making the diagnosis potentially has important implications for daily living choices (use of alcohol or over-the-counter medications, maintenance of healthy body weight), public health considerations, and timely treatment after pregnancy.

Outcome of Mother-to-Infant Hepatitis C in Affected Infants

The outcome of mother-to-infant hepatitis C requires clarification. Subtleties of disease course are relevant to this discussion. Some infants may have transient viremia without real infection. Other infants may have acute, self-limited infection that is clinically inapparent (very early spontaneous resolution). The data for very early spontaneous resolution of mother-to-infant hepatitis C are compelling in those children who developed biochemical evidence of hepatic inflammation at the time of hepatitis C viremia.^{44,60-63} In one study, three fourths of the infants identified with mother-to-infant hepatitis C cleared the HCV RNA by 2 years of age.^{23,64} In another study, all 5 infants with mother-to-infant hepatitis C lost detectable serum HCV RNA by 6 months of age.⁶⁵ Thus, outcome of mother-to-infant transmission of HCV is usually considered in terms of evolution to chronic hepatitis C, with later spontaneous clearance of HCV infection or progressive chronic liver disease. Whether children are more likely to clear chronic HCV infection than adults and whether transfusion-associated chronic hepatitis in children runs a different clinical course from chronic hepatitis C acquired by mother-to-infant transmission remain unanswered questions currently being investigated.

Future Research Needs

Although the scope of the problem of mother-to-infant transmission is fairly well demarcated, numerous theoretical and practical problems require further attention. Approximately 1% of pregnant women have chronic hepatitis C, and the overall risk of transmitting infection to their infant is approximately 4% to 7% per pregnancy. The risk of transmission is generally much higher in women co-infected with HIV, and transmission appears more likely if the concentration of HCV in blood is high, especially in the third trimester. The utility of anti-viral treatment, elective Cesarean section, and avoidance of other invasive procedures in managing labor and delivery is not established for pregnant women who have chronic

hepatitis C alone, but these approaches to management have important validity for HIV co-infected women. An immediate practical research goal is to determine clinical and laboratory features in women with chronic hepatitis C which indicate a high probability of mother-to-infant transmission so that modifications in obstetric management can be specifically used for these women. The course of mother-to-infant hepatitis C in the infant remains uncertain, but a substantial number of infants appear to recover from the acute infection. The biology of mother-to-infant transmission of HCV requires further examination, along with the mechanism(s) that may attenuate HCV infection in the newborn infant. The long-term outcome of the effect of pregnancy on chronic hepatitis C in women and the extended course of mother-to-infant chronic hepatitis C in affected infants need more detailed description. Although the numbers appear small on a percentage basis, mother-to-infant hepatitis C will become the predominant form of the disease in the pediatric age bracket, and it poses an important challenge world wide. Ultimately, developing effective methods to prevent maternal-infant transmission of HCV, including innovative pharmacologic agents suitable for administration to pregnant women, is the major research goal.

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