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REVIEW

Vertical transmission of hepatitis C virus: Current knowledge and perspectives

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Abstract

Hepatitis C virus (HCV) infection is a major global health issue. Infection by the HCV can cause acute and chronic liver diseases and may lead to cirrhosis, hepatocellular carcinoma or liver failure. The World Health Organization estimates that approximately 3% of the world population have been infected with HCV and the worldwide prevalence is between 1% and 8% in pregnant women and between 0.05% and 5% in children. Following the introduction of blood product screening, vertical transmission becomes the leading cause of childhood HCV infection. The prevalence of pediatric HCV infection varies from 0.05% to 0.36% in developed countries and between 1.8% and 5% in the developing world. All children born to women with anti-HCV antibodies should be checked for HCV infection. Though universal screening is controversial, selective antenatal HCV screening on high-risk populations is highly recommended and should be tested probably. Multiple risk factors were shown to increase the possibility of HCV vertical transmission, including coinfections with human immunodeficiency virus, intravenous drug use and elevated maternal HCV viral load, while breastfeeding and HCV genotypes have been studied to have little impact. At present, no clinical intervention has been clearly studied and proved to reduce the HCV vertical transmission risk. Cesarean section should not be recommended as a procedure to prevent vertical transmission, however, breastfeeding is generally not forbidden. The high prevalence of global HCV infection necessitates renewed efforts in primary prevention, including vaccine development, as well as new approaches to reduce the burden of chronic liver disease. Future researches should focus on the interruption of vertical transmission, developments of HCV vaccine and direct-acting antivirals in infancy and early childhood.

Key words: Hepatitis C virus; Vertical transmission; Perinatal infection; Chronic liver disease

Core tip: Hepatitis C virus (HCV) infection is a major global health issue. World Health Organization estimates that the worldwide prevalence is 1%-8% in pregnant women and 0.05%-5% in children. Vertical transmission becomes the leading cause of childhood

HCV infection. Current understanding of the epidemiology of mother-to-child transmission of HCV is limited. At present, no clinical intervention has been clearly studied and proved to reduce the vertical transmission risk. Though universal screening is controversial, selective antenatal HCV screening on high-risk populations is highly recommended and should be tested probably. This review provides the current knowledge and perspectives of HCV vertical transmission and summarizes the updated follow up guidelines for clinical practice.

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GLOBAL EPIDEMIOLOGY OF HEPATITIS C INFECTION

Hepatitis C virus (HCV) infection is a major global health issue[1]. Infection by the HCV can cause acute and chronic liver diseases and may lead to cirrhosis, hepatocellular carcinoma or liver failure[2]. The World Health Organization estimates that approximately 3% of the world population have been infected with HCV[3]. There are approximately 170 million HCV patients worldwide, and three to four million cases are newly diagnosed every year[4,5]. It is estimated that about 0.2% to 26% of the general population in different countries are chronically infected by HCV[6]. The prevalence of HCV infection in the United States between 1999 and 2002 was found to be 1.6%[7]. In China, approximately 40 million people are infected with HCV, and 50% to 85% of them may develop chronic hepatitis; of these patients, 20% to 30% progress to liver cirrhosis and/or hepatocellular carcinoma[8,9].

Before blood product screening for HCV was introduced, transfusion represented an important route of HCV transmission for infants and children[10]. Following the introduction of blood product screening, vertical transmission becomes the leading cause of childhood HCV infection and approximately 4000 new cases are diagnosed each year in the United States[11]. It is estimated that the prevalence varies from 0.05% to 0.36% in developed countries and 1.8% to 5% in the developing world[12,13].

PREVALENCE OF HCV INFECTION IN PREGNANT WOMEN

The worldwide prevalence of HCV infection is between 1% and 8% in pregnant women and between 0.05% and 5% in children[14]. Antenatal HCV infection rates vary worldwide, from 1% to 2.5% in the United States and Europe to more than 10% in some sub-Saharan countries[15-17]. Studies have shown the prevalence to be as high as 40% in some parts of Egypt[18]. According to the result of the maternal HCV screening project conducted in Tottori Prefecture, Japan, the prevalent rate of HCV carrier mothers who were both anti-HCV and HCV RNA positive was 0.39%, while the rate of vertical transmission was found to be 8%[19]. However, the above maternal HCV prevalent rates may be underestimated since the current practice of HCV screening among high-risk pregnant women might miss a large number of HCV-infected patients, and besides there are no large scale HCV serosurvey studies available at present[20].

In a recent study performed in Taiwan, a total of 7355 healthy asymptomatic pregnant women were screened for anti-HCV during a 6-year study period, 44 (0.6%) were found to be HCV-infected and 22 mothers were enrolled[21]. Half of the anti-HCV positive mothers were found to be positive for HCV RNA. All the mothers were negative for anti-HIV, 9 had invasive obstetric procedures such as amniocentesis. Of the 22 mother and baby pairs who were successfully followed up, two (9.1%) had eventually confirmed infected with HCV. Both of them were born to mothers with high viral load (HCV RNA > 10^5 copies/mL).

However, a methadone program in Australia showed that more than 70% of the pregnant women in this program are HCV positive, but less than 20% of their offsprings are examined for HCV status[22]. As a result of the lack of awareness of HCV in this high-risk population, many of these children are lost to follow-up and not diagnosed[23,24].

PATHOGENESIS OF HCV INFECTION DURING PREGNANCY

The pathogenesis of HCV infection during pregnancy remains poorly understood[14]. Recent studies have demonstrated there is a decrease of levels of serum alanine aminotransferase (ALT) during the second and third trimesters of pregnancy. However, the HCV viral load increases and reaches a peak during the third trimester[25-26]. Postpartum exacerbation of clinical HCV manifestations were found[27]. Conversely, seroconversion in pregnancy has been demonstrated and pregnancy may improve the natural course of HCV infection in some studies[26,28].

Besides, recent researches suggests that HCV infection during pregnancy may increase the risks for preterm delivery, low Apgar scores, low birth weight, gestational diabetes, congenital malformations and overall perinatal mortality[29-31]. Other risk factors, such as limited prenatal care and intravenous drug use, are also found to be more prevalent in HCV patients[32] which could influence maternal and fetal morbidities and outcomes[26]. Conversely, increased risks for these obstetric complications were not shown in other studies[27,33].

INCIDENCE OF VERTICAL TRANSMISSION

As mentioned previously, vertical transmission becomes

a leading cause of pediatric HCV infection after blood product screening for hepatitis C was introduced, and it is also the leading cause of pediatric chronic liver disease in developed countries[34]. Although vertical transmission leading to chronic infection is reported in 4%-8%, transient HCV perinatal infection also occurs, with an incidence of about 14%-17%[35,36]. Incidence of HCV vertical transmission has been documented to be 3%-10%[14,33,37,38] and are higher in infants born to mothers coinfected with human immunodeficiency virus (HIV).

RISK FACTORS OF VERTICAL TRANSMISSION

Multiple risk factors were studied to increase the risk of HCV vertical transmission, including coinfections with HIV, intravenous drug use, high maternal HCV viral load, mode of delivery, preterm labor, prolonged rupture of membranes and amniocentesis, while breastfeeding and HCV genotypes have little impact on vertical transmission[14,30,39-41]. However, most of the reports are still controversial.

HIV

Multiple researches have demonstrated that HCV vertical transmission rate increases 2-4-fold if coinfected with HIV[10,42,43]. Vertical transmission in the group of infants in which the mother was HIV coinfected antenatally was 5.9%, and thus supports the current recommendations for cesarean delivery in HIV and HCV coinfected mothers[13]. It has been demonstrated that coinfections with HCV and HIV during pregnancy increase the vertical transmission odds by 90% according to a meta analysis of 10 studies[43].

Viral load

Another main risk factor identified for vertical transmission was maternal hepatitis C viremia. For mothers who tested positive for HCV RNA, vertical transmission was significantly higher at 7.1% when compared with 0% transmission for those who tested HCV RNA negative antenatally[10]. This has been reported previously in the literature and reflects that viremia holds a higher risk of vertical transmission[44,45]. Many studies have demonstrated that the risk of HCV vertical transmission increases if the maternal serum HCV viral load is above 10^6 copies HCV-RNA/mL, however there are many uninfected infants even though their mothers have a higher HCV viral load[46-48]. Since the maternal serum HCV-RNA viral load may fluctuate during pregnancy, it is recommended to repeat the HCV-RNA load in the third trimester[38].

Although there are a few reports of vertical transmission in which the mother did not have viremia detected antenatally[49,50]. Maternal HCV RNA status can be of benefit in the patients counseling, patients can be reassured and advised that the risk of vertical transmission is minimal if hepatitis C RNA is not detected antenatally.

Mode of delivery

More controversial is the effect of mode of delivery on vertical transmission. Whereas some studies have shown a protective benefit from cesarean section (CS) delivery[51,52], many have not[25,53-55]. Few studies in the past recommend the use of elective CS to prevent the possible obstetric risks in order to lower the incidence of HCV vertical transmission[56]. Okamoto *et al*[19] previously reported that children born to mothers with high viral loads had a significantly higher incidence of vertical transmission when delivered transvaginally. However, other studies, including a large-scale multicenter research project conducted in Europe, have failed to show significant evidence to prove its protective effect[25,47,57]. Some questioned the results since probably because most of the studies did not analyze high viral loads incidence along with elective CS.

Several conditions must be elucidated before the recommendation of elective cesarean section to prevent HCV vertical transmission[58]. Though studies show that the HCV vertical transmission rate is low in the infants born to mothers with high viral load[38], however, taking into consideration the risks involved in CS and the natural course of HCV in infants, most research studies do not recommend elective CS for vertical transmission prevention at present[38,50,59,60]. Thus, the majority of the published literature would suggest that mode of delivery is not a key factor influencing HCV vertical transmission.

In 2008, the Japanese Society of Obstetrics and Gynecology's guideline recommended informing high viral loads women that the risk of vertical transmission might be significantly reduced by elective CS[61]. However, emergency CS should be considered separately from elective CS because emergency CS may allow conditions such as maternal blood contamination of the fetus and other complications[58,62]. However, cesarean delivery has been recommended for HCV-positive women coinfected with HIV as mentioned before[63].

Breast-feeding

Breast-feeding does not increase the vertical transmission rate[38,60,64]. Avoidance of breast feeding is not an effective way for preventing HCV vertical transmission[65]. It is true that HCV RNA has been detected in breast milk and colostrum[66], however breast-feeding does not shown to be a route of maternal to infant transmission[45,67,68]. HCV infected mothers are encouraged to breast-feed if there are no other contraindications, such as HIV co-infection[69]. The Centers for Disease Control and Prevention (CDC) suggests mothers should interrupt breast-feeding temporarily if there are bleeding or traumatized nipples, which could increase infants' HCV exposure[70].

Premature rupture of the membranes

Premature rupture of the membranes is considered a risk factor for HCV vertical transmission by exposing the fetus to maternal HCV in the birth canal[45,54]. The duration of rupture has been found to be significantly longer in

infected children[45,54,60]. These parameters are potentially related to contamination of the fetus with infected maternal blood in the birth canal.

Other factors

Besides, the European Paediatric HCV Network described the significance of infantile sex as a risk factor for HCV vertical transmission, girls are twice as likely as boys to be infected[60], however, no significant difference is found in other study[46]. In addition, some experts recommend avoiding invasive procedures that promote fetal exposure to maternal blood, such as fetal scalp monitoring[45,68]. As described previously, other parameters, such as birthweight, Apgar score, gestational age and bleeding volume during delivery were not significant risks for HCV vertical transmission[45,46,55,71,72]. Besides, HCV genotype was not associated with vertical transmission of HCV[73]. Despite an increased understanding of the risk factors involved, its transmission mechanisms and timing are still unknown and recommendations regarding prevention are limited[41,53,74].

NATURAL COURSE OF HCV-INFECTED INFANTS

HCV infection may lead to chronic hepatitis, cirrhosis and hepatocellular carcinoma in adult populations. However researches about the natural history of hepatitis C in children is little. Studies showed that perinatally-acquired HCV infection becomes chronic in approximately 80% of cases[45,75,76], similar to that observed in adults[77], but higher than that reported in children who were infected through contaminated blood products[78]. Most studies show that HCV infected children are mostly asymptomatic[75,79]. Spontaneous clearance have reported rates ranging from 21% to 75%[76,78,80,81]. The European Paediatric HCV Network evaluated 266 children with vertically-acquired HCV infection and found clearance occurred in 21%-25%. Among cases of neonatal infection, 25% demonstrated spontaneous clearance by 7.3 years[80].

However it has not been studied clearly whether the virus is completely eliminated, and there is possibility the infants will become HCV-RNA positive again later in their life. In a study performed in United Kingdom, the overall rate of spontaneous viral clearance was 17.5% with higher clearance (27%) in the transfusion group compared to the vertically acquired group (9%). Most children are asymptomatic with mildly abnormal hepatic transaminases[82]. An infected infant becomes HCV-RNA positive between 0 and 3 mo after birth[38]. Fortunately there is no case of fulminant hepatitis reported among infected infants to date.

Long-term outcomes for young HCV infected children in general are good[83-85]. Studies following patients for 10 to 20 years after perinatal acquisition of HCV show that 5% to 12% of them has significant fibrosis and 5% has cirrhosis[79,86]. No studies have yet studied the incidence of cirrhosis and hepatocellular carcinoma in adults who acquired vertical HCV infection.

DIAGNOSIS OF PERINATAL TRANSMISSION

A practical and widely acceptable recommendation by most studies is to consider children born to anti-HCV positive mothers infected with HCV when: (1) HCV RNA is detected in at least two serum samples and at least three months apart during the first year of life; and (2) HCV antibody is positive after 18 mo of age[73]. There is agreement on delaying PCR testing until 3 mo of age and to repeat it, if positive, at 6 mo of age. Testing of HCV antibody is of limited value before 18 mo of age due to passive transfer of maternal antibodies[60,73,87].

TREATMENT AND PREVENTION

Interferon and other treatments for women with high viral load who are of child-bearing age are useful for decreasing HCV levels, both for women as carriers and to decrease the risk of possible vertical transmission in future deliveries[58]. However, the available pharmacological therapies are contraindicated in pregnancy: ribavirin for its teratogenic effects and pegylated interferon alfa for its possible effects on fetal growth[88]. Thus, these treatments of HCV are contraindicated during pregnancy and there are no antiviral treatment recommendations for HCV-infected women at present[89]. Finally, whether CS is effective in preventing vertical transmission of HCV is still unclear as stated previously[42,60,90,91].

Generally, children who are younger than 3 years should not be treated, and treatment is not approved in this age group. There are no published studies or reports of treatment in children who are younger than 3 years[92]. At present, treatment modalities that were initially restricted to adult subjects are now recommended for the treatment of HCV in children 3-17 years of age[93,94]. Treatment should consider several aspects including age, severity of disease, its adverse effects and compliance to treatment[92].

PRENATAL SCREENING

According to the recent recommendations published by the American College of Obstetricians and Gynecologists and CDC, routine prenatal HCV screening is not recommended in the general population[20,95,96]. However, women with significant risk factors should be offered screening. Generally, selective antenatal HCV screening is used on the basis of risk factors for exposure to the virus, such as a history of intravenous drug abuse[10]. However, there are currently no official recommendations addressing how often high-risk populations should be tested probably due to a lack of available data[37].

In clinical practice, HCV screening in pregnancy has proven difficult, and it is likely that most HCV infected pregnant women are not identified[97-99]. Forty to 70% of

HCV-infected pregnant women do not initially report major risk factors[25,100]. In fact, a study in the United Kingdom showed that only one-third were identified through selective antenatal screening, suggesting that there may be many unidentified perinatally infected children in the absence of routine maternal antenatal screening[81]. A recent report by Delgado-Borrego *et al*[101] estimated that about 85% to 95% of HCV-infected children in the United States have not been identified. Given the inherent inadequacies of risk factor-based screening, researches have investigated whether universal HCV screening in pregnant women would be a worthy approach.

In 2012, the CDC added recommendations for universal screening of all United States "baby boomers" regardless of reported risk factors[102]. This new recommendation was prompted by a recognition of the increasing rate of HCV complications in the United States and the failure of risk factor-based screening to identify most infected infants. Universal screening would ensure that infants born to HCV-infected women are properly identified and evaluated. However, when Plunkett and Grobman modeled universal screening in a pregnant population with 1% HCV seroprevalence, they found that it was not cost-effective, even when benefits of HCV diagnosis and treatment were considered for both mothers and infants and assuming that CS eliminated perinatal transmission[103].

Prenatal screening itself is expensive, even in developed countries. An effective screening strategy utilizes an inexpensive and sensitive test to identify asymptomatic individuals at risk of a disease that has reasonably high prevalence, serious consequences if left untreated, and an effective treatment available[58,104].

FOLLOW UP GUIDELINES

Chronic pediatric HCV infection is usually associated with minimal or mild liver disease, however some cases may progress to advanced liver damage[80,105,106]. A broad range of ALT levels have been observed during the first year of life, with some infants exhibiting acute hepatitis pictures and others showing normal or mild elevated levels[75,105,107].

In 2008, Shiraki *et al*[38] presented guidelines for doctors in consulting and treating HCV-carrying pregnant women and their infants basing on current knowledge of vertical transmission. For those infants born to mother who is positive for anti-HCV and negative for HCV-RNA, an anti-HCV test should be performed later than 18 mo after birth to confirm that the infant is negative for anti-HCV. If the infant is still anti-HCV positive, the infant is considered to have been infected with HCV, HCV-RNA viral load and ALT level should be examined to determine whether the infection is a past one or whether it has continued up to the present time.

For those infants born to HCV-RNA-positive mother, tests for AST and ALT levels and HCV-RNA load should be performed 3 or 4 mo after birth. When HCV-RNA is positive, tests for AST, ALT, HCV-RNA and anti-HCV should be performed every 6 mo starting from the 6 mo of birth to determine the persistence of infection. If the infant is negative for HCV-RNA 3 or 4 mo after birth, an HCV-RNA test should be performed at the ages of 6 mo and 12 mo to confirm the infant's negativity[38].

CDC guidelines recommend testing for anti-HCV in children born to HCV infected mothers after 12 mo of age. However, if earlier testing is required, nucleic acid-based testing for HCV RNA is recommended 1 to 2 mo after birth[96,102]. If positive for either anti-HCV or HCV RNA, children should be evaluated for liver disease, and those with persistently elevated ALT levels should be referred to a specialist for medical management[96,108,109]. To further confirm HCV-RNA negativity, anti-HCV is tested at 18 mo of age if possible, and follow-up tests are no longer required when anti-HCV is also negative.

CONCLUSION

HCV infection affects a large number of women of reproductive age worldwide, and vertical transmission remains a serious public health problem. The high prevalence of global HCV infection necessitates renewed efforts in primary prevention, including vaccine development, as well as new approaches to reduce the burden of chronic liver diseases.

Based on present knowledge of perinatal transmission of HCV, all children born to women with anti-HCV antibodies need to be tested for HCV infection. Though universal screening is controversial, selective antenatal HCV screening on high-risk populations is highly recommended and should be tested probably. At present, no intervention has been clearly demonstrated to reduce the risk for HCV vertical transmission. Cesarean section should not be recommended as a method to prevent vertical transmission of HCV, however, breastfeeding is generally not forbidden.

Awareness of HCV infection status in those high-risk population is mandatory. Novel approaches need to be considered to improve the knowledge of HCV transmission and hopefully improve HCV-associated health outcomes in high-risk populations. Future researches should focus on the interruption of vertical transmission, developments of HCV vaccine and direct-acting antivirals in infancy and early childhood. To prepare a more comprehensive and concrete standard for the prevention of HCV vertical transmission, a large scale and long-term follow-up study of children should be organized, as this may establish the need for more aggressive measures for prevention and treatment. Eventually, we believe that the number of new patients with HCV vertical transmission can be further decreased in the future.

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