Update on the management of hepatitis B and C infections in the neonatal period

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Abstract

Hepatitis B virus and hepatitis C virus have received a significant amount of attention in recent years, and both viruses share a significant amount of similarities with one another beyond just that they both primarily target the liver. In recent years, cases of both infections have been fueled by a nationwide epidemic of injection drug use. Most relevant to this audience, they are both transmitted from mother to child. The increased cases in young adults combined with mother to child transmission translate into more exposed infants that will need to be managed and followed. Screening of pregnant women for hepatitis B infection coupled with appropriate treatment and prophylaxis measures are incredibly effective to preventing transmission. Prevention of hepatitis C infection is not yet possible, but advances in antiviral therapy make interruption of transmission a future possibility.

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Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) have received a significant amount of attention in recent years, and both viruses share a significant amount of similarities with one another beyond just that they both primarily target the liver. In recent years, cases of both infections have been fueled by a nationwide epidemic of injection drug use. Most relevant to this audience, they are both transmitted from mother to child (MTCT).1–3 The increased cases in young adults combined with MTCT translate into more exposed infants that will need to be managed and followed. This review will summarize the relevant background of both HBV and HCV, review the clinical manifestations of each and rationale for screening and prevention and offer a glimpse of what may be ahead in the future. A summary of the similarities and differences between the two viruses is presented in the Table.

Hepatitis B virus

Virology

HBV is a double-stranded DNA virus that is classified within the Hepadnavirus family.4 The major proteins produced during infection are the surface antigen (HBsAg), the core antigen and the e antigen. Core and e antigens are formed from the same precursor pre-Core protein. The virus has two features to its lifecycle that are notable. First is that it forms a closed circular chromosome of DNA (cccDNA) that exists within the nucleus of an infected cell and serves as a template for RNA transcription. This location is protected from antiviral agents or cellular immune responses, so the cccDNA represents a sanctuary site where HBV infection can exist without external influences. Second is that HBV has an RNA to DNA replication stage mediated by the viral polymerase late in its lifecycle that is analogous to the reverse...
transcriptase of true retroviruses. This step is the reason why many of the antivirals used against HBV are also used to treat HIV infection.

**Transcription and epidemiology**

HBV is transmitted by bloodborne transmission, sexual transmission and MTCT. Transmission via transfusion is exceedingly rare in the current era of widespread screening of the blood supply in the US, but this may not be true in resource-poor areas of the world. Screening of pregnant women for HBsAg, initiating prophylaxis for those that test positive and universal infant immunization have all served to reduce MTCT. Overall, cases of HBV had been dropping over the last 30 years in the US from over 200,000 cases per year in the 1980s to less than 38,000 by 2010. Over the last 5 years, cases have been on the rise in many states driven by widespread injection drug use, contaminated needles and sexual transmission associated with drug use or drug seeking.

**Clinical manifestations**

Infants infected with HBV in the neonatal period have very different outcomes than adults. While less than 10% of adults with HBV infection will progress to chronic infection, in the absence of any prophylaxis more than 90% of infants once infected will have persistent detection of HBV surface antigen on long-term follow up. Studies done prior to widespread prophylaxis showed that a minority of infants developed severe hepatitis that could fulminate and even lead to death. Because of these two important differences in infants, there was a high priority placed on instituting preventive measures against HBV MTCT.

In the current era, neonates that acquire HBV at birth are most often asymptomatic. They enter a phase of the infection that is called the "Immune Tolerant" phase. It is characterized by the lack of symptoms and normal liver enzymes, coupled with very high HBV DNA levels and the presence of the e antigen. The natural history of these children is that they stay in this phase for many years, and only in their late teenage or early adult years does their immune system begin to react to the virus. At this point is when they develop symptoms of more active hepatitis and when they become candidates for antiviral therapy. The specific discussion of therapy is beyond the scope of this review.

**MTCT patterns and risk factors**

Prior to any prophylaxis, studies showed that about 40% of infants became infected. What those studies also showed was that the more active disease a pregnant woman had, which at the time was very high HBsAg levels, the higher the rate of transmission. Early efforts used HBIG and then vaccine independently, but a well-designed study looking combining the two yielded >90% reduction in MTCT. As a result of this very high efficacy, the practice of administering HBIG and HBV vaccine within the first 12 hours of life has been the standard of care for many years. A recent study from the Centers for Disease Control and Prevention demonstrated that providers adhere to this standard more than 90% of the time. However, the same study also showed that there is still a consistent subset of pregnant women for whom standard of care prophylaxis fails to protect against MTCT. These women have the highest levels of HBV DNA (>10^7 copies/ml or >200,000 IU/ml) and they are e antigen positive. This has been noted in several studies, and so efforts have been initiated to determine if using antiviral treatment in these women to reduce their HBV DNA would be effective in addition to standard of care prophylaxis. Early studies used lamivudine, but the results were mixed due to low potency of the drug and low barrier to resistance. More recent studies

<table>
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<th>Pathogen</th>
<th>Double stranded DNA Hepadnavirus</th>
<th>Single stranded RNA Flaviviridae Genetic variability</th>
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<td>Mode of transmission</td>
<td>Bloodborne MTCT Sexual transmission</td>
<td>Bloodborne MTCT Sexual transmission-MSM</td>
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<td>Risk of chronicity after acute infection</td>
<td>Low—adults High—infants</td>
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<td>Risk of MTCT</td>
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<td>Treatment in neonate</td>
<td>Post-exposure prophylaxis Vaccine HBIG</td>
<td>None available</td>
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MTCT: mother to child transmission; MSM: men who have sex with men; HBIG hepatitis B immunoglobulin.
have focused on using tenofovir, which has many advantages: an extensive history of being used to treat HIV-infected pregnant women, a much higher potency agent and a much higher barrier to resistance. The studies using tenofovir beginning at 28–32 weeks of gestation and continuing until 1–2 months post-partum have demonstrated reduced rates of infants with transmission compared to those only receiving standard of care prophylaxis.13-16 This practice is now part of the American Association for the Study of Liver Diseases (AASLD) HBV guidelines for management of pregnant women.17 Real world studies have demonstrated that identification of pregnant women at high risk for transmission can be done and antiviral therapy can be used with high efficacy in preventing transmission.18 Future efforts will need to focus on expanding this practice so that all pregnant women with HBV can enjoy the benefits or prevention and pre-emptive therapy.

**Diagnosis of neonatal HBV infection**

As in adults, the presence of surface antigen diagnoses an infected child. Surface antigen should not be measured within 1 month of hepatitis B vaccination to avoid confusion. An important reminder for practitioners seeing infants that have received HBV prophylaxis with HBV vaccine and HBIG is to re-evaluate the infants at 9–12 months for presence of HBV surface antibody and absence of HBV surface antigen. These results confirm that the infant was protected, and many children with breakthrough infection after prophylaxis are not detected for several years because follow up testing was never performed.

**Hepatitis C virus**

**Virology**

HCV is a single stranded enveloped RNA virus that belongs to the Flaviviridae family.19 Six main genotypes have been described and all can be transmitted to the mother to the infant. Within an infected individual, there also different viral genomes that evolve in response to immune pressure, a phenomenon that is called “quasispecies”.19,20 This prodigious genetic variability contributes to the inability of the host's immune response to eliminate the virus and offers a major obstacle in the development of an effective vaccine. HCV specific T cell responses also may also impact persistence of infection in those individuals unable to clear the virus.21 For adults and children, the stronger the cellular response the more likely the infection will resolve.22

**Transmission and epidemiology**

The most common routes of HCV transmission in adults are unsafe healthcare procedures (in low resource settings) and injection drug use, whereas in children the main route of infection is MTCT.23-26 Sexual transmission can occur but is primarily limited to men who have sex with men.27 In 2015, approximately 71 million people in the world were infected chronically with HCV and great variation of prevalence within countries exist.25 In the US, after implementation of blood transfusion safe practices, HCV infection rates decreased for several years, but increase of cases has been documented in association with the intravenous drug (IV) epidemic. Recent data estimate that 2.5–4.7 million people in the US population are chronically infected with HCV affecting mainly white young people living in rural areas.2,28 Reproductive age women have subsequently been affected, with a disproportionate number of HCV cases among them and many more exposed infants.2,29

A recent study from the CDC calculates that the number of reproductive-aged women with HCV infection had doubled from 15,550 in 2006 to 31,039 in 2014, and estimated that almost 30,000 infected women gave birth about 1700 infected infants in 2014.30 However, those numbers are known to be an underestimation because of risk-based screening practices and lack of mandatory reporting to public health departments. Several studies have suggested that risk-based screening during pregnancy will miss cases, and that universal screening can be cost effective.31-35

**Clinical manifestations**

While HCV chronically infected pregnant women are usually asymptomatic, their infants are more likely to have complications such as low birth weight, intrauterine growth retardation, small for gestational age, late neonatal death, or requiring neonatal intensive care.36-38 Similar to adults, infants infected with HCV in the neonatal period are asymptomatic. Some infants may have an early phase of elevated liver enzymes and high level viremia. Regardless of symptoms, infants will spontaneously clear the infection at higher rates (25–50%) than adults (~15–25%).36,39

**MTCT patterns and risk factors**

MTCT has been recognized as an important mode of infection shortly after the HCV was discovered. Yet the mechanisms of infection remain unclear. Different series have reported a wide range of transmission rates, but a recent meta-analysis including only studies using second or later generation tests reported the risk of vertical HCV infection being 5.8% (95% CI: 4.2%–7.8%) among those born to HIV-negative women.40 Concomitant infection with human immunodeficiency virus (HIV) was associated with increased risk of transmission in the past, but currently, with highly active anti-retroviral therapy (HAART) available for HIV pregnant women the transmission risk has been estimated to be the same for infected and non-infected women.41-44 These findings are explained largely by HIV-induced immunosuppression in the absence of adequate viral control with subsequent higher HCV viral load.45 During pregnancy, most infected women have increased viremia followed by decreased viral load after delivery. The observation that some women are able to spontaneously clear their HCV infection in the postpartum period has been attributed to stronger T cell responses as well as favorable IL28B genetic alleles.45,46 Although MTCT has been documented only in the setting of maternal viremia, high viral load has been inconsistently associated with vertical transmission.41,43,47,48 Other risk factors associated with MTCT included prolonged rupture of membranes (>6 hours), invasive fetal monitoring,
intrapartum contamination with infected secretions, and being born second in a twin delivery.\textsuperscript{40,41,48,49} In addition, the use of maternal intravenous drugs in the past or during pregnancy and infection of peripheral blood mononuclear cells have been associated with higher rate of MTCT due to high viral heterogeneity related to repeated infections with different strains and quasispecies secondary to the use of contaminated needles.\textsuperscript{43,44} On the other hand, mode of delivery (cesarean vs vaginal) and breastfeeding (unless the nipples are traumatized) have not been associated with increased risk of MTCT.\textsuperscript{41,47,50,51}

**Diagnosis of neonatal HCV infection**

The Society for Maternal-Fetal Medicine (SMFM) recommends HCV testing for pregnant women who have risk factors at the first prenatal visit, and if negative, to repeat testing later in pregnancy if risk factors remain present. Also, they recommend HCV-positive pregnant to be screened for other sexually transmitted diseases and counsel them against alcohol consumption.\textsuperscript{52} Unlike hepatitis B, HCV treatment with new direct-acting antiviral (DAAs) has not been studied assessing the tolerability or efficacy in pregnant women. Therefore, SMFM recommends that DAAs not be used outside the setting of a controlled clinical trial. Additionally, SMFM suggests counseling HCV positive women on the limited data on MTCT after prenatal invasive testing in case it is required, and recommends providers to avoid internal fetal monitoring, prolonged rupture of membranes, and episiotomy. Finally, they discourage cesarean delivery or avoiding breastfeeding merely because of the mother’s HCV infection.\textsuperscript{52}

Being born to an HCV positive mother is a risk factor to acquire HCV infection, and those children should be evaluated.\textsuperscript{53} However, HCV antibody is not useful to identify infected neonates due to maternal transfer of antibodies. Unfortunately, IgM antibodies are not available commercially and there are no studies evaluating their utility in predicting MTCT. For these reasons, nucleic acid testing (NAT) should be used during the first months of life to evaluate exposed infants. The most common NAT used is quantitative real-time polymerase chain reaction (qRT-PCR), which has demonstrated better sensitivity than other methods to detect low levels of viremia.\textsuperscript{50} The American Academy of Pediatrics (AAP) recommends antibody testing at 12–18 months when maternal antibodies should have cleared, but testing between 1 and 2 months with NAT is an alternative to earlier diagnosis and to decrease parental anxiety.\textsuperscript{50} There is little data to support the initial time frame for testing, and there are no studies confirming the number of negative qRT-PCR needed to rule out MTCT in those exposed infants. Some experts recommend only one negative NAT and a non-reactive antibody after 12–18 months of age rule out infection, while others recommend two NAT.\textsuperscript{54,55} There is general agreement that NAT at 2–6 months is a reasonable time to test and may also limit the number of visits required. In real practice, the evaluation of HCV exposed neonates is challenging as long-term follow up rates are extremely low.\textsuperscript{55} Better infrastructures of maternal-fetal clinics and education of the providers along with more evidence-based recommendations for testing will be critical to improve outcomes.

**Treatment**

The treatment of HCV infection in adults has evolved rapidly over the last few years. Rates of sustained virologic response (SVR) using DAAs surpass 95% and safety has not been an issue transforming the paradigm of chronic infection into a “curable” infection. Many have asked if DAA therapy is now recommended for all children. Due to the lack of symptoms and higher spontaneous resolution in infants, no therapy will ever be recommended before age 3. However, there is not treatment for neonates or infants as there are no biomarkers that identify which infants will clear the infection spontaneously. DAA-based therapy is now FDA approved for children older than 12 years of age, clinical trials evaluating younger children and other DAA regimens are underway.\textsuperscript{56} It is conceivable that with this additional data and cost reductions of the regimens that much more widespread treatment recommendations for children.

**Summary**

Enormous advances on treatment of adult patients chronically infected with HBV and HCV have occurred during the last years, but little has been applied to infected pregnant women and their infants. HBV infected women should be evaluated and depending on the HBV DNA level, they should be treated with antiviral therapy. All children born to mothers with HBV should receive HBV vaccine and hepatitis B immunoglobulin at birth. After completion of hepatitis B vaccine series, post-vaccination titers should be performed to ensure they are protected. Many unanswered questions regarding mechanism of MTCT and management of perinatally exposed HCV children contribute to the lack of standardization. Given the increase incidence of HCV infections, pregnant women with risk factors should be screening actively and that opportunity should be used to link those infected mothers to care after delivery as many of them will not be identified otherwise. Finally, there is room for improvement in the management and follow up of perinatally infected children and strategies to change that paradigm will involve the collaborative work between obstetricians, pediatricians, neonatologists and health department authorities.

**Author disclosures**

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**REFERENCES**


2. Koneru A, Nelson N, Hariri S, et al. Increased hepatitis C virus (HCV) detection in women of childbearing age and potential


42. Pappalardo BL. Influence of maternal human immunodeficiency virus (HIV) co-infection on vertical transmission of


