Hepatitis B virus (HBV) infection, the most common form of chronic hepatitis worldwide, is a major public health problem affecting an estimated 360 million people globally. Mother-to-child transmission (MTCT) is responsible for more than one third of chronic HBV infections worldwide. An estimated 15%–40% of persons chronically infected develop HBV-related complications, such as cirrhosis and hepatic carcinoma, and 25% die from these complications. MTCT can occur during pregnancy or during delivery. Screening pregnant women for HBV infection, providing infant postexposure prophylaxis, and maternal treatment with antiviral medications are strategies for reducing MTCT transmission rates and the global burden of new chronic HBV infections. Administration of hepatitis B immune globulin (HBIG) and hepatitis B (HepB) vaccine within 24 hours of birth, followed by completion of the vaccine series, is 85%–95% efficacious for prevention of MTCT. Despite timely post-exposure prophylaxis, MTCT occurs in 5%–15% of infants. Hepatitis B surface antigen (HBsAg) positive, hepatitis e antigen (HBeAg) positive mothers with HBV DNA level ≥10^6 copies/mL (>200 000 IU/mL) are at greatest risk of transmitting HBV to their infants. Consensus recommendations and evidence-based guidelines for management of chronic HBV infection and screening of pregnant women have been developed. The safety and efficacy of antiviral drug use during pregnancy are areas of ongoing research. Substantial advances have been achieved globally in reducing MTCT, but MTCT remains an ongoing health problem. Attaining a better understanding of the mechanisms of MTCT, implementing existing policies on maternal screening and infant follow-up, and addressing research gaps are critical for further reductions in MTCT transmission.

Key words. antivirals; hepatitis B; hepatitis B immune globulin; hepatitis B vaccine; hepatitis B virus; mother-to-child transmission; perinatal transmission.

BACKGROUND AND EPIDEMIOLOGY

HBV infection is the most common form of chronic hepatitis worldwide and a potentially preventable global health problem. The World Health Organization (WHO) estimates more than 2 billion people have been infected with HBV, 360 million people are chronically infected, and 600 000 people die annually from complications of HBV-related liver disease [1, 2]. The prevalence of chronic HBV infection is >8% among people in sub-Saharan Africa, Asia, and the Amazon Basin; 2%–8% in the Middle East, Eastern Europe, and the Indian subcontinent; and <2% in Western Europe, Australia, and most of the Americas [2, 3]. In the US, approximately 25 000 infants are born annually to HBsAg-positive pregnant women [4], and up to 90% of perinatal infections become chronic [5–12] compared with approximately 5% of adult infections [9, 13]. MTCT is responsible for more than one third of chronic HBV infections worldwide [1, 6, 14–19]. Strategies for reducing the overall global burden of new chronic HBV infections include: maternal screening, postexposure prophylaxis (PEP) consisting of HepB vaccination starting at birth (ideally with passive immunoprophylaxis), and the use of newer antiviral medications for high-risk pregnant women infected with HBV.

Pathogen

HBV is a 42-nm double-stranded enveloped virus of the Hepadnaviridae family. It is composed of a nucleocapsid core (HBeAg) and a viral envelope containing HBsAg. Eight HBV genotypes (A–H) and 2 provisional genotypes (I, J) have varying regional prevalence and possible differences in disease severity [1, 20, 21]. HBV is transmitted by
percutaneous and mucosal inoculation in blood and body fluids. The virus remains viable on environmental surfaces for at least 7 days [21].

A reactive (positive) HBsAg test indicates acute or chronic infection; HBsAg is the marker used to screen for HBV infection in pregnant women and to estimate chronic HBV prevalence. HBeAg typically correlates with higher levels of HBV DNA (viral load) and active replication [20]. Total antibody (immunoglobulin [Ig]G and IgM) to HepB core (anti-HBc) indicates previous or ongoing infection; IgG anti-HBc persists for life. Antibody to HBsAg (anti-HBs) indicates immunity after either infection or vaccination.

Mother-to-Child Transmission
Approximately 90% of infants of HBsAg-positive, HBeAg-positive women and 5%–20% of infants of HBsAg-positive, HBeAg-negative women become infected without intervention [6, 7, 10, 15, 16, 22–27]. The most important risk factor for MTCT is the maternal HBV DNA level [8, 15, 16, 28, 29]. Most MTCT infant PEP failures occur at thresholds of maternal HBV DNA levels of \( \geq 10^6 \) to \( \geq 10^8 \) copies/mL [10, 15, 30–32]. When HBV is acquired during pregnancy, third-trimester infections carry the highest risk for MTCT [21]. MTCT can occur during pregnancy or intrapartum [8, 15, 33, 34].

Pre-embryonic and Assisted Reproductive Therapy. HBV has been detected in sperm, oocytes, and embryos [6, 34–38]. Limited data suggest HBV transmission can occur in germ line cells [37, 39]. The risk of HBV transmission from persons with chronic HBV during assisted reproductive therapy is unknown, but transmission is theoretically possible [34, 35, 37, 40]. Storage of cryopreserved sperm and embryos in the nitrogen vapor state, sperm washing, and double-sealing cryocontainers are suggested methods for reducing the possible risk of transmission [40].

Prenatal. The rate of intravascular transmission is unknown but considered to be low [21]. The presence of maternal HBeAg is associated with higher HBV DNA levels, and HBeAg is the only structural HBV protein that can pass through the placenta. Some authors speculate HBeAg might establish chronic HBV infection through induction of T-cell tolerance to HBV in utero [6, 18, 41–45]. A case-control study found significantly greater MTCT following amniocentesis (3 of 6) compared with controls (3 of 67) only when maternal HBV DNA levels were \( \geq 10^7 \) copies/mL [46].

Intrapartum. MTCT during delivery is most common. Exposure occurs through micro-transfusion or hematologic leaks of mother’s blood to the fetus during contractions, or through inoculation of mucosal membranes or breaks in the skin (eg, scalp electrodes) [24, 47, 48]. Detection of HBV DNA in cord blood might indicate MTCT [10, 24], but HBV DNA detection could represent maternal-fetal transfusion during labor and delivery or contamination of cord blood samples [24, 47, 48].

Most studies find no difference in MTCT among babies delivered by operative/spontaneous vaginal delivery or caesarean section when the infants receive PEP [49–53]. One study found elective caesarian section reduced MTCT rates in HBeAg-positive mothers with predelivery levels of HBV DNA \( \geq 10^6 \) copies/mL [51]. Caesarian section is not recommended for reducing MTCT in the US.

Breastfeeding. Markers of HBV are detectable in breast milk and colostrum from HBsAg-positive women. Reported rates of HBV-infection among breastfed and non-breastfed infants are similar, although some studies did not account for maternal HBV DNA levels [54–59]. A meta-analysis of studies in which the mothers did not have cracked or bleeding nipples did not identify an increase in MTCT when breastfed infants received PEP [55].

Clinical Features
Symptoms of acute HBV infection are indistinguishable from those of other types of hepatitis including nausea, vomiting, anorexia, low-grade fever, myalgias, and fatigue. The clinical spectrum of acute HBV infection is similar for pregnant and nonpregnant women. However, acute HBV infection increases the risk of preterm delivery [39, 60]. Fulminant hepatitis occurs in \( \leq 1\% \) of acute infections, including perinatal infections, and can result in irreversible liver failure and death [20]. Most acute and chronic HBV infections are asymptomatic. Chronic HBV infection has 3 immunologic phases: immune tolerant (no or minimal hepatic inflammation, high viremia), immune active (alamin aminotransferase [ALT] rises, high viremia, liver inflammation, possible fibrosis), and inactive carrier (ALT normal, inflammation and fibrosis improve, anti-HBe is present) [61–63]. The immune-tolerant phase occurs most often among persons infected via perinatal transmission from HBeAg-positive mothers [63]. An estimated 15%–40% of persons chronically infected develop HBV-related long-term complications [10, 64, 65], such as cirrhosis and hepatocellular carcinoma, and 25% die from these complications [13].

One study found an association between chronic HBV infection and gestational diabetes mellitus, antepartum hemorrhage, and threatened premature labor [66]. Pregnant women with cirrhosis risk rupture and bleeding from esophageal varices. Physiologic changes during pregnancy, including high levels of adrenal corticosteroids and estrogen hormones, can increase HBV viremia with resulting liver damage from heightened immune response to the virus when endogenous steroids decline. Hepatic flare
occurs at the end of pregnancy or postpartum and can result in hepatic failure and death [41, 67, 68]. Monitoring HBV DNA and liver enzymes near the end of the third trimester and postpartum is done to manage disease activity, including consideration for initiating or continuing antiviral treatment [69, 70].

STRATEGIES FOR PREVENTION

The Advisory Committee on Immunization Practices (ACIP) recommends screening pregnant women (including women previously vaccinated or previously tested) for HBsAg during the first prenatal visit of each pregnancy. Unvaccinated HBsAg-negative pregnant women at continuing risk for HBV exposure should initiate vaccination during pregnancy. Women at risk include those who are household contacts or sex partners of HBsAg-positive persons, injection drug users, have endstage renal disease, HIV infection, chronic liver disease, diabetes, or other factors. Women who are not screened prenatally, or who continue to be at risk for HBV infection, should be screened or re-screened at presentation for delivery. HBsAg positive tests are reportable in all states of the US [71]. Since 1990, perinatal hepatitis B prevention programs located in state health department immunization programs have assisted in the management of HBsAg-positive women and their infants to prevent MTCT [4].

Care and Treatment for HBsAg-Positive Pregnant Women

No global policies exist for management of HBV infection among pregnant women. ACIP recommends all HBsAg-positive pregnant women receive evaluation and medical management for chronic HBV infection. Algorithms for initial assessment of liver disease activity are similar for pregnant and nonpregnant women and consist of testing for HBeAg and quantitative HBV DNA, liver enzymes, and might include evaluation for liver damage [30, 61, 72–74]. The results guide management decisions and the timing of intervention (ie, immediate care or after delivery). Consensus recommendations for management of chronic HBV infection and prevention of MTCT, with evidence-based clinical practice guidelines have been developed [32, 61].

Prevention of MTCT-Infant

Bathing. Skin contamination with HBV might increase the risk for transmission (eg, injection), and it can present a risk for occupational exposure. Bathing newborn infants (eg, with mild soap solution) to remove HBV-contaminated blood and body fluids might minimize the risk [75].

Postexposure Prophylaxis. Prevention of MTCT by PEP, consisting of administering HBIG and a monovalent HepB vaccine within 12 hours of birth, followed by completion of the vaccine series, has 85%-95% efficacy [8, 33, 42, 76–78]. A systematic review found higher efficacy against MTCT with addition of HBIG compared with HepB vaccine alone (risk ratio, 0.54; 95% confidence interval, 0.41–0.73); most studies included infants of HBsAg-positive, HBeAg-positive pregnant women [79]. HBIG provides a short-term increase in anti-HBs that might improve protection until the infant responds to vaccine [80]. WHO recommends HBIG as an adjunct to HepB vaccine starting within 24 hours of birth, although the added benefit of HBIG is less clear among term infants of HBsAg-positive, HBeAg-negative women [2]. Worldwide, administration of HBIG might not be feasible, because of supply, safety, or cost issues [2].

Postexposure prophylaxis relies on timely completion of a ≥3-dose HepB vaccine series, either as monovalent or combination vaccine. Postexposure prophylaxis for infants weighing <2000 grams includes a dose at birth, which is not counted toward a ≥3-dose HepB vaccine series [71]. Factors associated with failure of PEP include maternal HBeAg positivity and high HBV DNA levels, delay in receipt of the HepB birth dose, failure to complete the vaccine series [81], failure to receive HBIG, nonresponse to vaccine [11, 82, 83], and, rarely, HBV mutations [11, 43, 79, 83]. MTCT occurs in 5%-15% of infants despite timely prophylaxis [16, 18, 23, 79, 83, 84].

Universal Birth Dose. In 2005, ACIP recommended HepB vaccine for all infants of HBsAg-negative pregnant women to be administered as soon as feasible but before discharge from the birthing hospital. The birth dose provides a safety net for infants of HBsAg-positive women who might not be identified for PEP because of medical errors in interpreting or documenting maternal screening results [71]. Errors or omissions are also made in administering infant PEP [4, 83, 86]. Likewise, WHO recommends all infants receive HepB vaccine as soon as possible after birth, regardless of HBsAg status of the mother, preferably within 24 hours [1, 2].

Post-HepB Vaccination Testing

ACIP recommends post–HepB vaccination testing (PVST) for all infants born to HBsAg-positive women. Testing consists of HBsAg for infection and anti-HBs for response to vaccination [71]. The optimal timing for detecting protective antibodies is 1–2 months after the final HepB vaccine dose at ≥9 months of age [82]. Testing at intervals <1 months after the final vaccine dose might detect HBsAg from vaccination; testing before 9 months of age might miss HBV-infected infants with prolonged HBV incubation due to HBIG at birth; testing at increasing intervals >2 months after the final dose might result in unnecessary revaccination of infants whose anti-HBs levels have declined to below the detectable limit [71, 82]. In 2008,
PVST results were known for <60% of infants of HBsAg-positive pregnant women [4]. Centralized case management and home visits assist in obtaining high rates of PVST [87].

More than 90% of term infants who receive PEP and complete at least 3 doses of HepB vaccine achieve concentrations of antibody associated with protection (anti-HBs ≥10 mIU/mL) [80]. Uninfected infants who do not show protective levels receive a second HepB vaccine series and repeat PVST [71]. Follow-up studies conducted for ≥22 years suggest that immune memory and long-term protection are maintained among responding infants [12, 88].

**Treatment During Pregnancy and Delivery**

In making treatment decisions, clinicians should consider the potential benefit of preventing MTCT, any risks to the mother and the fetus including possible teratogenicity, efficacy, length of therapy, and potential for antiviral drug resistance [32, 89]. The risks of stopping or withholding treatment for the mother should be weighed against any potential risks of the medications to the fetus. Seven drugs are approved by the US Food and Drug Administration (FDA) for treatment of chronic HBV infection: FDA pregnancy category B, telbivudine, tenofovir; C, lamivudine, adefovir, entecavir; X, interferon (standard, pegylated) [32, 74, 90]. Although none of the medications are approved in pregnancy, both tenofovir and lamivudine have been used extensively in pregnant patients infected with HIV. The Antiretroviral Pregnancy Registry, a prospective registry that collects information on drug exposures to assess potential teratogenicity, has collected information on nearly 2000 pregnancies with exposure to tenofovir and over 4000 pregnancies with lamivudine exposure with no evidence of increases in birth defects over baseline. Animal safety and clinical trial data on telbivudine, a newer drug with less extensive published experience is with lamivudine, a reverse-transcriptase nucleoside analog inhibitor with activity against HBV. Early resistance and virus mutations after long-term use of lamivudine are a concern [32, 72, 96]. A meta-analysis including 15 RCTs reported lamivudine is well tolerated and is more effective than HBIG or control (placebo or no treatment) in preventing MTCT among HBsAg-positive, highly viremic mothers treated from 28 weeks gestation [68]. Another meta-analysis including 10 RCTs reported similar MTCT results with lamivudine administered from 28 weeks gestation compared with HBIG administered during pregnancy. The difference between the groups was not significant, possibly due to small sample size. No significant adverse effects of lamivudine prophylaxis were noted [97].

Telbivudine is a synthetic thymidine nucleoside analog with activity against HBV. A high incidence of resistance is reported in HBsAg-positive nonpregnant women with high viral load [32, 72]. A systematic review and meta-analysis of 6 studies among Chinese women treated with telbivudine in late pregnancy reported significantly higher seropositivity rates of HBsAg or HBV DNA at birth and at 6–12 months compared with infants of women who were not treated. The included studies were limited by small sample size and nonrandomized controls [93]. No adverse effects were found [92, 93].

Tenofovir disoproxil fumarate (TDF) is a potent nucleotide analog reverse-transcriptase inhibitor. It is considered safe and efficacious with no reported HBV resistance based on studies in HIV, HBV, and HIV/HBV coinfected women [88, 98, 99]. There are increasing data on its use in pregnant women with high HBV DNA load to suppress viral load and reduce MTCT [72, 89, 98]. A recent systematic review of 13 studies suggested TDF is safe for pregnant women. However, evidence on bone health and growth
Table 1. Research Gaps

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<tr>
<th>Topic</th>
<th>Subtopics</th>
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<tr>
<td>In utero transmission, including via oocytes and embryos</td>
<td>Improve understanding of the mechanisms of MTCT transmission and foster development of targeted approaches for prevention, including prevention during medically assisted reproduction</td>
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<tr>
<td>Caesarean versus vaginal delivery</td>
<td>In pregnant women with high-level HBV DNA, evaluate for any added benefit from elective caesarean-section compared with other types of delivery for the prevention of MTCT</td>
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<tr>
<td>Antiviral agents during pregnancy and breastfeeding</td>
<td>(1) Determine the safety (mother, infant), efficacy, and timing of antivirals in pregnancy to prevent MTCT (2) Understand the effects of infant exposure to antiviral agents in breast milk</td>
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<td>Hepatitis B vaccine (birth dose)</td>
<td>Quantify protective efficacy of MTCT by time of first HepB vaccine dose: day of life 0 (baseline-first 12-24 hours) versus days of life 2-3, 4-7, or later, relative to maternal HBV DNA load</td>
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<tr>
<td>Neonatal antiviral prophylaxis</td>
<td>Determine the indications, safety, and efficacy of antiviral prophylaxis for exposed, newborn infants, to enhance or replace HBIG for prevention of MTCT</td>
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<td>HBIG</td>
<td>(1) Examine the added benefits of HBIG for prevention of MTCT with and without HBIG at birth for infants of HBsAg-positive/HBeAg negative mothers (2) Efficacy (if any) of HBIG for prevention of fulminant hepatitis among infants born to HBsAg-positive/HBeAg-negative women (3) Quantitate increase in HBV incubation period and potential for “missing” HBsAg-positive infants by postvaccination testing at 9 months versus a later interval after HBIG at birth</td>
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<tr>
<td>HBV DNA</td>
<td>Determine an optimal HBV DNA level for initiating antiviral treatment for prevention of perinatal HBV transmission in conjunction with infant postexposure prophylaxis</td>
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Abbreviations: HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; MTCT, mother-to-child transmission.

outcomes in the infants is limited [99]. A prospective cohort study evaluating safety among treated HIV-exposed and noninfected infants found small but significantly lower length and head circumference z-scores at 1 year in the TDF-exposed compared with TDF-unexposed infants [100]. The significance of this finding for long-term development is not known. TDF is cleared by the kidney and there is potential for slower filtration in infants leading to toxic levels and reduced bone mass.

CONCLUSIONS

Major progress has been made globally in reducing MTCT of HBV. Modeling suggests that perinatal transmission might be controlled by 2020 in China with a combination of screening, antiviral treatment, infant PEP, and postvaccination testing [77]. Other countries have had similar successes. Despite these predictions, transmission from pregnant women with chronic HBV infection remains a substantial problem. As the US population of women with chronic HBV infection ages out of childbearing years, the success of global efforts will determine in large part the extent of future US HBV infection risk for newborn infants. Addressing MTCT research gaps (Table 1) could provide data and results critical for reducing the 5%–10% perinatal prophylaxis failure rate and the global burden of chronic HBV infection.

Supplementary Data

Supplementary materials are available at the Journal of the Pediatric Infectious Diseases Society online (http://jipids. oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Acknowledgments

Financial support. This work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development — National Institutes of Health.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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*Please see references 41–100 as supplementary data online at http://jpids.oxfordjournals.org.