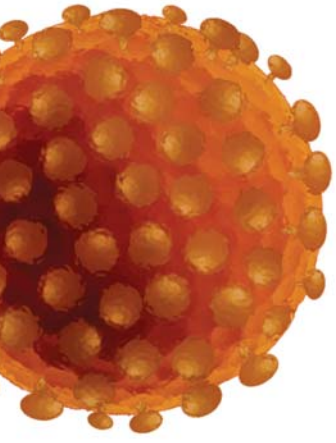
Chronic Hepatitis B in Pregnancy

A Workshop Consensus Statement on Screening, Evaluation, and Management, Part 1

Joseph Apuzzio, MD; Joan M. Block, RN, BSN; Samuel Cullison, MD; Chari Cohen, MPH, DrPh (c); Shou Ling Leong, MD; W. Thomas London, MD; James A. McHugh, MD; Richard L. Neubauer, MD†; Robert Perrillo, MD; Robert Squires, MD; Dianne Tarrant, MSN, APRN; Brian J. McMahon, MD; for the Hepatitis B Foundation.



Infection with the hepatitis B virus (HBV) can lead to both acute and chronic hepatitis. For more than 2 decades, the Centers for Disease Control and Prevention (CDC) has recommended that all pregnant women be screened for the marker of active hepatitis B, the hepatitis B surface antigen (HBsAg).[1] According to a recent report from the Institute of Medicine (IOM), most obstetrical care providers do screen pregnant women for hepatitis B and advise that newborns of HBsAg-positive mothers receive both hepatitis B immune globulin and hepatitis B vaccine, ideally immediately after birth. However, knowledge among obstetricians about hepatitis B is limited, and the IOM concluded in their report that only one-half to two-thirds of obstetrical care providers offered hepatitis B information to patients or referred their HBsAg-positive pregnant patients to a specialist for management of chronic hepatitis B.[2]

On March 10 and 11, 2010, the Hepatitis B Foundation sponsored a meeting of practitioners in primary care medicine, maternal and fetal medicine, and hepatitis and liver diseases. This panel developed recommendations, including an algorithm based on existing evidence-based guidelines, to help primary care providers routinely identify and manage their patients with hepatitis B.[3] The panel agreed that a separate set of recommendations should be developed for obstetrical and women's health care providers. An easy-to-follow algorithm was developed to aid providers in evaluating and managing HBsAg-positive pregnant women. This 2-part article discusses the problem of hepatitis B in pregnant women and outlines the panel's consensus recommendations to improve hepatitis B-related outcomes during and after

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pregnancy. [Note: The above-mentioned algorithm appears in Part 2.]

Screening for Hepatitis B

In the United States, the prevalence of chronic hepatitis B is estimated to be at least 1.4 to 2 million (1% to 2% of the population).[4,5] Persons with chronic hepatitis B (defined as HBsAg-positive for more than 6 months) are at a very high lifetime risk of developing severe complications including cirrhosis and hepatocellular carcinoma.[6] Although the CDC and the American Congress of Obstetricians and Gynecologists recommend universal screening of pregnant women for HBsAg, it is important for women's health care providers to also be aware of the groups defined by CDC as being at higher risk for hepatitis B (Table 1).[7]

When screening all pregnant women for HBsAg, women's health care providers are recommended to query their patients about potential risk factors. Those at higher risk for acquiring HBV should also be tested for the antibody to hepatitis B surface antigen (anti-HBs). Persons who are negative for both markers and who are at risk for infection should be vaccinated. CDC recommendations endorse vaccination during pregnancy

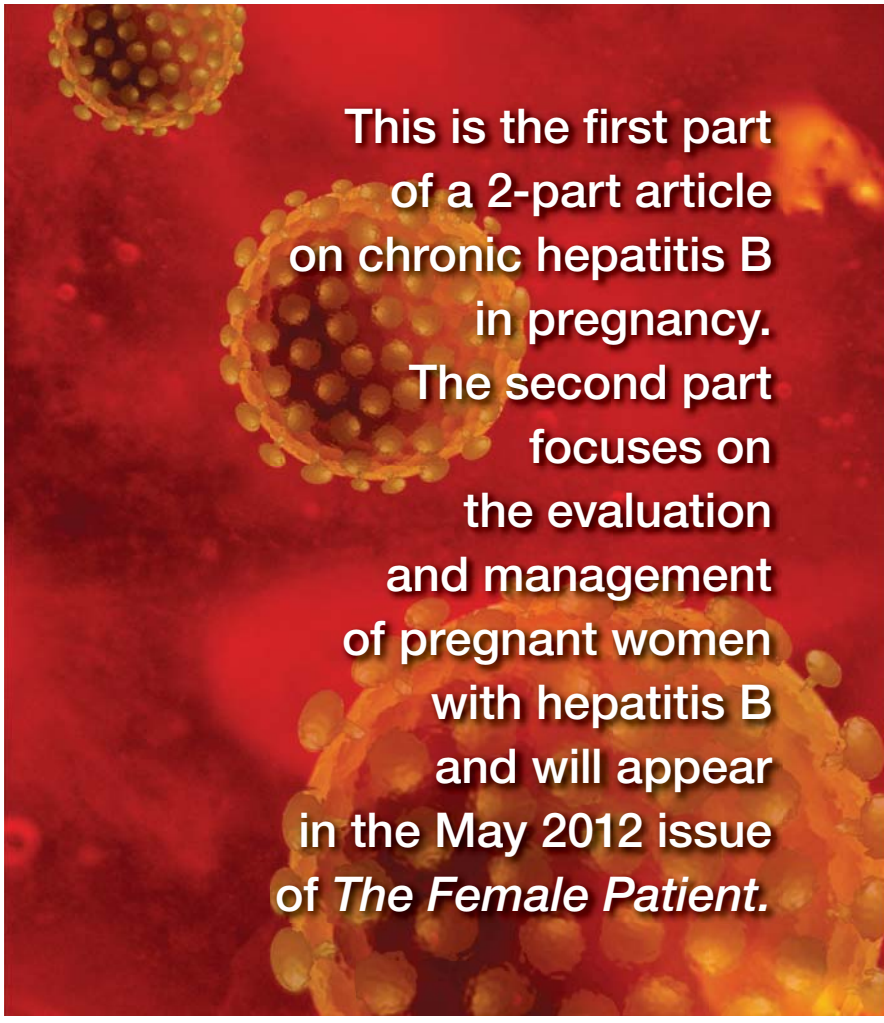

TABLE 1. Groups That Should Be Routinely Screened For Hepatitis B[a]

- Persons born in regions of the world where hepatitis B prevalence is 2% or higher (including Africa, Asia, Pacific Islands, Middle East, Eastern Europe, Spain, Malta, Mexico, Central America, the Caribbean, areas of South America, and indigenous populations in Alaska, Northern Canada, and Greenland)
- Injection drug users
- Men who have sex with men
- Persons with conditions that may require immunosuppressive or immune-modifying therapy
- Persons with elevated liver enzymes of unknown etiology (ALT; AST)
- Blood or tissue donors[b]
- Pregnant women[b]
- Infants born to HBV-infected mothers
- Hemodialysis patients
- Household members or sexual contacts of HBV-infected persons
- HIV-positive persons

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HIV, human immunodeficiency virus.
[a] Data from Weinbaum et al.[7]
[b] Blood and tissue donors and pregnant women are screened to help prevent the transmission of HBV via donated blood/tissue, or to a newborn during birth, respectively.

of women who are at high risk of contracting hepatitis B.[1]

Persons found to be infected (HBsAg-positive) have a high probability of transmitting the virus to others, especially to household contacts. HBV can remain infectious outside of the body for a week or more and can be spread from person to person via blood and other body fluids on environmental surfaces. In addition, HBV is the most infectious of all viruses that can be sexually transmitted. Because HBV is so highly infectious, the CDC recommends that all household and sexual contacts of HBsAg-positive persons be screened for HBsAg and anti-HBs, and those who are seronegative should be vaccinated.

Natural History and Management of Chronic Hepatitis B

Persons with chronic hepatitis B go through several stages of infection.[6] In the *immune tolerant* phase, the serum level of HBV DNA is high (> 20,000 IU/mL); hepatitis B e antigen (HBeAg) is detectable in serum; alanine aminotransferase (ALT) level is normal; and there is minimal or no liver inflammation and fibrosis. Most of these persons were likely infected at birth and did not receive prophylaxis at that time.

Later in life, as the immune system begins to recognize HBV as a foreign invader, the host mounts an attack on the virus, resulting in an elevated ALT level. During this *immune active* phase, HBV DNA levels are usually above 20,000 IU/mL, and most persons will "seroconvert" from HBeAg-positive to HBeAg-negative and may develop antibody to HBeAg (anti-HBe). Liver inflammation and fibrosis are usually present.

The majority of individuals will eventually enter an *inactive HBsAg "carrier"* phase, where HBV DNA levels decline (< 2,000 IU/mL or undetectable); ALT level normalizes; HBeAg is undetectable and anti-HBe may be present; and there is minimal to no liver inflammation. However, not all persons will enter the inactive phase, and some that do may experience a *reactivation* to active liver disease, in which HBV DNA levels increase; ALT level may be normal or elevated; and HBeAg may once again

TABLE 2. Approved Therapies for the Treatment of Hepatitis B[a]

	Interferon alfa-2b	Pegylated Interferon alfa-2a	Lamivudine[b]	Adefovir	Telbivudine	Entecavir	Tenofovir
Mechanism	Immuno-modulator	Immuno-modulator	Nucleoside analogue	Nucleotide analogue	Nucleoside analogue	Nucleoside analogue	Nucleotide analogue
Pregnancy Category	C	C	C	B	B	C	B
Adult Dosage	5 MIU subcutaneously Once daily for 16 weeks	180 µg subcutaneously Once weekly for 48 weeks	100 mg orally Once daily	10 mg orally Once daily	600 mg orally Once daily	0.5–1.0 mg orally Once daily	300 mg orally Once daily
Most Common Side Effects	Depression, muscle aches, fatigue, low-grade fevers	Depression, muscle aches, fatigue, low-grade fevers	Headache, fatigue, diarrhea, and ear, nose, throat infections	Asthenia, headache, nausea, diarrhea, flatulence, dyspepsia	Headache, fatigue, diarrhea, dyspepsia, rash, myopathy	Headache, fatigue, diarrhea, dyspepsia	Asthenia, headache, nausea, diarrhea, rash, depression

[a] Data from product package inserts.

[b] Lamivudine is widely used in pregnancy among HIV-infected women with no known increased adverse outcomes for mother or infant, and there has also been a lot of experience with tenofovir being used in the third trimester of pregnancy of these women as well.

become detectable. Others may develop continuing smoldering chronic hepatitis owing to selection of an HBeAg-negative HBV mutant. Because of the unpredictable nature of HBV, and the risk of serious complications of active disease, all persons found to be chronically (longer than 6 months) positive for HBsAg need lifetime follow-up with at least semiannual surveillance.

In women who are positive for HBeAg, the chance of transmitting HBV to their newborns at birth is nearly 100%. Up to 90% of the newborns born to these mothers go on to develop chronic hepatitis B if they do not receive hepatitis B immune globulin and hepatitis B vaccine at birth.

Seven antiviral medications are currently FDA-approved for the treatment of hepatitis B. A more thorough discussion of these medications and recommendations for treatment can be found in the evidenced-based guidelines developed by the American Association for the Study of Liver Diseases Practice Guidelines Committee.[9] Of the licensed medications, 5 are nucleoside/nucleotide analogues and are oral: lamivudine, adefovir, telbivudine, entecavir, and tenofovir; 2 are interferons and injectable: interferon alfa and pegylated interferon alfa (Table 2). Of the oral medications, tenofovir and entecavir are the preferred drugs of choice because they are both potent and have high barriers to resistance; that is, the use of these drugs is less likely to lead to the development of antiviral resistant strains of HBV.[10,11]

This is the first of a 2-part article. Part 2 focuses on the evaluation and management of pregnant women who screen positive for HBV, including ordering additional laboratory tests and the timely referral of infected mothers and screening of close contacts, and includes an easy-to-follow flow chart to aid women's health care providers.

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rate, and private foundation grants, and individual charitable donations. No commercial support was provided for the March 10-11, 2010 workshop.

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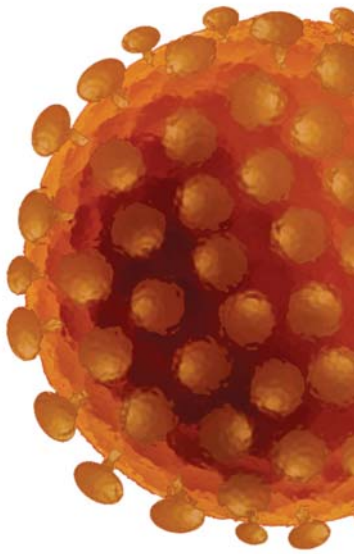

Chronic Hepatitis B in Pregnancy

A Workshop Consensus Statement on Screening, Evaluation, and Management, Part 2

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Decreasing the Risk of Infection in Newborns

Despite judicious screening efforts by most providers who care for pregnant women, about 1,000 newborns in the United States acquire a chronic hepatitis B virus (HBV) infection each year.[1] Reasons for failure to prevent HBV infection in these infants include the following:

1. *Failure to identify hepatitis B surface antigen (HBsAg)-positive pregnant women.* Although it has been estimated that 95% of all pregnant women are screened for HBsAg during pregnancy, about 5% slip through the cracks.[2] Vigilance to maintain high rates of screening needs to be reinforced.

2. *Delay in administering the hepatitis B vaccine and hepatitis B immune globulin (HBIG).* While 94% of infants receive HBIG and the hepatitis B vaccine, many do not receive prophylaxis immediately after birth, when there is the greatest chance of preventing perinatal transmission. Beyond 12 hours after birth, the efficacy of prophylaxis decreases, and HBIG is ineffective if not given within the first week of life.

3. *Failure despite timely prophylaxis.* A small percentage of infants born to infected mothers with high viral loads will acquire HBV despite adequate prophylaxis. Use of an oral antiviral drug in the third trimester of pregnancy might be effective in preventing HBV transmission. While several randomized clinical trials of lamivudine versus placebo in the third trimester have been conducted, they all suffered from poor design and/or small sample size.

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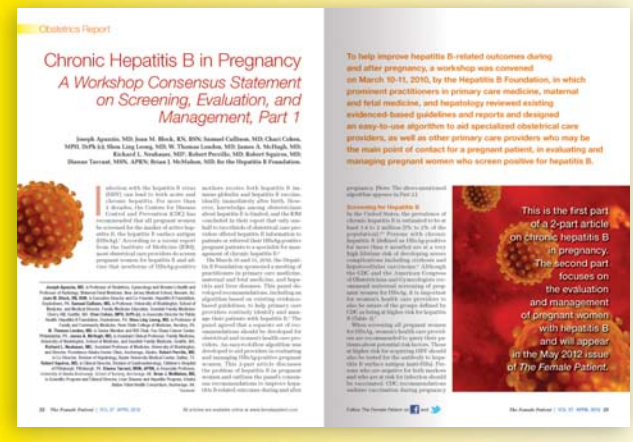
In addition, in most studies, information on matching participants by the timing of HBIG and the hepatitis B vaccine after birth is often lacking, making it impossible to predict the extent to which transmission might have been prevented with immediate prophylaxis after delivery.

Published studies have suggested that transmission is most likely if the level of HBV DNA is above 10^8 copies/mL (20 million IU/mL).[3,4] A recent meta-analysis concluded that lamivudine administered in the third trimester might prevent HBV transmission.[5] If a woman has transmitted HBV in a previous pregnancy despite adequate newborn prophylaxis, then the clinician, in consultation with an HBV specialist, may consider antiviral prophylaxis in the third trimester. However, antiviral prophylaxis likely confers no benefit to those HBsAg-positive pregnant women with low (< 20,000 IU/mL) or undetectable levels of HBV DNA and may uncommonly contribute to the development of antiviral-resistant strains. Thus the use of antivirals for HBV during pregnancy should be approached with the utmost caution and after consultation with a specialist.

Referral of HBsAg-Positive Pregnant Women to Experienced Providers

The most pressing finding of the Institute of Medicine (IOM) report concerning chronic HBV infection in pregnancy was that about 40% of obstetrical care providers did not refer their HBsAg-positive patients to specialists in the management of HBV infection, either prior to or after

This is the second part of a 2-part article. The first part, published in the April issue, described hepatitis B virus (HBV) infection in the general population, screening for HBV, and the natural history and management of chronic HBV infection. (*The Female Patient.* 2012;37[4]:22-27.)


Obstetrics Report

Chronic Hepatitis B in Pregnancy

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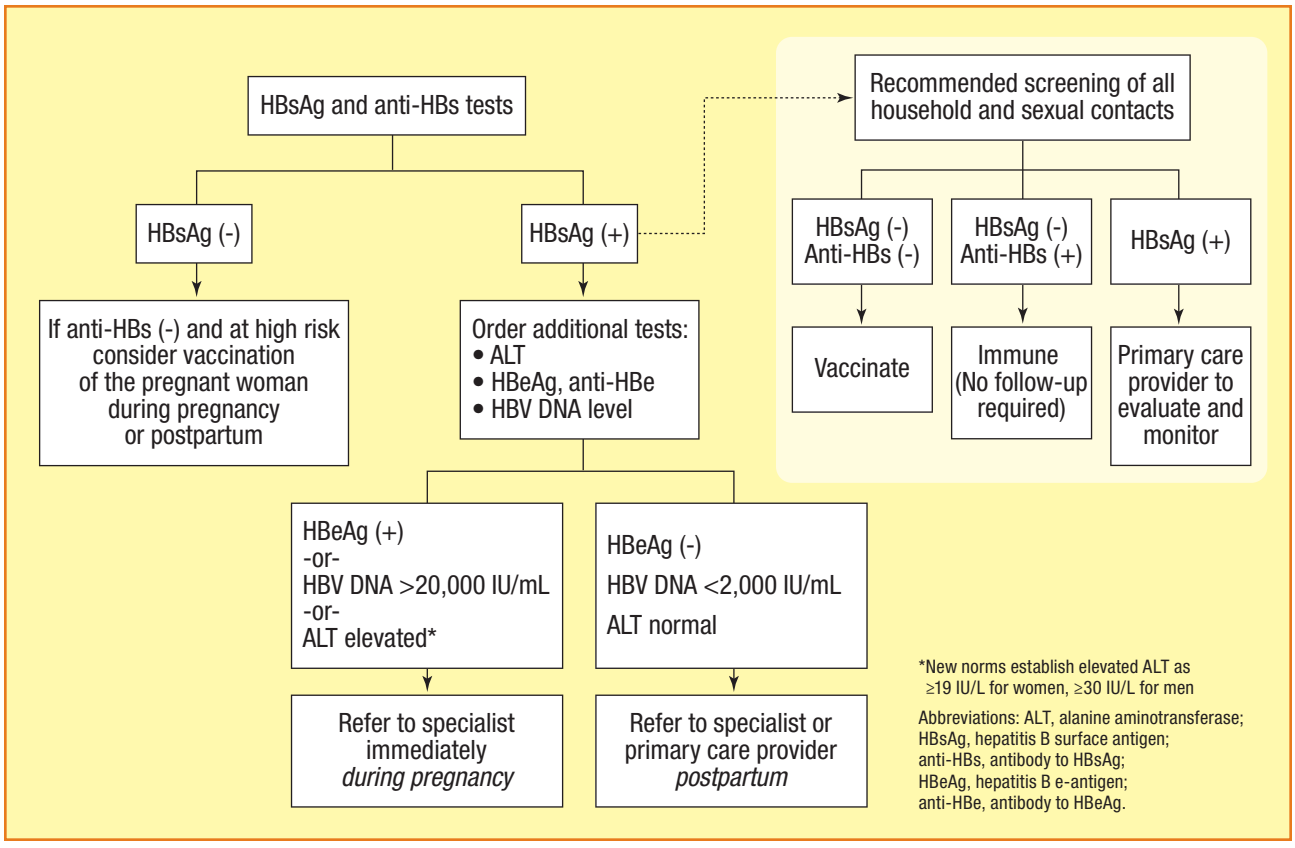
This is the first part of a 2-part article on chronic hepatitis B in pregnancy. The second part focuses on the evaluation and management of pregnant women with hepatitis B and will appear in the May 2012 issue of *The Female Patient*.



Recommended Approach for Hepatitis B Virus (HBV) Screening, Evaluation, Vaccination, and Referral of Pregnant Women

delivery. Women with chronic hepatitis B infection may develop cirrhosis or hepatocellular carcinoma, usually after menopause, but need lifetime follow-up to detect treatable complications and determine if antiviral therapy is appropriate.

Recommendations for Obstetricians and Women's Health Care Providers

The algorithm provided here outlines key decision points in managing pregnant women who are found to be HBsAg-positive:

1. The obstetrical care provider should perform additional laboratory testing including hepatitis B e-antigen (HBeAg) and antibody to HBeAg (anti-HBe), HBV DNA level, and liver function tests, especially alanine aminotransferase (ALT).

2. Based on the laboratory results, the provider should advise those women without active disease (ie, HBeAg negative, low or no HBV DNA, and normal ALT level) to seek specialist or primary care follow-up after delivery. It is important to note that flares of hepatitis in HBsAg-positive persons with a normal ALT level can occur postpartum, possibly due to changes in immunologic status during and after pregnancy. To facilitate follow-up, advice and information about the importance of lifetime monitoring should be included in the discharge summary provided to the patient.

3. For women who have evidence of active disease (ie, HBeAg and/or HBV DNA positive with an elevated ALT level using new norms [see algorithm]), the provider should refer the patient during pregnancy to a practitioner skilled at managing HBV infection. If this is not practical, or if the provider who receives the patient wants to take a more active role in the management of HBV-infected

women, they can utilize the algorithm developed for primary care providers at this same meeting.[6] The obstetrical care provider should advise the HBsAg-positive woman that her household and sexual contacts need to be screened for HBV seromarkers and vaccinated if they are negative for both HBsAg and antibody to HBsAg (anti-HBs).

FOCUSPOINT➤

It is very important that obstetrical care providers communicate with the newborn's pediatrician or family physician to ensure that infants of HBsAg-positive mothers receive HBIG and the hepatitis B vaccine.

In conclusion, it is important that all providers who care for pregnant women (including specialized obstetrical care providers as well as primary care providers who may be the main point of contact for a pregnant patient) are aware of the importance of routine screening of all pregnant women for HBsAg and understand the initial management of the HBV-infected pregnant woman, including conducting additional laboratory workup and recommending screening and vaccination of close contacts.

Furthermore, it is very important that obstetrical care providers communicate with the newborn's pediatrician or family physician to ensure that infants of HBsAg-positive mothers receive HBIG and the hepatitis B vaccine preferably at birth in the delivery room, or within the first few hours after birth, to have the highest chance of preventing perinatal transmission of HBV.

Finally, all obstetrical care providers need to refer their HBsAg-positive patients to a specialist or other provider with experience in managing HBV, either during pregnancy, or if laboratory tests show that the disease is inactive, shortly after delivery.

Financial Support: The workshop was convened and funded by the Hepatitis B Foundation (www.hepb.org) from its general operating funds. The Hepatitis B Foundation is a 501(c)3 nonprofit research and disease advocacy organization supported by federal, state, corporate, and private foundation grants, and individual charitable donations. No commercial support was provided for the March 10-11, 2010 workshop.

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