

Hepatitis B in Pregnancy

¹S Shantha Kumari, ²Prashant Prakash, ³Ruchika Garg, ⁴Prabhat Agarwal

ABSTRACT

Antiviral therapy with lamivudine, tenofovir, or telbivudine in the 3rd trimester can decrease mother-to-child transmission (MTCT) to <5% and should be used in women with high viral loads in the 3rd trimester. Postpartum flares of liver disease are common, and therefore, careful monitoring is warranted in women who stop therapy. The decision to breastfeed while on antiviral therapy should be individualized, but current evidence suggests that it is safe.

Keywords: Fibrosis, Hepatitis B, Lamivudine.

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INTRODUCTION

Hepatitis B is an infectious disease and it is a global public health problem with greater than 300 million people with this chronic infection worldwide. Virus is transmitted via parenteral route, vertical transmission, sexual contact, and rarely through breast milk. Globally, mother-to-child transmission (MTCT) remains the most common mode of infection, especially in areas of high endemicity, where approximately 10% of women of childbearing potential are chronically infected. The risk of transmission to fetus range from 10% in 1st trimester to as high as 90% in 3rd trimester. So it is important that pregnant women with HBV infection are diagnosed and properly managed throughout the pregnancy, since timely pre- and

peripartum management can decrease vertical transmission from >90 to <5%.

HOW TO APPROACH A PREGNANT FEMALE WITH HEPATITIS?

Before Conception

Many young women are in the immunotolerant phase of disease and do not warrant antiviral therapy for themselves; others may have liver inflammation, fibrosis, and high viral loads and meet current guidelines for treatment (Table 1).¹ If treatment is not urgently required [persistent mild liver enzyme elevation (2*ULN, i.e., ~40–50 U/mL) but little or no fibrosis], providers should discuss timing of antiviral initiation, consider waiting to initiate therapy once childbearing is complete, or a stronger need for antiviral therapy arises.

Tenofovir is the preferred drug in pregnancy because it is safe, potent, and has low risk for resistance with long-term use.

Lamivudine (pregnancy class C), telbivudine, and tenofovir (both pregnancy class B) are considered to be safe in pregnancy (Table 2), only tenofovir is recommended as a first-line therapy outside of pregnancy. Interferon should not be used in pregnancy (pregnancy class C). Antivirals are effective for HBV but are not recommended in pregnancy. There are limited data on adefovir and entecavir (pregnancy class C). Animal models have reported reproductive and embryo-fetal toxicity and therefore should not be used during pregnancy.²⁻⁷

Telbivudine is neither used for management of HIV, nor as first-line therapy for HBV. Since 2006, data in HBV monoinfected women collected in the Antiretroviral Pregnancy Registry (APR) showed no adverse fetal outcomes in the 10 women observed.

First and Second Trimesters

The current guidelines recommend that all pregnant women be screened for HBV infection in the 1st trimester.¹ A number of asymptomatic women discover that they have HBV via this screening protocol. For women with newly discovered HBV infection, it is appropriate to order the routine baseline tests that one would order outside of pregnancy. These include HBV viral load, HBe antigen and HBe antibody, HIV screen, HCV and HDV antibodies, and liver enzymes. First-degree family members should be screened for HBV and be vaccinated if not immune. Liver

¹Professor and Head, ^{2,4}Associate Professor, ³Assistant Professor

¹Department of Obstetrics and Gynecology, Malla Reddy Medical College for Women, Hyderabad, Telangana, India

²Department of Medicine, Sarojini Naidu Medical College, Agra Uttar Pradesh, India

^{3,4}Department of Obstetrics and Gynecology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India

Corresponding Author: S Shantha Kumari, Professor and Head, Department of Obstetrics and Gynecology, Malla Reddy Medical College for Women, Hyderabad, Telangana, India

biopsy is contraindicated and fibroscan is not approved for use in pregnancy. Platelets can occasionally be decreased in otherwise normal pregnant women⁸ making noninvasive measure of advanced fibrosis inaccurate.

Discontinuation of antiviral therapy in pregnancy can be associated with viral reactivation and flares, which in some cases can be severe (defined as increase in liver enzymes to five times the upper limit of normal).

Some providers recommend ALT and HBV DNA every 1 to 3 months, but in the absence of active disease or advanced fibrosis, there is no need for additional follow-up, specifically for HBV until the 3rd trimester.

INTRAUTERINE TRANSMISSION

Most MTCT occurs around the time of delivery; however, there are data to suggest that intrauterine HBV infection may also occur, possibly through placental infection. A possible increase in MTCT rates in women with high viral loads undergoing amniocentesis (among women with ≥ 7 log copies/mL: vertical transmission 50 vs 4.5% in controls without amniocentesis), $p=0.006^9$; however, additional studies are warranted before treatment recommendations can be made.

Third Trimester Management to Prevent MTCT

Antiviral therapy in the 3rd trimester can reduce the rate of MTCT in women with high HBV viral loads. Therapy should be initiated between 28 and 32 weeks to allow for sufficient time for DNA levels to decrease, and reduce the risk of HBV transmission.

Mother-to-child transmission analysis found that transmission was significantly reduced with lamivudine with an overall risk of 0.43 (95% CI, 0.25–0.76).¹⁰ Of note, significant heterogeneity existed in lamivudine administration and control arm characteristics. Evidence is mounting that tenofovir is a safe and efficacious alternative to lamivudine for prevention of MTCT and is preferred as it is more potent, has faster decline in HBV DNA, and no resistance reported as yet.

Telbivudine is an alternative option for the prevention of MTCT. A number of studies suggest that it is effective and safe in pregnancy,¹¹⁻¹³ though long-term data are lacking. Zhang et al¹⁴ prospectively enrolled 700 women with HBV DNA > 6 log copies/mL receiving telbivudine ($n=263$), lamivudine ($n=55$), or no prophylaxis ($n=374$), based on patient preference. Antiviral therapy was started between weeks 28 and 30. All infants received immunoprophylaxis within 6 hours of birth and HBV vaccination. Six hundred forty-eight women were followed for the full duration (52 weeks). The mean decline in HBV DNA was > 4 log for telbivudine and > 3 log for lamivudine. Fetal outcomes, including rates

of congenital abnormalities, were similar between groups. Among the infants who completed follow-up, no vertical transmission was seen in the treated group by on-treatment analysis (vs 2.84% in the control, $p=0.002$). By intention to treat, a lower rate of MTCT was still seen in the antiviral group compared to control (2.2 vs 7.6%, $p=0.001$). Failure rates did not differ significantly based on antiviral therapy used [telbivudine 1.9% (5/262) vs lamivudine 3.7% (2/54) by ITT]; no failures in either arm by on-treatment analysis.

Peripartum

Majority of vertical transmission of HBV occurs at the time of delivery. Children born from mothers infected with HBV be given passive/active immunoprophylaxis (HBIG as well as HBV vaccination series), regardless of maternal HBV DNA or HBeAg/Ab status.¹⁵ HBIG and the first vaccination should be given within 12 hours of birth. The second vaccine at 4 to 8 weeks of age and the third at 3 or 6 months. Children should be screened for HBV infection between 9 and 12 months of age.¹⁵ Transient viremia and surface antigen positivity is common in babies born of HBV-positive mothers (up to 25% in some studies), regardless of antiviral treatment status and maternal HBV DNA at the time of delivery.¹⁴

Antiviral studies that administered immunoprophylaxis within 12 hours of delivery found that HBIG/vaccine failures had higher maternal viral load cutoffs (> 7 log copies/mL),¹⁶ than antiviral studies that administered prophylaxis within 24 hours (> 6 log copies/mL),¹²⁻¹⁷ highlighting the importance of early immunoprophylaxis with HBIG and the first dose of HBV vaccine.

There is insufficient evidence to recommend caesarean section for HBV prevention in women with high viral loads at the time of delivery, especially given that 3rd trimester antiviral initiation is an excellent method to reduce maternal viral loads at delivery and is an effective adjunct to immunoprophylaxis for prevention of MTCT.

Postpartum Care

If a woman was placed on antiviral therapy solely for the purpose to decrease perinatal transmission, therapy can be discontinued postpartum. Most studies of antiviral use to prevent MTCT continue antivirals for 4 to 12 weeks after delivery, and HBV flares can occur in the postpartum period, thought to be due to immune-reconstitution after the relative immune-tolerance of the pregnant state.¹⁸

All patients should be monitored in the postpartum setting for disease flare. If HBV flare is persistent or severe, initiation or re-initiation of antiviral therapy

should be considered. Use or length of antiviral therapy in the postpartum period neither impact the incidence nor severity of flare, and therefore, the duration of postpartum therapy should be dictated by individual patient characteristics including desire to breastfeed.

Breastfeeding

Tenofovir and lamivudine are safe in breastfeeding, and WHO guidelines support their use in resource-poor settings for women with HIV infection.¹⁹

Currently, no data exists on the safety of breastfeeding with telbivudine use.

Lamivudine freely crosses the placenta and also is concentrated and excreted in breast milk.

Tenofovir also crosses the placenta, but less freely than lamivudine. Both animal and human studies demonstrate that tenofovir concentrations are lower in breast milk than in maternal serum or cord blood. Patients may choose to start breastfeeding immediately after delivery given the very low infant bioavailability of tenofovir and lamivudine or alternatively may choose to pump for 2 to 3 days and discard milk to ensure that antiviral concentrations in breast milk are negligible.

Patients diagnosed with hepatitis B during pregnancy require ongoing follow-up for this chronic disease. HBV is associated with increased risk for cirrhosis and hepatocellular carcinoma and these women require ongoing follow-up and care, not only during pregnancy but lifelong. A recent study suggests that fewer than half of women with HBV diagnosed in pregnancy obtained specialist follow-up and overall only 19% had appropriate laboratory tests for monitoring HBV at 1 year postdiagnosis.²⁰

CONCLUSION

With these measures, HBV MTCT can be decreased to <3% even in high-risk subgroups. For women with treatment indications separate from their pregnancy (immune-active disease or fibrosis), tenofovir is preferred.

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