Managing hepatitis B virus in pregnancy and children

KEY POINTS

- All pregnant women should be tested for hepatitis B surface antigen (HBsAg). A woman identified as HBsAg positive should be tested for hepatitis B e antigen (HBeAg) and hepatitis B virus (HBV) DNA, to determine risk of transmission to the infant and the degree of infectivity.
- If a pregnant woman has HBV, health professionals should take the opportunity to provide education about disease management, plan ongoing care, and test family and close contacts.
- The risk of mother-to-child transmission of HBV can be significantly reduced. The baby should be given a combination of hepatitis B immunoglobulin (HBIg) and the first dose of hepatitis B vaccine within 12 hours of birth, followed by a full course of hepatitis B vaccine.
- For HBsAg-positive women with high viral loads (> 200,000 IU/mL), referral should be made to a specialist for consideration of antiviral therapy started between 28-32 weeks gestation, to further reduce the risk of perinatal transmission.
- There is no evidence of HBV transmission as a result of breastfeeding.
- All children of HBsAg-positive mothers should be tested for HBsAg and anti-HBs at 9–12 months of age (at least 3 months after final dose of HBV vaccine). Most children with HBV infection develop chronic infection. They are asymptomatic and have little liver damage, but have high viral loads.
- Children with chronic hepatitis B (CHB) should be monitored annually, with liver function tests and HBV serology and viral load.
- Ensure adolescents with chronic hepatitis B infection are appropriately transferred from paediatric to adult care.

General considerations

In some areas of the world, up to 20% of women of child-bearing age have chronic hepatitis B (CHB) infection (1). In Australia, people who have migrated from countries with high hepatitis B virus (HBV) prevalence are often unaware of their infection, because testing has not been part of all routine migration health assessment. Pregnancy is the only time universal testing for infection with HBV occurs; and as a result, this is often the first time women become aware of their HBV infection. HBV can have significant health implications for the mother and her baby, and the issues for each should be considered independently.

Initial assessment of the woman should include consideration of the likely duration of infection; any prior or current therapy; liver function tests; and pregnancy liver ultrasound, liver biopsy or non-invasive assessment of liver fibrosis (e.g. FibroScan®). This consultation is an important educational opportunity. The mother should receive information about infection control, routes of transmission, vaccination, the phases of HBV infection and recommendations for follow-up at each phase (see Health Professional.
Mother-to-child transmission

Universal testing for HBV is recommended in every pregnancy, to allow for interventions to reduce transmission to the infant. This is important because more than 90% of infants with the infection will develop chronic infection, with the potential for significant adverse health outcomes. In contrast, 80% of older children and 95% of adults are able to clear HBV after infection. One hypothesis to explain the infant's failure to resolve HBV infection is that maternal hepatitis B e antigen (HBcAg) crosses the placenta and has a tolerising effect on the developing fetal immune system (2).

Preventing perinatal transmission

All babies of HBsAg-positive mothers should:

1. be given HBlG and the first dose of HBV vaccine within 12 (ideally within 4) hours of birth (3)
2. have three subsequent doses of HBV vaccine, at 2, 4 and 6 months of age
3. be tested for HBsAg and anti-HBs after 9-12 months of age (at least 3 months after final dose of HBV vaccine).

During pregnancy, the mother's viral load should be tested; if it is high (>200,000 IU/mL (5.3 log_{10} IU/mL)), international guidelines recommend that third-trimester antiviral therapy should be considered (4, 5).

anti-HBs: antibodies to surface antigen; HBlG: hepatitis B immunoglobulin; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; IU: international unit

The cornerstone of prevention of mother-to-child transmission (MTCT) of HBV is the combination of hepatitis B immunoglobulin (HBlG) and the first dose of hepatitis B vaccine, which is delivered within 12 hours of birth (3), followed by a full course of hepatitis B vaccine. Children should be checked at least 3 months after completing the primary course usually at 9-12 months of age for HBsAg to diagnose infection and antibodies to surface antigen (anti-HBs) to confirm vaccine response. Overall efficacy of this strategy is reported to be greater than 95% (5). There is no evidence that prematurity, premature rupture of membranes, low birth weight, meconium staining or breastfeeding lead to the failure of immune prophylaxis (7). Previously such failure was thought to be largely the result of protocol error; however, it has become clear that failure of immune prophylaxis is related to HBcAg positivity and higher maternal HBV DNA levels (7-9). In one Australian study, transmission despite appropriate prophylaxis was documented only in mothers with high viral load (>10,000,000 IU/mL (>7 log_{10} IU/mL)), at rates approaching 10% (8).

Based on available evidence, HBV transmission usually occurs during the birth process (as opposed to earlier in pregnancy). In support of this hypothesis, there has been some evidence that elective (but not urgent) caesarean delivery may be protective; however, the evidence for this approach is conflicting and the studies that support caesarean delivery are not high quality. Currently no international obstetric guidelines including the World Health Organization recommend caesarean delivery to prevent MTCT. Other strategies are more effective and are discussed below (3-11).

Antiviral therapy to prevent mother-to-child transmission

Antiviral therapy to prevent MTCT of human immunodeficiency virus (HIV) infection is well established and...
Antiviral therapy to prevent postnatal HBV transmission has been shown to be safe and is emerging as an effective strategy to reduce transmission in HBV infection. The recommendations from a number of recent reviews are now incorporated into national and international treatment guidelines. (4, 12, 13-16).

Despite the paucity of randomised trials in this setting, the available data confirm the efficacy of antepartum lamivudine in reducing perinatal transmission, although the effect is modest and variable (17-19). Despite short duration of antiviral exposure in this setting, lamivudine's lack of antiviral potency and selection of HBV mutants resistant to antiviral therapy make it a suboptimal choice (20,21).

Tenofovir disoproxil fumarate (TDF) has superior potency to lamivudine and telbivudine, and no emergence of resistance mutations has been described to date (22). There is clear evidence of the efficacy of TDF in pregnancy to reduce MTCT including a randomised placebo control trial and two observational cohort studies (16,23,24). Thus TDF is the optimal choice, and should be considered from 28-32 weeks gestation in mothers with viral loads above 200,000 IU/mL (5.3 log_{10} IU/mL). Optimal viral thresholds have not been clearly established (many studies report in copies/mL rather than IU) and thus this level remains simply a recommendation at which to consider addition of antiviral therapy (4,5). Therapy should continue for at least 2 weeks postpartum, and possibly up to 12 weeks (the latter may be preferable for reasons related to maternal health, as discussed below).

**Antiviral safety**

The Therapeutic Goods Administration (TGA) pregnancy categories for HBV therapies reflect the limited human safety data but absence of human toxicity; thus, all therapies are classified in category B. The differences lie in evidence of animal toxicity. Interferons (IFNs) are generally contraindicated in pregnancy and cessation should be recommended when a woman becomes pregnant. There are limited data on the safety of entecavir in pregnancy, and its use is therefore not recommended. Seeking specialist advice is recommended. Lamivudine and TDF are categorised by the TGA as B3 and telbivudine as B1, based on animal toxicity data. Toxicity concern with TDF is based largely on animal models where, in the setting of high doses, an effect on fetal growth and development was observed. Human data (albeit mainly in the setting of HIV) are available. TDF has not been shown to be teratogenic; concerns about growth and bone density have not been completely resolved, but findings are reassuring overall (25).

Reassuring human data regarding the safety of both TDF and lamivudine are provided by a prospective registry, largely in the setting of HIV infection. The registry shows no increase in birth defects after exposure to either of these agents (26). However, the registry is limited by the voluntary reporting structure, review but not verification of submitted information, lack of long-term follow-up or information on developmental delay, and low sensitivity (able to detect only a twofold increase in birth defect rates). Nevertheless, results of studies in the setting of HIV that more closely examine the effect of in utero exposure to TDF, with a follow-up of up to 4 years, are reassuring, with only one report of isolated reduced growth parameters at age 1 year (but not 2) in one study (27).

If a woman with HBV infection becomes pregnant while taking antiviral therapy, a re-evaluation of the need for therapy should be undertaken and, depending on the safety profile of the agent and the level of indication based on the severity of her liver disease, continuation, switch or discontinuation can be considered. If discontinuation is decided, then careful monitoring during and after pregnancy should be performed as flares may occur.

**Advice about breastfeeding**

There is no evidence of HBV transmission as a result of breastfeeding. Tenofovir, and not the bioavailable pro-drug, TDF, is present in the breast milk (14,28). In addition, when used in children, TDF has been shown to be safe. Therefore, women should be provided the available information and not discouraged from breastfeeding. Although no definitive recommendation is possible, it is reasonable for a woman to consider breastfeeding after being given the available information (29).
A major consideration in care for a pregnant woman is for the optimal health of the developing fetus; however, the mother’s health is also of prime importance. During the relatively immune-tolerant state of pregnancy, hepatitis B is usually silent (ALT normal, no liver injury evident), but a flare of hepatitis commonly occurs in the postpartum period (in 30–50% of HBeAg-positive mothers with high viral load), with onset at approximately 10 weeks postpartum (30). Postpartum flares have also been observed in HBeAg-negative mothers. Flares are usually asymptomatic and settle spontaneously (30). If a flare is noted, it can be observed for up to 6 months to assess whether it will resolve spontaneously, or require treatment. It does not appear that antiviral therapy in pregnancy will increase the rate or severity of postpartum flares (18,31,32), nor that extending antiviral therapy beyond birth prevents the postpartum flare, although data are limited (30). During the postpartum period, the mother’s liver function should be monitored every 1–2 months. All HBsAg-positive women should be enrolled in ongoing care, and have a plan formed for the management of their HBV. See Clinical assessment of patients with hepatitis B virus infection and Treatment of chronic hepatitis B for more information on this topic.

In summary, the goal in management of HBV during pregnancy is complete prevention of every case of perinatal transmission. In Australia, the optimal regimen for women with viral loads > 1,000,000 IU/mL (6 log_{10} IU/mL) is tenofovir 300 mg daily, commencing at 28–32 weeks gestation, continuing for up to 12 weeks postpartum, with subsequent ongoing monitoring and care of the mother. Detailed discussion by experts with expectant parents is required to explain the risks and benefits of this strategy. Ongoing contribution to the international pregnancy registry of antiviral therapy or participation in observational research or data collection will help to improve the Safety Data Set.

Hepatitis B in children

**Natural history**

Most children who have perinatally acquired HBeAg-positive HBV infection remain in the immune tolerance phase, with high viral loads and little liver damage. Cirrhosis is uncommon (although not unheard of) with 1.7–4.5% of children acquiring the infection at birth having cirrhosis at liver biopsy; only 0.01–0.03% will develop hepatocellular carcinoma (HCC) during childhood (33). In specific populations a slow rate of seroconversion (from HBeAg to antibodies to e antigen [anti-HBe]) during childhood has been shown, with up to 25% in the first decade and up to 65% by the second decade becoming HBeAg negative (34). After seroconversion, most patients will remain in the immune control phase, with normal liver function tests and low viral loads. In childhood, about 10% will develop HBeAg-negative chronic hepatitis with moderate or high viral loads and abnormal alanine aminotransferase (ALT), with a more severe disease progression and higher risk of HCC.

**Clinical manifestations**

Acute HBV infection in children is usually asymptomatic; however, when clinical manifestations do occur, they are generally similar to those in adults. Fulminant disease is uncommon, but in infants it appears to be associated with maternal HBeAg-negative CHB. Most CHB in children is asymptomatic, and is accompanied by normal physical examination and normal growth (35).

**Management**

Children diagnosed with HBV infection should be considered for referral to a paediatric hepatitis specialist. Management of children with CHB involves counselling the patient and family regarding the natural history of the disease, modes of transmission and treatment options. All susceptible household members should be tested for HBV infection, and vaccinated if not immune. The child with HBV infection should also be vaccinated against hepatitis A, if susceptible. Frequency of monitoring is based on low-quality evidence and (largely) on expert opinion. In general, children should be reviewed every 6 months from diagnosis – with clinical examination, liver function tests, and hepatitis B e antigen – and monitored every 6–12 months.
Clinical examination, liver function tests and hepatitis B serology — and monitored every 6–12 months for HCC if there is evidence of cirrhosis (35). Degree of fibrosis may be assessed using FibroScan® in children, and is available in specialist centres, but is not yet validated in HBV. In those with persistently abnormal liver function tests who are being considered for treatment, a liver biopsy may be required.

**Monitoring of children with chronic hepatitis B**

Children with chronic hepatitis B should have all of the following:

- 6-monthly clinical review
- liver function tests
- hepatitis B virus serology (HBeAg and anti-HBe).

HBeAg: hepatitis B e antigen; anti-HBe: hepatitis B e antibody

**Which children should be prioritised for referral?**

Children should be prioritised for referral if they have:

- abnormal liver function tests
- signs of chronic liver disease (e.g. splenomegaly, spider naevi)

**Antiviral therapy**

The selection of patients for antiviral therapy is based on an elevated ALT that is repeatedly more than 1.5 times the upper level of normal, DNA of over 2000 IU/mL and moderate-to-severe inflammation or fibrosis on liver biopsy (5). The treatments studied in children to date include monotherapy with conventional interferon-alfa (IFN-alfa), or nucleoside analogues including lamivudine, adefovir, tenofovir, entecavir or a combination of IFN and a nucleoside analogue (35). The advantages of IFN-alfa are the finite duration of therapy and lack of induction of antiviral resistance. IFN is tolerated better in children than in adults and may also be more effective. Several studies are now available looking at mono and combined therapy in children in the immunoreactive and immunotolerant phases. An international randomised controlled trial in 161 children with immunoreactive HBV comparing PEG IFN to placebo has shown HBeAg seroconversion rate of 26% vs 6% (p < 0.005) and HBsAg loss in 9% vs 0% (p = 0.03) (36). A randomised controlled trial in 180 children with e antigen positive HBV treated with entecavir vs placebo showed that after 48 weeks of therapy, e seroconversion occurred in 24% vs 10% in the placebo group (p=0.02). Treatment was well tolerated, however HBsAg loss was low (1.7%) and the same as the placebo group (36). Preliminary results from a multicentre study using entecavir and pegylated interferon in children in the immunotolerant phase suggests a lack of efficacy (37) Given the rapid changes in this area, treatment of HBV in children should only be undertaken after specialist review.

**Management of adolescents**

At the age of 18, or the end of secondary education, children should be transitioned to adult viral hepatitis care, either in primary care or an adult viral hepatitis clinic that is convenient to their place of study or work. Often the primary care practitioner is best placed to suggest a local specialist for ongoing care. If the patient has advanced disease, then the paediatric gastroenterologist may suggest an adult hepatologist service with expertise in management of HBV-related advanced liver disease.

**Complex situations Co-infection and Immunosuppression**

**References**


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