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 e antibody (anti-HBe) to determine the 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, prenatal care, and newborn and infant care.

- 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 as soon as possible after birth and ideally within 48 hours, followed by a full course of hepatitis B vaccine.

- For HBsAg-positive mothers with high viral loads (>200,000 IU/mL or 5 log10 IU/mL), referral should be made to a specialist to discuss consideration of tenofovir for 2 to 4 weeks gestation, in order to reduce the risk of perinatal transmission.

- There is no evidence of vertical transmission as a result of breastfeeding.

- All children of HBsAg-positive mothers should be tested for HBsAg and anti-HBs at 1-2 months of age (at least 3 months after the last dose of HBV vaccine). Children with hepatitis B surface antigen (HBsAg) should be monitored annually with liver function tests and HBV serology and at age 11 or 12 years.

- HBV-infected adolescents with chronic hepatitis B infection are appropriately transferred from paediatric to adult care.

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General considerations

In some areas of the world, up to 20% of women of childbearing 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 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. Why can have significant health implications for the mother, the baby, and the health of the community, and the issues for each should be considered independently.

Initial assessment of the HBsAg-positive woman should include consideration of the likely duration of infection, any prior or current therapy, liver function tests, HBV status, and HIV status, and assessment for the presence of clinical liver disease. 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 Resources). This is also an opportunity to offer testing to family members, and household and sexual contacts of the patient. Any treatment decisions (e.g., initiating or stopping therapy in the case of an unexpected pregnancy) should take into consideration the toxicity of therapies on the developing fetus (see below).

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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 80% of infants with the infection will develop chronic infection, with the potential for significant adverse health outcomes. In contrast, 60% of older children and 50% 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 antigen (HBsAg) crosses the placenta and has a stimulating effect on the developing fetal immune system (1).

Preventing perinatal transmission

During pregnancy, the mother's viral load should be tested if it is high (<200,000 IU/mL; >5 log10 IU/mL). International and national guidelines recommend that mother-infant antiviral therapy be considered in certain situations (1).

- All babies of HBsAg-positive mothers should:
  1. Be given HBIG and the first dose of HBV vaccine within 12 hours of birth
  2. Have three subsequent doses of HBV vaccine at 1, 2, and 6 months of age
  3. Be tested for HBsAg and anti-HBs after 9-12 months of age and 2-3 months after final dose of HBV vaccine.

Anti-HBs antibodies to surface antigen (anti-HBs) should be measured in all infants born to mothers with high viral load (>200,000 IU/mL; >5 log10 IU/mL), before age 12 months, and at age 6 months.

The cornerstone of prevention of mother-to-child transmission (MTC) of HBV is the combination of hepatitis B immunoglobulin (HBIG) and the first dose of hepatitis B vaccine, which is delivered as soon as possible after birth, ideally within 48 hours, and should be completed within 12 hours, followed by a full course of hepatitis B vaccine (1) (see GESA Consensus Recommendation 24). Children should be checked at least 3 months after completing the primary course (usually 9-12 months of age) for HBsAg diagnosis and antibodies to surface antigen (anti-HBs) to confirm vaccine response (see GESA Consensus Recommendation 24). Testing of infants should be prioritised for those from mothers with high viral load. Overall efficacy of this strategy is reported to be greater than 85% (1).

There is no evidence that previous successful infection or vaccination protects against re-infection (2).

Based on available evidence, HBV transmission occurs during the birth process as opposed to earlier in pregnancy. In support of this hypothesis, there has been some evidence that effective but not urgent cesarean delivery may be protective; however, the evidence for this approach is conflicting and the studies that support cesarean delivery are not high quality. Currently, there is no international obstetric guideline including the World Health Organization recommendation that cesarean delivery prevent MTC. Other strategies may be more effective and are discussed below (6,11).

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Antenatal therapy to prevent mother-to-child transmission

Antenatal therapy to prevent MTCT of human immunodeficiency virus (HIV) infection is well established and is emerging as an effective strategy to reduce transmission in utero. The recommendations from a number of recent reviews are now incorporated into national and international treatment guidelines. [4, 12, 13-16]

There is clear evidence of the efficacy of TDF in pregnancy to reduce MTCT including a randomised placebo-controlled and two observational cohort studies (16,32,34). Treatment should be continued for 28 weeks gestation in mothers with viral loads above 200,000 copies/mL (0.86 log10) at Midwifery Consensus Recommendation 22. The baby should continue for at least 2 weeks postpartum, and possibly up to 12 weeks (there is limited data to determine the optimal time to stop therapy although considerations of postpartum flare have encouraged some clinicians to continue to 12 weeks.)

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Antenatal safety

The Therapeutic Goods Administration (TGA) pregnancy categories for HIV therapies reflect the limited human safety data but absence of human toxicity thus all therapies are classified in category B. Prospective registries have provided significant reassuring data about TDF in pregnancy, such that its use can be recommended with confidence. The registry shows no increase in birth defects after exposure to either of these agents [43]; however, the registry is limited by the voluntary reporting structure, review and not verification of submitted information, lack of long-term follow-up or information on developmental delay, and low sample size. The samples included only a two-fold increase in birth defect rates. Nonetheless, results of studies in the setting of trial that more closely mimic 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 (57).

Interferons (IFN) are generally contraindicated in pregnancy and cessation should be recommended when a woman becomes pregnant. There are limited data on the safety of etravirine in pregnancy, and its use is therefore not recommended. Because this antiretroviral agent is usually well tolerated, it should also be considered in young women who may become pregnant.

If a woman with HIV infection becomes pregnant while taking antiretroviral 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, discontinuation, switch or discontinuation can be considered. If discontinuation is decided, careful monitoring during and after pregnancy should be performed as flares may occur.

Advice about breastfeeding

There is no evidence of HIV transmission as a result of breastfeeding. Tenofovir, and the not bioavailable pro-drug, TDF is present in the breast milk (14-20). 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 (59).

Postpartum period – care of the mother

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 competent 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 HIV/HBV co-infected mothers with high viral loads, with onset at approximately 10 weeks postpartum (60). Postpartum flares should be managed using HBV-therapeutic agents. HBV viremia is generally low but hepatitis B e antigen (HBeAg) positive mothers. Flares usually asymptomatic and most settle spontaneously (61). 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 antiretroviral therapy in pregnancy will increase the rate or severity of postpartum flares (62, 63), nor that extending antiretroviral therapy into the postpartum period prevents the postpartum flare, although data are limited (62). During the postpartum period, the mother’s liver function should be monitored every 1-2 months. All HBV/HIV positive mothers 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 HIV during pregnancy is to complete prevention of every case of perinatal transmission. In Australia, the optimal regimen for women with viral loads 200,000 copies/mL (1.31 log10) is tenofovir 300 mg daily, commencing at 24-26 weeks gestation, continuing for up to 12 weeks postpartum, with subsequent ongoing monitoring and care of the mother.

Detailed discussion by experts and expectant parents is required to explain the risks and benefits of this strategy. Ongoing contribution to the national pregnancy registry and/or postpartum flare will help to improve the Safety Data Set.

Hepatitis B in children

Natural history

Most children who have perinatally acquired HBV infection remain in the HBsAg-positive chronic infection phase (previously referred to as immune tolerance phase) with high viral loads and little liver damage. Cirrhosis is uncommon although not unheard of. In 1.7-4.5% of children acquiring the infection at birth having cirrhosis at liver biopsy; only 0.1-0.6% will develop hepatocellular carcinoma (HCC) during childhood (65). In specific populations, a slow rate of seroconversion from HBsAg 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 HBsAg negative (66). After seroconversion, most patients will remain in the immune competent phase, with normal liver function tests and low viral loads. In childhood, about 10% will develop HBV-negative chronic hepatitis with moderate or high viral loads and abnormal liver 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. Nonspecific disease is uncommon, but in infants it appears to be associated with maternal HBV-negative chronic hepatitis B virus (CHB) in children is asymptomatic, and is accompanied by normal physical examination and normal growth (67).

Management

Children diagnosed with HBV infection should be considered for referral to a pediatric hepatologist. 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 available evidence and largely on expert opinion; in general, children should be reviewed every 6-12 months for diagnosis – with clinical examination, liver function tests and hepatitis B e antigen testing – and monitored every 6-12 months for HCC. If there is evidence of cirrhosis (68), degree of fibrosis may be assessed using FibroScan in children, and is available in specialist centers, 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-month clinical review
- Liver function tests
- Hepatitis B virus serology (HBsAg and anti-HBs)
- HBV DNA level
- HBsAg, anti-HBc and anti-HBe antibody

Which children should be prioritised for referral?
Management of adolescents

At the age of 10, on the end of secondary education, children should be transitioned to adult vsid hepatocare clinic that is convenient to their place of study or work. Often the primary care practitioners 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 with expertise in management of HBV related advanced liver disease.

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References
