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TITLE

Managing hepatitis B virus in pregnancy, prevention, prophylaxis, treatment and follow-up: position paper produced by Australian, United Kingdom and New Zealand Key Opinion Leaders

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LIST OF ABBREVIATIONS

CHB: chronic hepatitis B; HBV: hepatitis B virus; MTCT: mother-to-child transmission; NHMRC: National Health and Medical Research Council; ACIP: US Advisory Committee on Immunisation Practices; HBIG: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen; GP: general practitioner; DNA: deoxyribonucleic acid; HBV: hepatitis B virus; HCV: hepatitis C virus; FDA: US Food and Drug Administration; HIV: human immunodeficiency virus.

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KV and JS conceived the ideas behind the project and writing of the manuscript, KV [and JS](#) are also the lead authors. GD, MG, MLW, NP, SW, SL, SGL, EG, MN, WH, BC, SB, SS and ML was responsible for writing, reviewing and editing of manuscript.

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INTRODUCTION

Chronic hepatitis B (CHB) is a major global health problem affecting more than 400 million people, 75% of whom live in Asia and the Western Pacific (1) and in Sub-Saharan Africa (2). In Australia, an estimated 209,000 people are chronically infected with hepatitis B virus (HBV)(3). The progression of disease may lead to cirrhosis, hepatic decompensation and hepatocellular carcinoma. Mother-to-child transmission (MTCT) is thought to be responsible for the majority of prevalent cases. Because HBV infection in infancy or early childhood often leads to chronic infection, appropriate prophylaxis and management of HBV in pregnancy is crucial to prevent MTCT.

There are many practical and clinical challenges in managing hepatitis B in pregnancy. These include lack of a cohesive strategy for managing and following up mothers and their babies; risk of postpartum HBV flares; lack of randomised trial data on the efficacy and safety of antiviral treatment in pregnancy, lack of head-to-head studies comparing different antivirals in pregnancy, and the epidemiology of infection across different populations globally.

The aim of this document is to provide review of the management of women with HBV infection prior to conception, throughout each stage of pregnancy and postpartum, as well as recommendations for the follow-up of children born to infected mothers, based on available evidence and data in the literature.

METHODS

This review was developed from two meetings (one in 2010 and the other in 2012) and a review of literature up to July 2015, where each author researched a specific question related to the management of HBV in pregnancy. Each topic was discussed, and input was gathered from all authors and other meeting attendees and a position consensus was agreed upon regarding a range of issues and their implications. This paper summarises the information considered, and lists the recommendations from the meetings.

As part of this process authors also performed a literature search around each topic. Authors also sourced data from conference abstracts and bibliographies from selected studies.

Literature search terms included, but were not limited to, hepatitis B virus, women, pregnancy, antivirals, treatment, transmission, safety, efficacy, obstetrics, breast feeding, ethnicity, flares, screening and vaccination. Authors also sourced data from conference abstracts and bibliographies from selected studies.

To aid comparison between studies, HBV DNA levels are expressed in IU/mL. Where studies reported HBV DNA levels in copies/mL, measurements were converted to IU/mL using the conversion factor 5 HBV DNA copies/mL = 1 IU/mL.

HBV IN PREGNANCY: EVIDENCE AND RECOMMENDATIONS

ANTENATAL HBV SCREENING AND THE HBV REFERRAL PATHWAY

Universality vs selectivity: what is the most effective approach to HBV screening and vaccination?

Antenatal HBV screening and infant vaccination programs have evolved from being selective to being universal in response to poor outcomes with the former approach. Experiences and data from the US, the UK and Australia are outlined below.

The US experience

In 1982, the US Advisory Committee on Immunisation Practices (ACIP) recommended screening women in high-risk groups for the hepatitis B surface antigen (HBsAg; a selective screening approach) and administering HBV vaccine and hepatitis B immune globulin (HBIG) to infants of infected mothers (4); however, in 1988, the ACIP acknowledged major problems in implementing these recommendations and recommended universal screening instead (5).

The US Preventive Services Task Force strongly recommended universal antenatal screening at first visit in 2004 (6) and reaffirmed this in 2009 (7).

The US implemented universal infant vaccination for HBV in 1991, in line with World Health Organisation (WHO) recommendations (8). In 2004, more than 92% of children had completed vaccination, and the incidence of acute HBV in children and adolescents fell by 94% compared with the incidence in 1990 (9). In addition, more than 95% of women were screened antenatally (9). In

areas of the US with large migrant populations, the yield of antenatal screening has remained stable or increased since the 1990s (10).

The UK experience

In 1988, the UK Department of Health Joint Committee on Vaccination and Immunisation (JCVI) recommended antenatal screening for high-risk women; however, in 1992, the JCVI acknowledged the failure of this selective strategy for some women and recommended universal antenatal screening instead, which was implemented by April 2000 (11).

There is still no universal infant HBV vaccination program in the UK. A 1993–1995 study showed only 38% of infants born to HBsAg positive mothers were fully immunised (12). A 2000–2007 study reported an antenatal screening uptake of approximately 95% and an increased prevalence of maternal HBsAg from approximately 0.9% in 2000 to 1.2% in 2007 (13); however, a 2006 study showed less than half of infants born to HBsAg positive mothers were fully vaccinated before they turned one year old and less than half of the mothers were referred to a specialist (14).

The Australian experience

The Australian NHMRC recommended selective antenatal screening and vaccination in 1983, but 5 years later it changed its recommendation to universal antenatal screening (15). Compliance appears to be high, with approximately 97% of obstetricians self-reporting they always screen for HBV (16); however, a 2003–2006 study indicated poor subsequent management of mothers found to be HBsAg positive (17). Among 295 HBsAg-positive mothers, 78% had previously documented HBsAg, but none had received education on HBV transmission and 93% had no documentation of referral or follow-up plans (17).

A number of studies have shown that the selective infant vaccination approach was a failure, with modest vaccination rates achieved (57–73%) (18–20). In 1996, the NHMRC recommended universal infant vaccination as the best and most cost-effective protection against HBV.

Universal HBV vaccination has been shown to be cost-effective in areas of high, intermediate and low prevalence (21, 22). Recent evidence suggests that newer vaccines may have better efficacy in this setting (23).

In Summary: There are no alternatives that are more effective or ethical than universal antenatal screening at first visit and universal infant vaccination with birth dose. In accordance with the National Hepatitis B Strategy 2010–2013, any woman diagnosed with chronic HBV antenatally should be referred to a clinician with expertise in managing viral hepatitis during pregnancy.

The ideal referral pathway if antenatal screening for HBV identifies an infected woman?

Midwives, obstetricians, general practitioners (GPs) and specialist physicians play an important role in the care pathway of pregnant women with HBV infection. It is important to consider these different roles at the antenatal, peripartum and postpartum stages.

Antenatal

The current referral pathway at the antenatal stage involves HBsAg-positive pregnant women being identified through universal screening and then referred to a viral hepatitis clinic or community-based HBV surveillance program. These women are triaged and evaluated in terms of infectivity risk, need for intervention, and frequency and type of monitoring. A variation of this model in New Zealand tests all HBsAg-positive women and arranges therapy if indicated. Only those who require therapy are seen in a tertiary referral clinic.

The main issues at this stage include possible lack of contact with these women until the postpartum stage, loss to follow-up of women with low replication levels, and incomplete vaccination of infants. Dealing with minority groups who do not have English as their first language may make complex discussions around HBV education and treatment even more difficult.

Assessment of patients should include staging of disease and serological assessment as well as risk of infectivity (hepatitis B e antigen [HBeAg] and HBV DNA status and history of prior maternal infant transmission). Although non-invasive measures of fibrosis such as FibroScan[®] and FibroTest have now largely supplanted liver biopsy for the assessment of fibrosis, at present, there is no evidence of the accuracy, validity or safety of these technologies in pregnancy. FibroScan[®] is currently not approved for use in pregnancy. Antenatal evaluation requires assessment and education by a clinician with experience and knowledge of this specialised area, such as a midwife, physician or

obstetrician, to fully evaluate the risk to mother and infant. The responsibility for testing during pregnancy may fall on the lead maternity carer, specialist physicians, hepatitis nurses or, in some countries, GPs.

Education around hepatitis B at the antenatal stage should include disease staging and natural history, interpretation of serological markers, residual risk of transmission (as outlined in Table 1), indications for treatment or prophylaxis, and management during pregnancy. This may be the responsibility of the lead maternity carer, a specialist physician, a nurse or a community-based HBV surveillance program such as the Hepatitis Foundation of New Zealand.

Peripartum

An appropriate follow-up schedule for treatment of mothers and vaccination of infants should be put in place; however, carrying out the infant vaccination course may be beyond the remit of specialist physicians. Establishing community clinics may be one way to provide continuing care because attendance at clinics to complete immunisation courses can be impractical.

Postpartum

At this stage, the main questions revolve around care of the mother: when treatment should be continued and what should be done for mothers already on treatment, for example in the context of flare risk. It is often not clear if ultimate responsibility for care of mothers lies with viral hepatitis clinics, specialist postnatal clinics or GPs. A decision needs to be made (likely by specialists) on continuing antiviral therapy following delivery and who will monitor mothers in the postpartum period given the risk of flares

Specialised, dedicated clinics are needed to ensure proper follow-up of mothers and infants postpartum to ensure they receive appropriate treatment. There is an opportunity for shared care with GPs in terms of managing the ongoing treatment of mothers, although this is not in place in most countries. There is a danger however, that cross-referral between healthcare providers may result in lack of a cohesive strategy for appropriate patient care postpartum.

In Summary: There is currently a lack of cohesive strategy and continuing care following screening, which presents challenges for managing the ongoing treatment of mothers as well as follow-up of infant vaccinations. Establishing shared care between tertiary centres and GPs, with clear responsibilities for each healthcare professional (specialists, GPs, nurses and midwives), is recommended to ensure proper care and follow-up.

HBV-TREATMENT CONSIDERATIONS IN WOMEN OF CHILDBEARING AGE

What is the ideal HBV treatment for women of childbearing age who need treatment for liver disease?

Pregnancy in women infected with HBV presents unique management questions. Aspects of care that need to be considered include effects of HBV on pregnancy, effects of pregnancy itself on the course of HBV infection, treatment of HBV during pregnancy and prevention of MTCT (24).

Effects of HBV on pregnancy

A large population-based study of pregnancy outcomes in pregnant women infected with HBV or hepatitis C virus (HCV) compared with all other pregnant women reported that HBV- or HCV-positivity was a risk factor (univariate analysis) for adverse perinatal outcomes including preterm delivery (<37 weeks gestation; 11.5 vs 7.9%, $p < 0.001$), premature rupture of membranes (8.9% vs 6.9%, $p = 0.026$), placental abruption (1.5 vs 0.7%, $p = 0.018$), labour induction (33.9 vs 28.1%, $p < 0.001$), Caesarean delivery (19.0 vs 13.2%, $p < 0.001$), perinatal mortality (2.3 vs 1.3%, $p = 0.016$), congenital malformations (7.2 vs 5.1%, $p = 0.01$) and low birth weight (<2.5kg; 10.4 vs 7.8%, $p = 0.009$) (27). In multivariate analysis, after adjustment for possible confounding factors, HBV- or HCV-positivity remained associated with perinatal mortality (OR 1.8; 95% CI: 1.1–2.9), low birth weight (OR 1.4; 95% CI: 1.1–1.7), congenital malformations (OR 1.4; 95% CI: 1.1–1.9) and preterm delivery (OR 1.4; 95% CI: 1.2–1.8) (25). Similarly, a case-control study of pregnant women infected with HBV reported that HBV infection was a risk factor (univariate analysis) for threatened preterm labour at <37 weeks (11.9 vs 6.3%, $p = 0.030$), preterm birth at <34 weeks (4.7 vs 1.2%, $p = 0.033$), gestational diabetes mellitus (19.0 vs 11.1%, $p = 0.012$) and antepartum

haemorrhage (11.5 vs 5.5%, $p=0.026$) (26). These findings are mainly from univariate analyses and need to be taken with caution; however, they suggest that careful surveillance of pregnant females and their babies infected with HBV or HCV may be warranted.

Effects of pregnancy on HBV of women of childbearing age

In most HBV-infected women, there is no worsening of liver disease during pregnancy and liver enzymes frequently normalise (24). There are, however, case reports of hepatic exacerbations/fulminant hepatic failure in HBV-positive pregnant women (27, 28). In addition, a proportion of women (approximately one-third) may experience hepatic flares postpartum(29-31). Cirrhosis is uncommon in young childbearing women.

Women of childbearing age are generally in the immune-tolerant phase, but patients in the immune-clearance phase (with risk of damage to the liver) are being increasingly seen, as women delay starting a family and enter pregnancy at older ages. The three main patient scenarios facing clinicians are: women of childbearing age not on antiviral therapy, women on antiviral therapy considering pregnancy, and women on antiviral therapy who become pregnant.

Current guidelines are similar in their recommendations of who to treat and what to treat with. The main goal of treatment is to reduce the risk of disease progression (1, 32), with agents used in pregnancy needing to be potent, well tolerated, preferably of a finite duration, safe in pregnancy, durable and accessible.

In women of childbearing age, the relevant advantages and disadvantages of commencing treatment should be carefully considered and discussed with the patient and their partners in terms of family planning. It may be prudent to delay treatment if the patient is planning a pregnancy soon, but this would need to be assessed against the severity of their disease.

In Summary: CHB therapy in pregnancy should balance considerations of the health of the mother with the safety of the fetus given that there is relatively limited experience with CHB drugs in the pregnancy setting. Treatment of mild disease should generally be deferred until after pregnancy. If pregnancy is being contemplated in the near future, it may be more prudent to delay therapy if possible. Because peginterferon is the only finite-duration treatment with a chance of off-therapy sustained virological response, it should be considered as a first-line treatment in patients with

favourable baseline characteristics. Note that patients will require contraception during treatment. If non-pregnant patients have favourable baseline characteristics and no contraindications, peginterferon should be considered; however, if a nucleos(t)ide analogue is required, entecavir and tenofovir are the most potent and should be recommended, with tenofovir preferred due to the amount of safety data available.

How safe are HBV antiviral drugs in pregnancy? Should therapy be switched in patients who become pregnant while on potentially inappropriate therapy?

Data on the safety of HBV antivirals in pregnancy are largely derived from the HIV-positive population where antiviral therapies are used in combination. A study comparing the growth of infants born to HIV-positive mothers who were treated with tenofovir during pregnancy with those whose mothers were not treated with tenofovir found no difference in infant growth between the two groups (33). Growth was measured through weight and height at birth and after 12 months (33). Exposure to tenofovir was *in utero* only, i.e. mothers were not allowed to breastfeed (33). Another study of infants born to HIV-positive mothers reported a similar rate of congenital abnormalities in infants whose mothers were treated with tenofovir during pregnancy to those born to women who were not treated with tenofovir (34).

Currently, among approved antivirals for CHB, only lamivudine and tenofovir have sufficient data in the Antiretroviral Registry database for review. Both drugs show no increased risk of birth defects compared with population-based controls (35). LMV does however have a low barrier to resistance (36).

Peginterferon use in pregnancy is not recommended because its safety in pregnancy is not established and it is known to have antiproliferative properties (37, 38). Telbivudine and tenofovir are US FDA pregnancy category B drugs, while entecavir, lamivudine and adefovir are category C drugs (Table 2) (37). Lamivudine reaches higher concentrations in amniotic fluid than in serum, and both lamivudine and tenofovir have been found to be excreted in breast milk (39).

The European Association for the Study of the Liver (EASL) guidelines recommend that family planning and risks associated with HBV treatment should be discussed with women of childbearing age prior to starting therapy. Interferon, entecavir and adefovir should be discontinued in women who become pregnant, and they should be switched to a category B nucleotide analogue, with tenofovir as the preferred agent (32).

There is no information on the management of resistance during pregnancy; it should be possible to switch to tenofovir monotherapy if the patient is resistant to all other agents.

In Summary: Re-evaluation of the appropriateness of therapy is necessary if a woman becomes pregnant while on treatment for CHB. If a woman is on a regimen that is deemed to have an inadequate safety profile, options include switching to an alternative, safer agent or occasionally discontinuation of therapy in those with mild liver disease. Pregnant women should be monitored for flares if therapy is stopped during pregnancy and/or after delivery. Tenofovir is a preferred antiviral in this setting due to available safety data and a high barrier to resistance. In the setting of antiviral resistance, the most appropriate agent(s) to use will depend on the particular resistance mutations detected and the efficacy of available HBV antiviral agents against these drug-resistant mutants.

What is the optimum mode of delivery in a HBSAg+ve mother?

When vertical transmission of HBV occurs, 95% of infected infants become chronically infected (40). In contrast, when horizontal HBV transmission occurs — through child-to-child contact, contaminated needles, sexual contact or transfusion — the rate of chronicity is dependent on age, with the risk of HBV becoming a chronic infection decreasing with increasing age (22, 40).

The mode of delivery and associated risks should be assessed by an obstetrician. An initial study reported risk for MTCT in infants who received HBV vaccine plus HBIG at birth was less than 6% in Caesarean section deliveries compared with 19.9% in vaginal deliveries ($p < 0.03$) (41). Similarly, a retrospective analysis of infants who received HBV vaccine and HBIG at birth and were born to HBsAg-positive mothers demonstrated that elective (but not urgent) Caesarean section was associated with a reduced rate of MTCT when compared with vaginal delivery (1.4% vs 3.4%,

respectively; $p < 0.032$) (42). No transmission was seen when viral load in mothers was $< 2 \times 10^5$ IU/mL (42). Other recent studies, however, do not support reduced risk for MTCT with Caesarean section deliveries. For example, Wang *et al* found delivery mode had no significant effects on the interruption of MTCT by immunoprophylaxis (43).

Among Maori and Pacific Islanders in New Zealand, the mode of HBV transmission tends to be early horizontal rather than vertical; neonatal vaccination may abolish this type of transmission (44, 45). Conversely, in Asian patients with HBV, more than 90% of HBV transmission is vertical and occurs at delivery (preventable by vaccination) or intrauterine (potentially preventable by antiviral therapy). (Upton A, personal communication) In Pacific Islander and Maori populations, more than 50% of HBV transmission is early horizontal and occurs before 10 years of age in areas where universal vaccination has not been implemented. (Upton A, personal communication).

Summary: At present there is no evidence to modify mode of delivery for MTCT reasons if HBIG vaccination is used

Are invasive obstetric procedures during pregnancy safe in HBV-infected women in terms of risk for MTCT of HBV?

Given the serious long-term consequences of congenital HBV infection, the future of children born to mothers infected with HBV relies on appropriate management and minimisation of risk for perinatal transmission by GPs, midwives, specialists and obstetricians.

Invasive procedures during pregnancy such as amniocentesis, chorionic villus sampling (which involves repeated needle passes), fetal blood sampling (which may be into the cord or directly into the intrahepatic portion of the fetal umbilical vein) and minimally-invasive or open fetal surgery may be important contributors to post-exposure prophylaxis failure. While the data regarding transmission risks associated with amniocentesis are minimal, the limited data available suggest that transmission rates are higher in the setting of HBeAg positivity and high viral load, or when transplacental amniocentesis is performed (46, 47). In a recent report, amniocentesis was shown to greatly increase the risk of vertical transmission in women with viral loads $\geq 2 \times 10^6$ IU/ml (50% vs

4.5% in women with viral loads $\geq 2 \times 10^6$ IU/ml and controls who did not undergo amniocentesis, respectively, $p=0.006$) although there appeared to be no increased risk from amniocentesis when the maternal HBV DNA level was below this level (46). It is concerning that a recent Australian survey has reported that 60% of specialists do not routinely check blood borne virus status (including Hepatitis B) prior to performing invasive procedures, and that most respondents stated they were either unsure of the risk of MTCT of HBV with invasive procedures (22%), or felt the risk was unknown (30%)(48).

In mothers who require prenatal diagnostic procedures, it is important to consider non-invasive alternatives, particularly for those women with a high viral load who are presumed to be at greatest risk of iatrogenic infection. The advent of non-invasive prenatal testing for fetal aneuploidy has revolutionised prenatal testing, allowing highly sensitive and specific testing for common fetal aneuploidies, such as Trisomy 21, to be performed with a maternal blood test. HBsAg-positive women with a high-risk test result for aneuploidy using conventional screening modalities should be offered non-invasive prenatal testing as an advanced screening test to minimise the risk of requiring an invasive procedure and potential iatrogenic perinatal transmission of HBV. Among women who require or request invasive testing, amniocentesis is preferable to chorionic villus sampling, and where possible transplacental amniocentesis should be avoided. The risks and benefits of any invasive procedure should be discussed with the patient and informed consent documented.

A number of obstetric guidelines address management of pregnant patients with hepatitis B infection. For example, the Society of Obstetricians and Gynaecologists of Canada guidelines state that while the risk of fetal hepatitis B infection through amniocentesis is low, 'every effort should be made to avoid inserting the needle through the placenta' (49). These recommendations are similar to those found in the guidelines of Royal Australian and New Zealand College of Obstetricians and Gynaecologists; their updated guidelines also reinforce the importance of identifying women with a high viral load, and the value of non invasive prenatal testing to reduce the need for invasive procedures in high risk women. (50).

Compliance with current recommendations, however, is poor as shown by an audit of births at three hospitals in Victoria between July 2006 and June 2011 (51). Among 398 pregnancies in 344 HBsAg-positive women, the rate of assessment of viral replicative status — through HBeAg testing or viral

load — was low (51). In addition, there was no evidence that the number of invasive prenatal diagnostic procedures was decreased in this population; 24 invasive procedures were performed, 6 of which were chorionic villus sampling and 18 were amniocentesis (51). Assessment of HBeAg or viral load was performed in only 3 of 24 invasive procedures. In none of these cases was there evidence — in terms of patient consent regarding transmission or documentation of risk — that the person performing the procedure was aware of the patient's HBV status (51). These audit results suggest a poor uptake of current recommendations regarding risk stratification (through assessment of viral replicative status) and risk minimisation (through reduction of antenatal invasive procedures).

In Summary: Data are limited, but there is some evidence of an increased risk of transmission from mothers with a high viral load during procedures such as amniocentesis. Because data to base recommendations on are either low quality or non-existent, no specific recommendations can be made. This indicates the need for more high-quality data; however, uptake of current recommendations should be improved regarding risk stratification of each procedure and risk minimisation, including using non-invasive prenatal testing where possible to minimise the need for invasive testing. In addition, assessment of viral replicative status and HBeAg status should be improved. Barriers to care delivery exist in migrant groups and are increased when patients do not speak English.

How effective are antiviral agents in preventing mother to child transmission of HBV?

There are few clinical trials (only some of which were randomised) of antivirals for MTCT prevention (36, 52-56). Among antivirals for HBV, lamivudine has the most data in pregnancy. A meta-analysis of 10 randomised clinical trials of 951 mothers who were carriers for HBV where both groups received HBIG and vaccine, showed an overall lower rate of perinatal transmission (1.4-2.0%) at 9–12 months in women treated with lamivudine than in untreated women (53). Another, more recent, meta-analysis of lamivudine for interruption of MTCT found that lamivudine reduces MTCT in addition to HBIG (52). Lamivudine was not effective if HBV DNA was $>2 \times 10^7$ IU/mL before

treatment or $>2 \times 10^5$ IU/mL after treatment (52). One study reported that lamivudine was not effective if initiated at 32 weeks gestation (52). There was no difference in side effects between mothers who received lamivudine and those who did not (52).

Lamivudine is an antiviral with relatively low potency and a low barrier to resistance. When used in mothers with high viral load to prevent MTCT, lamivudine is associated with the selection of resistant mutants, which may compromise future therapies for the mother (36) These data suggest lamivudine is not an optimal choice for prevention of MTCT.

Studies have shown that telbivudine provides a marked reduction in viral load in pregnant women, although these studies are limited by being open label and therefore susceptible to bias and this means that some of the results may be difficult to interpret (54). In a non-randomised study by Han *et al*, MTCT rate was 0% in patients treated with telbivudine compared with 8% in the untreated group ($p=0.002$) (67). In a retrospective, non-randomised study of HBeAg-positive pregnant women with HBV DNA $\geq 2 \times 10^6$ IU/mL who received telbivudine, lamivudine or no treatment, there were no cases of MTCT in the treated groups (57). Similarly, a recent open-label study of 88 women given telbivudine in the second or third trimester or no treatment found that, at postpartum week 28, there was no MTCT in the telbivudine group vs 8.6% in the control group ($p=0.029$) (55). There was no difference in side effects between the two groups (55). Like lamivudine, telbivudine has a low barrier to resistance and, therefore, is not a first-line choice for HBV antiviral therapy in general (58). In the setting of pregnancy, telbivudine therapy has also been shown to select resistant mutants (54).

In a recent non-randomised study of pregnant women with CHB, tenofovir given in the last trimester of pregnancy substantially reduced MTCT of HBV, and was safe and well tolerated by both mother and infant (56). No randomised clinical trial of tenofovir in preventing MTCT of HBV has been conducted. Tenofovir may be the treatment of choice for the prevention of MTCT because it is an FDA (56, 59) category B drug and has good efficacy and a good resistance profile. It has also extensive experience in HIV settings and therefore a track record of safety in the pregnancy registry. Emerging data and recent data from China and Turkey suggest tenofovir is safe and effective in this setting(56, 60, 61).In fact a recent prospective trial from Taiwan involving 118

HBeAg positive women demonstrated that the tenofovir exposed infants vs unexposed had much lower HBsAg positivity at 6 months (1.54% vs 10.71%). Treated mothers in this study received drug from 30-32 weeks to 1 month post partum. (62)

In terms of a target viral load threshold, initial studies have suggested 2×10^7 IU/mL, although transmission of HBV at viral loads above 2×10^5 IU/mL has been observed (63). Others have suggested lower thresholds for transmission (64). The significance of these studies is uncertain and there is a need for stronger evidence to decide whether the threshold for intervention should be reviewed.

Immunoprophylaxis failure is associated with a viral load of $>2 \times 10^7$ IU/mL (52); however, the target viral load to completely prevent or reduce transmission is unknown. Perinatal transmission can still occur despite suppression of viral load to undetectable levels (65). For example, there may be viral translocation through the placenta to the fetus; in one study, 3.7% of babies born to HBsAg-positive mothers were found to be HBsAg positive at birth as a result of *in utero* infection (66). Furthermore, the presence of HBV has been observed in oocytes and embryos, regardless of which parent was infected (67). A new potential treatment that may be effective in preventing transmission of MTCT of HBV may be the HBV entry inhibitor Myrcludex B, which has the potential to be used in resource poor settings where there is difficulty getting access to IVIG, though this is still under investigation(68).

In Summary: There is a role for antiviral therapy in reducing MTCT of HBV, although there is limited evidence for current management strategies including viral kinetics of tenofovir. The risks and benefits of therapy should be discussed with patients, and treatment decisions should be made according to individual patient needs. In jurisdictions where tenofovir is not available telbivudine or lamivudine are reasonable alternatives.

When is it appropriate to start and stop HBV antiviral therapy in a woman who is being treated solely to prevent viral transmission?

It is important to recognise that pregnant women infected with HBV are usually in the immune tolerant phase and are HBeAg positive and tend to have high viral loads (29, 31, 69). The benefits of starting antiviral prophylaxis early include providing sufficient time for reducing HBV viral load to a level that prevents MTCT of HBV, particularly in cases of premature delivery. It is also important to remember that 12% of deliveries occur before 37 weeks gestation (70). The benefits of initiating therapy later, however, include reducing the infant's exposure to the antiviral drug and the attendant potential risk of toxicity, as well as minimising the mother's exposure to antiviral drug, which may also reduce the risk of resistance.

A number of studies have looked at commencing lamivudine at the following time points during pregnancy and these are summarised in Table 3:

Data on telbivudine have been published, with women treated from gestation weeks 20–32 showing a significantly lower rate of MTCT of HBV than controls (54).

In terms of when to stop treatment, discontinuing early may minimise infant exposure to antiviral drugs and their potential postpartum effects, and potentially allow breastfeeding. Stopping later may provide sufficient time for immunological changes of pregnancy to resolve, deferring or preventing hepatic flares in the early postpartum period (although this timeframe is not well defined).

Hepatic flares postpartum have been observed in several studies and may be associated with the use of antiviral therapy, and therefore prolonging antiviral therapy may alleviate this. A recent study of antivirals for the prevention of MTCT of HBV demonstrated that ending antiviral treatment at 12 weeks postpartum did not reduce the frequency or severity of hepatic flares compared with ending antiviral treatment at 4 weeks postpartum (31).

Summary: Available data suggest that starting HBV treatment in the third trimester (around 28–32 weeks gestation) may be sufficient to prevent MTCT of HBV. Although, given that 20% still have a viral load above 10^7 IU/mL at delivery and that premature delivery may occur, 28 weeks gestation may be more appropriate. Until more data become available and the time of immune resolution postpartum is defined, it is recommended to stop treatment at around 12 weeks postpartum and monitor carefully for flares after this period. There is an urgent need for more data to answer key

questions, when treatment should be stopped in relation to risk of hepatic flare and whether it can be stopped early to allow for breastfeeding.

POSTPARTUM CONSIDERATIONS IN HBV-INFECTED WOMEN

How significant are postpartum hepatic flares and how do we manage them?

Pregnancy has often been characterised as a state of relative immunosuppression that normalises during the peripartum and postpartum stages (92). Immunosuppression occurs to ensure the mother's immune system does not recognise the fetus as foreign (92). Although the timing and duration of immune suppression during pregnancy is not well defined, the cell-mediated immune response responsible for recognising foreign particles in the body through the use of T-helper cell 1 is suppressed, and the antibody-mediated humoral immune response takes over (92). Many autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, have demonstrated a period of remission during pregnancy, but they tend to flare up again during the postpartum period (71).

Approximately one-third of pregnant women infected with HBV demonstrate increased liver inflammation in the postpartum period, and flares may occur regardless of HBeAg status although they are more common in HBeAg+ve women(29, 30). Women treated with antivirals in the third trimester may be at an increased risk for hepatic flares postpartum after ceasing treatment; rates of approximately 50–60% have been reported (29, 31). Flares associated with rebound of the immune system postpartum are likely to contribute to HBV disease progression (29, 30, 72).

Hepatic flares are immune-mediated and may be beneficial, but little is known about their underlying mechanisms. Non-pregnant patients have been shown to clear HBeAg after a flare(30, 31, 73). In pregnant women some studies have been associated with HBeAg(31) clearance while others have not (30). Although the majority of hepatic flares are mild and asymptomatic, damage to the liver during flares may have an impact on disease progression, and may cause increased fibrosis and eventually cirrhosis. Flares may occasionally be severe and be fatal.

An observational study examining immune markers associated with hepatic flares showed that patients who experienced flares were similar in most respects to those who did not in terms of baseline characteristics. However, patients who experienced flares were more likely to be HBeAg positive (30). Expression of TLR2 by both monocytes and NK cells was upregulated around 10 weeks prepartum in patients who had a hepatic flare. This was accompanied by a sequential increase in viral load at partum and an increase in alanine aminotransferase at 15–18 weeks postpartum, suggesting flares may be important in disease reactivation (although increases in viral load did not occur in all patients)(30). Furthermore, conditioned peripheral blood mononuclear cells from flare patients were found to induce apoptosis of HepG2 cells via caspase activation, suggesting a tendency of these patients to an increase in necroinflammatory activity (30).

It is important to note that the majority of flares in these women settled spontaneously without the reintroduction of antiviral therapy. However, the amount of liver damage that occurs during postpartum flares has not been adequately quantified. Even though most flares normalise without treatment, it is probably reasonable to measure at least one post partum liver function test, at least in mothers with high viral loads.

In Summary: There is currently no consensus on how to manage hepatic flares; however, it is recommended to follow the approach set out in the EASL guidelines, which recommend close monitoring of both treated and untreated women after delivery because of the risk of hepatic flares. Further research is needed to identify predictive markers associated with hepatic flares, such as TLR2 expression, to help predict their occurrence as well as determine the risk period

Can a woman on HBV antiviral therapy safely breastfeed?

The Antiretroviral Registry database does not have any data on postpartum outcomes or breastfeeding. Available evidence on the safety of breastfeeding while receiving antiviral therapy for HBV are predominantly derived from studies of breastfeeding mothers with HIV undergoing antiviral therapy.

Current recommendations advise against breastfeeding for women co-infected with HIV and HBV to avoid vertical transmission of HIV to infants (74). In HBV mono-infection, the risk of HBV transmission from breastfeeding is negligible if infants are given HBIG or HBV vaccine at birth (43). Therefore, the only consideration on breastfeeding would be for mothers receiving antiviral therapy, due to potential exposure of the infant to drug and to any associated toxicities.

Lamivudine and breastfeeding

One study of 20 women with HIV treated with lamivudine 300–600 mg/day showed that the mean concentration of lamivudine in breast milk was only 0.183 µg/kg/day, which is much lower than the usual clinical dose of 4–8 mg/kg/day for an HIV-positive infant treated with lamivudine (75). However, another study of 18 women with HIV treated with lamivudine 300 mg/day showed only a small difference in the mean concentration of lamivudine in maternal serum (0.7 µg/mL) and breast milk (1.8 µg/mL), but a very low mean serum concentration in infants (0.03 µg/mL), indicating a very low absorption of lamivudine from the gastrointestinal tract of infants (76).

Tenofovir and breastfeeding

Tenofovir disoproxil fumarate (TDF) is a prodrug that is converted in tissues into tenofovir as the active moiety. Tenofovir has a very low oral bioavailability due to its anionic hydrophilic state (serum C_{max} is reached at 1–2 hours); however in *in vitro* studies, the intracellular half-life was 50 hours (59). To improve bioavailability, tenofovir is administered as the prodrug TDF, which is converted in tissues into tenofovir as the active moiety (59). Transmission of active drug from maternal circulation across the placenta into fetal circulation is minimal (77). In the lactating mother who is receiving TDF, the low amounts of active drug found in breast milk are not absorbed through the baby's GI tract. Hence, treatment of the mother with TDF results in minimal exposure of the fetus and the breast fed infant to active tenofovir (78, 79).

In a phase I trial of tenofovir administered to HIV-infected pregnant women in Malawi and Brazil at the onset of labour, or 4 hours prior to Caesarean section, tenofovir was detectable in 4/25 (16%) breast milk samples collected during the week following birth, with a median (range) concentration

of 13 (6–18) ng/mL (77). The median concentration of tenofovir measured in breast milk was approximately 3% of the median maximum concentration measured in serum samples(77, 80) (99).

A small pharmacokinetic study of HIV-positive mothers who received tenofovir at delivery postpartum found the median infant dose of tenofovir through breastfeeding was 4.2 µg/day, which is less than 0.03% of the proposed infant oral dose (80).

In a study of infants born to HIV-infected mothers who were treated with tenofovir during pregnancy, no significant differences in survival outcomes were observed between breastfed infants vs those who were never breastfed, at year 3 of follow-up; furthermore, there were few cases of transient decreases in phosphate or creatinine clearance (34). There was also no evidence of an effect of tenofovir exposure on infant growth at year 2 of follow-up (34). Longer term studies of the effects of tenofovir on the fetus is unclear. In a prospective study of 449 infants where the mother received tenofovir in a HIV setting, there was slightly lower values for length and head circumference at 1 year and a significantly decrease bone mineral content but the significance of this finding is unclear(81, 82).

A new oral prodrug of tenofovir, tenofovir alafenamide fumarate (TAF), is in development. TAF is a next generation oral prodrug of tenofovir that, compared to TDF, delivers targeted increased intracellular levels of tenofovir, allowing for a reduction in circulating tenofovir exposure (83, 84). It is expected that the improved safety profile of long-term TAF administration will lead to replacement of standard tenofovir with TAF within the next 5 years. The enhanced safety profile of TAF would make this the ideal antiviral to use in pregnant women and breastfeeding mothers.

Summary: While the current recommendation is that women co-infected with HIV and HBV should not breastfeed their infants to avoid vertical transmission of HIV and HBV the risk of HBV transmission with breastfeeding in mothers with HBV monoinfection will be negligible if infants receive HBIG/HBV vaccine at birth. Therefore, it is recommended that breastfeeding is only contraindicated in mothers with HBV monoinfection when the mother receives an antiviral therapy that is associated with significant exposure and toxicity in infants. An important question is whether mothers receiving tenofovir should be advised to continue breastfeeding. Based on available data,

(mainly in HIV infected patients) the pharmacology of tenofovir suggests that breastfeeding should not be contraindicated in women receiving tenofovir for prophylaxis or treatment.

How do we follow up children of HBV-infected mothers?

Key areas where current recommendations are lacking include how to follow up non-immunised infants (for example, if the mother had not been screened) and, in the case of immunised infants, how and when HBV vaccine responses should be assessed and how infants are followed up.

Most cases of vertical transmission can be prevented if infants are given appropriate prophylaxis, i.e. HBIG and HBV vaccine. It is very important to confirm that infants have responded to HBV vaccination. Risk for MTCT of HBV in HBeAg-positive, HBV-infected mothers may be reduced from 70–90% to 5–15% if infants are properly vaccinated; risk for transmission of HBV is even lower in the case of HBeAg-negative infections (Table 4) (9, 63).

Risk factors for immunoprophylaxis failure include high maternal HBV viral load, HBeAg positivity, incomplete HBV vaccination, and a small risk of vaccine-escape mutants in the 'a' determinant region (63). The American Association for the Study of Liver Diseases recommends that all children born to HBsAg-positive mothers should be tested at ages 9–15 months for seroconversion (85). Similarly, Australian national guidelines recommend testing anti-HBs antibody and HBsAg levels in infants born to HBsAg-positive mothers 3–12 months after completion of the primary HBV vaccine course. However, testing should not be performed before 9 months of age to avoid detection of passively transmitted anti-HBs antibodies from HBIG given at birth (86).

There are no robust natural history data available in children; therefore adult outcome studies are generally used. Children with HBV infection tend to appear healthy throughout childhood and are unlikely to present before adulthood due to events such as pregnancy or liver cirrhosis (87–89).

An Italian study that followed a large cohort of children with chronic HBV infection, mainly acquired horizontally, found that while the overall prognosis was favourable, 2% developed hepatocellular carcinoma and 6% had HBeAg-negative hepatitis over a period of about 20 years (87).

Summary/draft consensus statement: Most perinatally-acquired HBV can be prevented by appropriate prophylaxis. The current recommendation is for administration of HBIG and HBV vaccine to newborns to prevent MTCT of HBV. It is vital to confirm that vaccinated infants have responded to HBV vaccine, and for non-responders and non-vaccinated infants, follow-up by a paediatric gastroenterologist is required. There is currently no data to support cost-effectiveness, frequency or type of investigation or treatment.

SUMMARY

Summary/draft consensus statements developed by this group are briefly summarised below:

1. Universal antenatal screening for HBV and infant HBV vaccination is recommended over selective approaches. Screening should ideally occur in the first trimester. Any woman diagnosed antenatally with chronic HBV should be referred to a clinician with expertise in managing viral hepatitis during pregnancy.
2. Establishing shared care between tertiary centres and GPs may overcome the current lack of strategy for the continuing care of HBV-infected mothers, as well as follow up HBV vaccinated infants.
3. Family planning should be discussed with HBV-infected women of childbearing age and, if pregnancy is planned in the near future, it may be prudent to delay therapy until after delivery. If non-pregnant HBV-infected women have favourable baseline characteristics and no contraindications, peginterferon should be recommended; however, if a nucleotide analogue is required, tenofovir is preferred due to the amount of data available.
4. Evaluation of existing HBV therapy is necessary if a woman becomes pregnant while receiving HBV treatment.
5. The uptake of current recommendations on HBV transmission risk stratification through assessment of viral replicative status, and risk minimisation through reduction of antenatal invasive procedures, should be improved. **More data are needed** on HBV transmission risks associated with antenatal procedures. There is no need to modify delivery mode in HBV positive mothers if HBIG is used and Caesarean section should be reserved for usual obstetric indications.

6. There is a **need for more data** on antiviral resistance and viral kinetics to support recommendations on which antiviral agents to use during pregnancy. While available data suggest tenofovir is superior to lamivudine or telbivudine (no head-to-head, randomised trial data exist), there is a need for a long-term registry to follow up babies whose mothers received tenofovir during pregnancy to evaluate the safety of tenofovir in this setting. *In jurisdictions where tenofovir is not available telbivudine or lamivudine are reasonable alternatives.*

7. **More data are needed** on strategies that use antiviral therapy to prevent MTCT, especially in women with high HBV viral loads. Until more evidence becomes available, the consensus is starting treatment at 28–32 weeks gestation in women with viral loads $>10^7$ IU/ml, and stopping treatment at delivery, or up to 12 weeks postpartum, followed by careful monitoring for hepatic flares.

8. Pregnant women should be monitored closely for hepatic flares if HBV therapy is stopped during pregnancy and/or after delivery, although the majority of flares will settle without the reintroduction of antiviral therapy.

9. The risk of HBV transmission with breastfeeding in infants who receive HBIG and HBV vaccine is negligible. Breastfeeding is not contraindicated in women with HBV monoinfection receiving tenofovir.

10. It is essential to confirm that HBV-vaccinated infants of mothers who are carriers of HBV respond to the vaccine and, in the case of non-responders and non-vaccinated infants, follow-up by a paediatric gastroenterologist is required.

These summary/draft consensus statements are based on available data, which are minimal in some areas. There is a need for higher quality data on which to base decisions in almost all of the questions this expert panel considered. The development of protocols may go a long way in ensuring continued care, not only for women with HBV infection at the antenatal, peripartum and postpartum stages, but also for their children.

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Table 1

- Explain residual risk of transmission
- Explain risk of exacerbation of disease in mother
- Explain methods of prophylaxis
- Explain possibility of antiviral therapy
 - First and third trimester treatments
 - Choice of nucleos(t)ide analogue
- Set up appropriate scheduling peripartum and postpartum
- Explain limitations/risks of current prophylaxis in highly viraemic mothers
- Explain risks and benefits of breastfeeding in the context of antiviral therapy
- Discuss method of delivery

Table 2

	Lamivudine	Adefovir	Entecavir	Tenofovir	Telbivudine	Peginterferon alfa-2a
ADEC pregnancy category	B3	B3	B3	B3	B1	B3
FDA pregnancy category	C	C	C	B	B	C
Crosses the placenta	Yes	Unknown	Unknown	Yes	Yes (rats and rabbits)	Minimal due to large molecular size
Excretion in breast milk	Yes	Unknown	Unknown (yes in animal studies)	Unknown (yes in animal studies)	Unknown (Yes in animal studies)	Minimal due to large molecular size
Animal studies	Embryonic loss in rabbits at doses comparable to clinical doses; no effect in rats at exposure levels 51 x those in humans	Fetal development unaffected at AUC to 23 (rats) and 40 (rabbits) times maximum human exposure Embryo toxicity and malformations in rats >38 times maximum human exposure	Fetal development unaffected at AUC to 23 (rats) and 175 (rabbits) times maximum human exposure Fetal malformations and retarded development at maternotoxic doses (>2500 times human value)	No fetal abnormality in rats or rabbits at respective AUCs of 4–13 and 66 times maximum human exposure Subcutaneous treatment of pregnant monkeys at 30 mg/kg/d in the second half of pregnancy led to reduced fetal serum concentrations of phosphorus	No fetal abnormality up to 6 times (rats) and 37 times (rabbits) maximum human exposure An increase in early deliveries and abortions was observed in rabbits at plasma levels 37 times higher than the human therapeutic dose	Rhesus monkeys: significant increase in abortifacient activity; no teratogenic effects were seen in delivered offspring

Table 3:Lamivudine Prophylaxis for Mother to child transmission

Ref	Start LMV Tx	Cases		Controls		Follow up	Transmission rates		Statistical significance
		Description	N	Description	N		Cases	Controls	
Su(90)	1 st Tri	HBsAg+/HBeAg+, treatment continued throughout pregnancy	12	Historical controls with HBV vaccine 30 mg /30mg /10mg	81	12 months after birth	0	26%	P<=0.05
				Historical controls with HBV vaccine 30 mg /20mg /10mg	37	12 months after birth	0	35%	P<=0.05
Li (91)	28wk	HBsAg+	43	HBsAg+, Placebo (RCT)	52	24 hours after birth	16.3%	32.7%	P <=0.05
Xu (92)	32wk	HBsAg+, LMV/HBV vaccine/HBIG from 32wks-4wkspp	56 (13% dropout)	HBsAg+, placebo (RCT)	61 (31% dropout)	12 months after birth	18%	39%	P=0.14
Van Zonneveld)(93)	34-36wk	HBsAg+, High viral load	8	High viral load, historical controls	24	12 months after birth	12.5%	28%	NS
Van Nunen (94)	36wk	HBeAg+, High viral load	3	Historical controls, HBeAg+, High viral load	8	12 months after birth	0	50%	NS
Han (95)	20 weeks	HBsAg+, LMV	52	HBsAg+, HBIG beginning at 28weeks, every 2 weeks (RCT)	61	12 months after birth	0	16%	NS

Table 4

	HBeAg positive (%)	HBeAg negative (%)
No HBIG or HBV vaccine	70-90	<10
HBIG and HBV vaccine	7	?

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