

# Hepatitis B in Pregnancy: Specific Issues and Considerations

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## Abstract

Chronic hepatitis B affects over 350 million people worldwide. Vertical transmission is known to be the leading cause of infection and perinatal infection is associated with a very high rate of chronicity (up to 90%). Up to 40% of chronically infected individuals will die prematurely from complications such as acute liver failure, cirrhosis and hepatocellular cancer. Addressing perinatal transmission through the use of immunoprophylaxis can help contain the spread of HBV. Pregnant mothers with chronic hepatitis B have unique challenges and require specialised management during and after pregnancy.

This review will look at the screening of pregnant women for hepatitis B, passive and active immunoprophylaxis, mechanisms of perinatal viral transmission and therapeutic considerations in pregnancy including possible teratogenicity and efficacy of medication. Other issues such as the mode of delivery and breastfeeding will be covered.

**Keywords:** Hepatitis B; Pregnancy; Antiviral; Immunoprophylaxis

## Introduction

Chronic hepatitis B infection affects over 350 million people worldwide. Vertical transmission is known to be the leading cause of infection, and perinatal infection is associated with an extremely high rate of chronicity (up to 90%) [1]. Up to 40% of chronically infected individuals will die prematurely from complications such as acute liver failure, cirrhosis and hepatocellular carcinoma [2]. The spread of hepatitis B can be contained by addressing the issue of perinatal transmission via the use of immunoprophylaxis. Pregnant women with chronic hepatitis B infection have unique management challenges and require specialized hepatitis B management both during and after pregnancy.

This review will examine: the antenatal screening of pregnant women for hepatitis B infection; passive and active immunoprophylaxis; mechanisms of perinatal viral transmission; and therapeutic considerations in pregnancy, including possible teratogenicity of medication and efficacy of treatment. Other issues such as breastfeeding and the mode of delivery will also be covered.

## Screening

In Australia, pregnant women are universally screened for chronic infection with hepatitis B virus (HBV), which is defined as testing positive for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), or both, on routine antenatal serological screening, performed during an early antenatal visit, as recommended by the American Congress of Obstetricians and Gynecologists [3]. This practice ensures that women with hepatitis B receive optimal medical care, both during and after pregnancy, and that infants born to these women receive appropriate post-exposure prophylaxis. However, although many countries practice similar universal screening models for hepatitis B in pregnant women, some countries still use screening models that are driven largely by risk factors [4].

The hepatitis B vaccine is generally thought to be safe for use in pregnancy, with no significant maternal adverse events or foetal teratogenicity reported in the literature [5]. Pregnant women who test negative for HBsAg, and who are at increased risk of acquiring HBV infection, should be immunized during pregnancy. Those women considered to be at greatest risk include: those with multiple sexual

partners (more than two in the last 6 months); those who have a current or past history of sexually transmitted infections (STIs); those who are recent or current intravenous drug users; those who live in HBV-endemic areas; and those who have an HBsAg-positive sexual partner [6]. There is no requirement for women to be tested for absence of immunity to hepatitis B (absence of anti-HBsAg antibody) prior to being vaccinated.

## Immunoprophylaxis

In July 2004, the World Health Organization (WHO) released a position paper which recommended that the HBV vaccine be introduced into all national immunization programs and that infants born in HBV-endemic areas be given HBV vaccine at birth followed by 2-3 further doses to complete the primary series [7]. A three-dose vaccine course has been shown to confer protective antibody concentrations in approximately 95% of infants and children and 90% of adults [8,9].

In Australia, it is recommended that all infants be given an initial dose of HBV vaccine within 24 hours of birth, followed by 3 subsequent doses of a multivalent/combination vaccine at 2, 4 and either 6 or 12 months of age (depending on the vaccine used), with the infant being given a total of 4 doses of HBV vaccine [10]. Those infants born to mothers identified, during antenatal screening, as having chronic HBV infection, are given passive-active immunoprophylaxis with both an initial dose of HBV vaccine and a dose of hepatitis B immunoglobulin (HBIG) at or soon after birth, preferably in the delivery room, followed by 3 subsequent doses of HBV vaccine in the first year of life as above [10]. The main aim of this strategy is to prevent mother-to-infant transmission during the puerperium, as acute infection at this age

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results in the highest risk of chronic infection due to immunological tolerance by the immature infant immune system [8,9]. After completion of the vaccine series, testing for HBsAg and the antibody against HBsAg (anti-HBs) should be performed at 9 to 18 months of age [10]. HBsAg-negative infants with anti-HBs levels greater than 10 mIU/mL are considered immune and no further medical management is required. Those with anti-HBs levels less than 10 mIU/mL are not considered immune and should be revaccinated with a second three-dose series followed by retesting 1 to 2 months after the final dose.

The presence of maternal anti-HBs (which crosses the placenta and is expressed in breast milk), even at very high concentrations, in infants born to mothers with pre-existing immunity to hepatitis B, has not been shown to affect the long-term immunogenicity of the hepatitis B vaccine [11]. Thus, the current hepatitis B vaccination schedule for infants should remain effective in the future, even as more and more infants begin to show serological evidence of maternal anti-HBs due to the increasingly widespread vaccination against hepatitis B in adult population.

Passive-active immunoprophylaxis is reported to be safe and effective, and significantly reduces the risk of HBV transmission [12,13]. The combination of the HBV vaccine and HBIG is estimated to reduce chronic HBV occurrence by at least 90% compared to placebo or no intervention [13-18]. A meta-analysis of randomized controlled trials of hepatitis B vaccine administered at birth found that immunised infants born to mothers infected with hepatitis B were 3.5 times less likely to become infected with HBV (relative risk 0.28) [14]. The vaccine is also effective in reducing both the incidence and mortality of hepatocellular cancer [19,20].

Women who have serological evidence of both HBsAg and HBeAg have a significantly greater risk of transmission of HBV to their newborn baby as compared to women who have serological evidence of HBsAg only (85% compared to 10%) [13-15]. For those pregnant women who have serological evidence of both HBsAg and HBeAg, the risk of their infant developing HBV infection by the age of 6 months, in the absence of immunoprophylaxis, is 70–90%, with approximately 90% of these children remaining chronically infected [21,22]. Persistence of maternal HBeAg is an important risk factor for delayed spontaneous HBeAg seroconversion in children with chronic HBV infection [23]. HBeAg-negative mothers carry a 10% to 40% risk of transmission, with 40% to 70% of infants who become infected remaining chronically infected [24].

Immunoprophylaxis has been acknowledged as the most effective intervention to reduce the prevalence of HBV infection. As an example, a universal hepatitis B vaccination policy, which has been in place in New Zealand for over two decades, has led to a marked decline in the prevalence of hepatitis B infection in the antenatal population, particularly among women less than 20 years of age [25]. Many countries, and especially developing countries with high prevalence rates of hepatitis B, cannot afford the resources to institute national immunoprophylaxis programmes [8,26]. A paper produced by the Centres for Disease Control and Prevention (CDC) in the United States noted that only 36% of all newborns received the HBV vaccine at birth in the 87 countries in which chronic HBV infection is endemic (affecting 8% of the total population) [27]. Affordability, access and nationwide delivery and implementation of HBV immunoprophylaxis are just some of the major public health challenges faced by health organisations.

## Perinatal Transmission

Approximately one third of HBV infections occur via perinatal transmission [28], and perinatal transmission is the most important vertical transmission route of chronic hepatitis B infection. Perinatal transmission of HBV is mediated via three main modes: 1) Intrauterine transmission; 2) Intrapartum or labour transmission; and 3) Postnatal transmission.

Although passive-active immunoprophylaxis in infants of chronically HBV-infected mothers has been demonstrably effective in reducing perinatal transmission, a small percentage of infants still become HBV chronic carriers and ostensibly this is because HBV exposure can occur *in utero* prior to delivery [29]. In one Chinese study, 3.7% of babies of pregnant mothers with chronic hepatitis B tested positive for HBsAg at birth from *in utero* infection [30]. In Korea, despite administration of HBIG and HBV vaccine to infants of HBsAg-positive mothers, 4.2% of these infants still tested HBsAg-positive [31]. The mechanisms of intrauterine transmission of HBV are not fully understood but the presence of intrauterine infection has been shown in several studies, as indicated by the presence of newborn HBsAg and HBV DNA and from placental immunohistochemistry and PCR studies [32].

Leading theories on the mechanism of intrauterine transmission of HBV have come from studies carried out in the Republic of China and include infection through the placenta, transplacental leakage and genetic susceptibility [30,33-36]. Wang and Zhu [37] have proposed that HBV can be integrated into placental tissue leading to infection. Zhang and colleagues [38] have shown the ability of HBV to translocate through the placenta from the mother to the fetal trophoblast, suggesting a direct transplacental route of infection. Liu and colleagues have examined susceptibility genes that may be associated with intrauterine HBV infection [36].

Known risk factors predisposing to intrauterine infection include maternal HBeAg positivity, detectable HBV DNA, specific allelic mutations in maternal HBV, a history of threatened preterm labour, and acute hepatitis B acquired in pregnancy, particularly during the last trimester [29,30,39-41]. HBeAg-negative mothers with a high viral load (HBV DNA load > 10<sup>8</sup> IU/mL) are at great risk of transmitting the virus *in utero* to their infants [42].

Intrapartum or labour cases are thought to arise: from possible transfusion of the mother's blood to the foetus during labour contractions; as a consequence of membrane rupture; from HBV contaminated maternal blood or amniotic fluid/vaginal secretions being either swallowed by the foetus or entering the foetal blood circulation via placental rupture; or through direct contact of the foetus with infected secretions/blood from the maternal genital tract [43,44]. It is known that as little as 10<sup>8</sup> IU/mL of HBV-contaminated maternal blood entering the foetus can result in foetal HBV infection [22,45].

A recent nested case-control study of maternal-neonatal transmission of hepatitis B, again in a Chinese population, found that maternal first-degree family history of HBV infection, intrahepatic cholestasis and premature rupture of membranes were risk factors for perinatal transmission of HBV, whereas systematic treatment and HBV immunoglobulin injection, for mothers with HBV infection, were protective factors for maternal-neonatal transmission of HBV [46]. This study had the advantage of using venous blood from newborns as opposed to cord blood samples in which contamination from maternal

blood, and therefore the possibility of false positive results, cannot be definitively excluded.

Although postpartum transmission of HBV is known to occur, it is thought to account for only a very small proportion of cases of perinatal transmission [46]. The exact mechanisms by which postpartum transmission occurs remains unclear as, to date, there is scant data in the literature regarding this issue, beyond passing references in the literature to postpartum transmission as a potential mode of perinatal transmission. However, potential mechanisms of postpartum transmission, all of which involve close contact of the infant with HBV-contaminated maternal secretions, may include: infant ingestion of maternally pre-masticated food; maternal kissing of the infant on the mouth; and nosocomial infection due to poor hand hygiene practices amongst healthcare workers who are involved in the postpartum care of both mother and infant [47].

### Breast Feeding

Although HBsAg, HBeAg and HBV DNA have been shown to be excreted from the colostrum and breast milk of mothers with chronic HBV infection [48-50], there is currently no evidence that breastfeeding increases the risk of mother-to-child transmission of hepatitis B. A recent systematic review of ten prospective studies, evaluating the role of breastfeeding in mother-to-child transmission of HBV, found that breastfeeding after adequate immunoprophylaxis did not contribute to postnatal transmission of HBV [51]. Furthermore, the WHO has recommended that all infants be breastfed for at least 4 months (but ideally, at least 6 months) as there is a considerable risk of morbidity and mortality from hepatitis B among infants who are not breastfed [52]. However, although breastfeeding *per se* is not thought to be a mechanism of postpartum transmission of HBV, breastfeeding in the presence of concomitant nipple pathology may potentially result in postpartum transmission of HBV due to contamination of the breast milk by serous exudates from the nipple lesions [47].

### Causes of Immunoprophylaxis Failure

In countries where proper immunization is performed, up to 9% of infants whose mothers are HBsAg-positive will eventually become infected with HBV [24]. This failure of immunoprophylaxis requires an examination of the potential causes. Failure to identify chronically infected mothers, and inadequate newborn prophylaxis, are significant contributors to immunoprophylaxis failure [53]. In the Australian study conducted by Wiseman and colleagues, of the four children (2%) who were infected vertically, one was found to have been improperly immunized [54]. It would therefore be reasonable to expect that any delay in administering the second dose of vaccine would potentially increase the reported rate of immunoprophylaxis failure [55].

The high rate of reported failed immunoprophylaxis is more likely to be due to the above reasons rather than to true immunization failure where documented peripartum transmission occurs despite strict adherence to an appropriate immunization protocol. Such true cases of immunoprophylaxis failure have been linked to high maternal HBV DNA viral load. The current literature suggests that the quantity of HBV DNA thought to be associated with immunization failure is somewhere in the order of  $10^8$  IU/mL. Wiseman and colleagues [54], in their study, examined 313 HBsAg-positive pregnant women from the period 2002 – 2008. Of these women, 47 were HBeAg-positive and had HBV DNA viral loads greater than  $10^8$  IU/mL. Of the 47 infants born to these women, 4 were both HBsAg-positive and anti-HBs-negative. Moreover, all 4 infants received the full HBV vaccination regimen with

3 of these infants receiving passive immunoprophylaxis (HBIG) at birth. In newborns of mothers with HBV DNA viral loads less than  $10^8$  IU/mL, no HBV perinatal transmission was reported. The conclusion from this study is that HBeAg positivity and high maternal HBV DNA viral load correlate with perinatal transmission, a finding that has been replicated in a number of other studies [39,42,56].

Other potential determinants of immunoprophylaxis failure are thought to include escape mutations of HBsAg [57-60], cytokine polymorphisms involved in the immune response to HBV [61], and HBV surface genes [62]. However, their significance in contributing to immunoprophylaxis failure remains unclear and this remains an active area of ongoing research into hepatitis B.

### Minimizing Immunoprophylaxis Failure

In order to reduce vertical transmission, and reported rates of immunoprophylaxis failure, it is essential that immunoprophylaxis programmes be properly funded and implemented. A coordinated approach to the delivery of these programmes, with adequate political and organisational support, will play a key role in reducing the global burden of disease associated with hepatitis B.

Another approach that may help prevent perinatal HBV transmission is maternal administration of HBIG during pregnancy. Administration of HBIG, during pregnancy, to maternal HBV carriers can, in theory, reduce *in utero* HBV transmission by reducing maternal HBV DNA viral load via activation of the complement system [63]. In a recent meta-analysis [64], of 37 randomised controlled trials (mainly from China) examining the safety and efficacy of HBIG during pregnancy in preventing mother-to-child HBV transmission, involving almost 6000 mothers who received either three doses of HBIG (100–400 IU) or placebo during the third trimester (at 28, 32 and 36 weeks of gestation), it was found that administration of HBIG during pregnancy resulted in an overall lower rate of intrauterine infection, a lower proportion of infants with detectable HBV DNA and a higher rate of anti-HBs seropositivity in infants at 9-12 months of age as compared to controls.

However, a recent study has challenged the efficacy of immunoprophylaxis in preventing intrauterine infections. In a Chinese prospective study of 214 infants born to HBsAg-positive mothers, in which peripheral blood samples were collected from mothers and their newborns prior to receiving HBIG and HBV vaccine, it was found that all cases of perinatal transmission became HBsAg-negative while all cases of intrauterine transmission evolved into the carrier status [65]. The study concluded that infants infected via intrauterine transmission cannot be effectively protected from HBV infection by HBIG and HBV vaccine. However another recent Chinese study, examining foetal samples obtained from HBsAg mothers via amniocentesis or cordocentesis, found that the presence of intrauterine HBeAg and HBV DNA did not correlate with postnatal HBV infection and HBV vaccination failure [66]. As with cases of HBV infection due to exposure to HBV at birth, most of the seropositive foetuses in the study demonstrated successful seroconversion after postnatal prophylaxis. In order to resolve the discrepancy between these findings, larger multicentre studies with large sample sizes are required, with such studies likely to be conducted in China, where much of the current data on intrauterine HBV infection has been compiled.

### Antiretroviral Therapy

An electronic survey of physicians involved in the treatment

of patients with liver diseases found significant heterogeneity in the management of pregnant patients with hepatitis B [67]. This likely reflects a lack of consolidated data and highlights the need for specific treatment guidelines. Due to the documented risk of vertical transmission of HBV despite adequate immunoprophylaxis, especially in women with high HBV DNA viral loads who are at even greater risk of transmission, one therapeutic strategy that has been widely canvassed, in the hope that it might reduce maternal HBV DNA viral load and thus decrease the risk of HBV transmission to the neonate, is the use of antiretroviral drugs prior to delivery.

The mainstays of therapy for hepatitis B are the oral antiretroviral nucleoside or nucleotide analogues which work by reducing viral replication. These medications can be taken for prolonged periods of time with minimal side effects and are often prescribed indefinitely with switching between medications occurring only if treatment resistance develops. Women with chronic hepatitis B may be exposed to these medications during pregnancy so treating clinicians will need to be able to advise their patients appropriately regarding the potential implications of antiretroviral therapy for both the patient and their developing foetus.

### Teratogenicity

In Australia, the Therapeutic Goods Administration (TGA) has delineated categories for prescribing medicines in pregnancy [68] (Table 1), similar to the classification scheme used by the Food and Drug Administration (FDA) in the United States [69]. This classification scheme is based on the risk of teratogenicity in preclinical evaluations. Lamivudine, telbivudine, adefovir, tenofovir, entecavir, and emtricitabine are listed antiviral agents for treatment of HBV infection. These medications are able to distribute freely through the placenta and into the foetal compartment. The international Antiretroviral Pregnancy Registry, in a report released in December 2011, did not note any increased risk of overall birth defects, or specific defects, with the use of these antiretroviral medications when compared to data obtained from population-based surveillance systems for birth defects [70] (Table 2).

Telbivudine is classed as a Category B1 medication while all the other nucleos(t)ide analogues are classed in category B3. However

lamivudine has been used far more extensively in pregnant women. Although there is less documented clinical experience with tenofovir, it has been classified as a Class B agent by the FDA and has two principal advantages: a very high genetic barrier to resistance, with no reported resistance to date, and no excretion into breast milk [71,72]. Telbivudine is not commonly used in clinical practice due to minimal *in vivo* experience in pregnancy and a low genetic barrier to resistance [73].

In two published studies, pregnant patients were exposed to lamivudine and telbivudine in the third trimester with no birth defects reported [74,75]. Although due consideration needs to be taken regarding exposure to these antiretrovirals late in pregnancy (unlikely to affect organogenesis), on the basis of the existing evidence, it would appear that either of lamivudine or telbivudine could be used safely in pregnancy, especially during the third trimester.

The safety of interferon-alpha in pregnancy has not been clearly established so women of childbearing age are required to practise an effective method of birth control while on therapy. A recent systematic review of published data on the outcomes of pregnancies exposed to interferon-alpha (often in the setting of melanoma treatment) did not find any evidence of increased rates of major malformation, miscarriage, stillbirth or preterm delivery above those seen in the general population [76].

### Treatment Efficacy

Lamivudine has been shown in a large multi-centre randomised controlled trial in China to be successful, during the third trimester of pregnancy, in interrupting vertical transmission of HBV [75]. In this trial of 115 women who were HBsAg-positive with high HBV DNA viral loads, 59 women were enrolled as controls and 56 women were treated with 100 mg of lamivudine beginning in the third trimester of pregnancy and continuing until 4 weeks postpartum. In the treatment group, there was a reported 50% decrease in the rate of vertical transmission but this data was challenged due to a high drop-out rate in the control group.

As many of the studies evaluating lamivudine treatment in late pregnancy have been small in sample size, and their results controversial,

Category	Definition
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B1	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
B2	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
B3	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
D	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

**Table 1:** Definitions of the Australian categories for prescribing medicines in pregnancy (Therapeutic Goods Administration).

Antiretroviral medication	TGA Category
Lamivudine	B3
Telbivudine	B1
Tenofovir	B3
Entecavir	B3
Interferon-alpha	B3
Adefovir	B3
Emtrecitabine	B1

**Table 2:** Therapeutic Goods Administration Classification of Antiviral Medicines used in the Treatment of Hepatitis B.

a meta-analysis was necessary to pool data from the available studies. A recent meta-analysis by Han and colleagues [77] examined two specific questions: 1) At what level of maternal serum HBV DNA viral load does antiviral therapy have a clear beneficial effect?; and 2) How early in pregnancy should antiviral therapy be initiated?

The meta-analysis found that mother-to-child transmission of HBV, as indicated by the presence of serum HBsAg or detectable HBV DNA in newborns during the first 24hr of life or in infants 6-12 months after birth, was significantly interrupted by the use of lamivudine treatment in late pregnancy as compared to using placebo controls or HBIG. Lamivudine treatment was also found to be similarly effective in interrupting maternal HBV transmission both when used in mothers with HBV DNA viral load <10<sup>8</sup> IU/mL and when initiated at 28 weeks of gestation.

The meta-analysis concluded that lamivudine treatment for HBV carrier mothers should be initiated at 28 weeks of gestation. However, for HBV carrier mothers with viral load >10<sup>8</sup> IU/mL, antiviral treatment with lamivudine alone may be insufficient to interrupt mother-to-child transmission unless maternal HBV DNA viral load is able to be reduced to a level of <10<sup>6</sup> IU/mL by lamivudine treatment.

Lamivudine has been shown to be beneficial for pregnant women with hepatic failure secondary to hepatitis B. In a recent Chinese study, 70 pregnant women, with hepatic failure secondary to hepatitis B infection, were divided into either a study group (40 women) or a control group (30 women) according to their personal preferences [78]. In the study group, 14 women were treated with lamivudine, during the third trimester, and antiviral treatment postpartum. The 26 remaining women were treated with either lamivudine or entecavir postpartum only. It was found that the incidence of intrauterine infection and the overall rate of mortality were significantly lower in the study group than in the control group. There were no apparent abnormalities in newborns in either group.

The major limitation of lamivudine usage is emerging genetic resistance which is generally associated with the YMDD motif of the HBV polymerase gene [79]. However, this is not the case for tenofovir which has a very high genetic barrier to resistance. As such, some authors have encouraged the use of potent nucleos(t)ide analogues with high genetic barriers to resistance (such as tenofovir) wherever possible in order to provide the best chance of achieving treatment goals [80]. Tenofovir has been assessed for safety and efficacy in pregnant Rhesus monkeys [81]. The use of tenofovir resulted in significant reduction of viral load in simian immunodeficiency virus (SIV) -infected foetuses. A multi-centre prospective randomised open-label study is currently recruiting in China with the aims of determining the safety and tolerability of tenofovir in highly viraemic HBeAg-positive women, as well as its efficacy in reducing the rate of HBV vertical transmission

rate [82].

Telbivudine has been studied in highly viraemic HBeAg-positive women (HBV DNA viral load >10<sup>7</sup> IU/mL) in late pregnancy (i.e. after 20 – 32 weeks of gestation) in a recent trial that demonstrated a significant reduction in perinatal transmission [74]. Telbivudine treatment was associated with a marked reduction in both serum HBV DNA viral load and HBeAg levels and normalization of elevated ALT levels before the time of delivery. Of the 135 telbivudine-treated mothers, 44 mothers (33%), but none (0%) of the untreated controls, had PCR-undetectable viraemia (HBV DNA viral load <500 IU/mL) at the time of delivery. Furthermore, it was found that seven months after delivery, the incidence of perinatal transmission was lower in the infants born to telbivudine-treated mothers, who completed follow-up, as compared to controls (0% as compared to 8%; p=0.002). The use of telbivudine was shown to be safe for both mother and newborn with no significant increase in the rates of pregnancy and delivery complications, congenital deformities or impaired infant development. Another smaller open label study assessing telbivudine use in HBeAg-positive pregnant women confirmed the reduced rates of perinatal transmission with no increase in congenital deformities or pregnancy complications noted [83].

### Management Algorithm

In devising this algorithm (Figure 1), which is adapted from an algorithm by Yogeswaran and Fung [84], it should again be noted that in HBsAg-positive pregnant women with high HBV DNA viral load, the use of lamivudine in the third trimester of pregnancy, followed by passive and active immunization of the newborns, has been proven to be effective in preventing transmission of HBV to the foetus and is currently considered to be safe for both the mother and the developing foetus. Administration of HBIG during pregnancy is expensive and there is currently insufficient evidence to justify its widespread use.

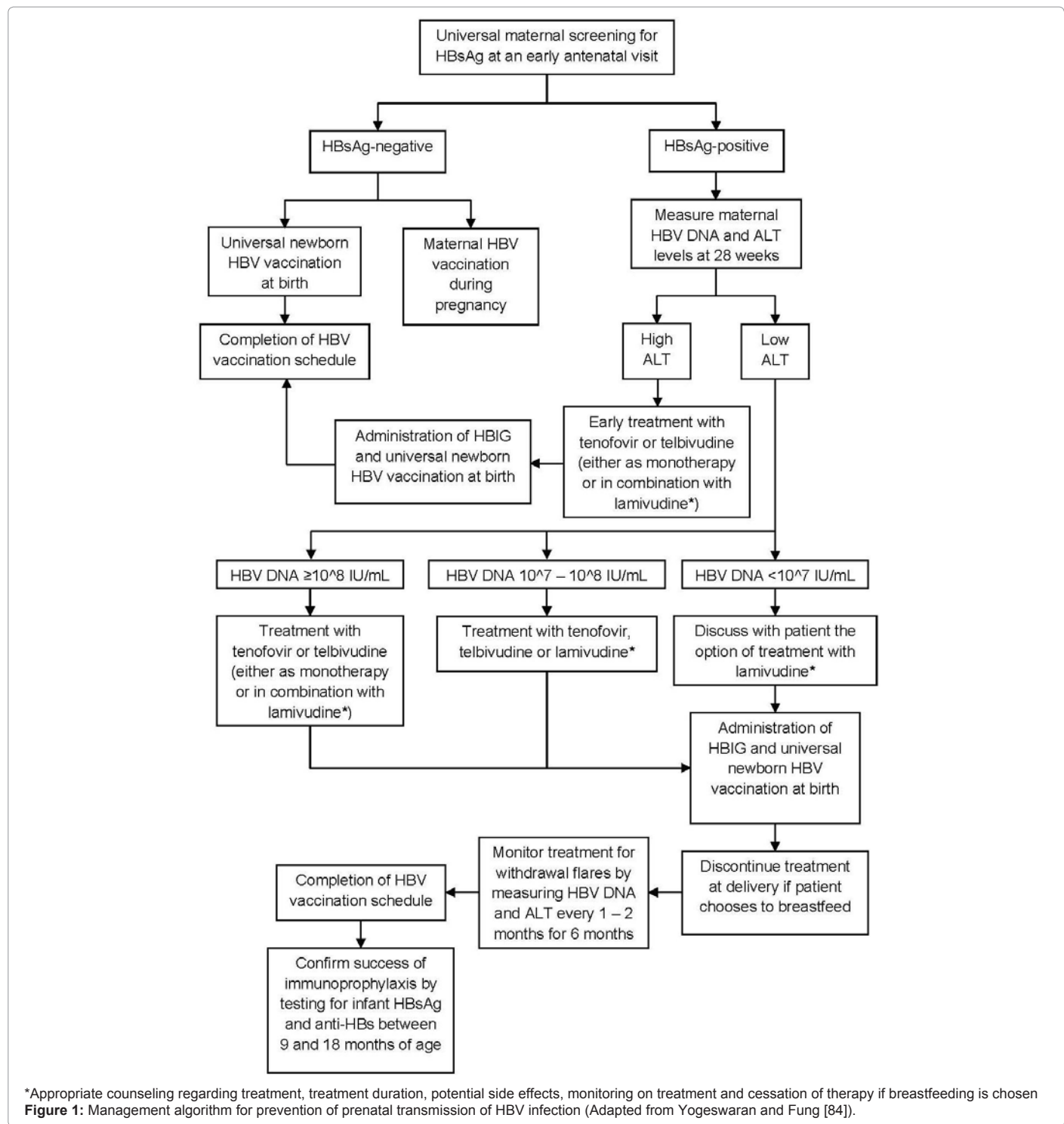
A number of algorithms have proposed an HBV DNA viral load level of 10<sup>7</sup> IU/mL as being an appropriately high cut off level at which there is a significant risk of vertical transmission however there is some evidence that intrauterine transmission may be associated with a lower level of maternal HBV DNA viral load [85]. The results of a recent meta-analysis concluded that lamivudine treatment should be commenced at 28 weeks of gestation for optimal interruption of maternal-foetal HBV transmission. However, the same meta-analysis also noted that, an HBV DNA viral load of 10<sup>8</sup> IU/mL, lamivudine monotherapy may be insufficient to effectively interrupt maternal-foetal transmission of HBV.

Although antiviral therapy, used to treat pregnant women with chronic hepatitis B infection, is generally thought to be safe for use in pregnancy, treatment should be discontinued postpartum, in those mothers who choose to breastfeed due to the extremely limited amount of clinical data available regarding the safety profiles of these agents in the context of breastfeeding [86].

Non-gravid women who are being treated for chronic hepatitis B infection with antiviral therapy should not discontinue treatment if they subsequently fall pregnant as the potential benefits of treatment far outweigh the theoretical risks of harm to the developing foetus [87].

### Mode of Delivery

The influence of the mode of delivery on vertical transmission



and passive-active immunoprophylaxis has remained uncertain until recently [88,89]. An abstract presented at a recent hepatology conference revealed that, in highly viraemic HBeAg-positive pregnant women, elective caesarean section resulted in a reduction in the rate of perinatal transmission of HBV as compared with either vaginal delivery or emergency caesarean section, with no significant difference in the rate of immunoprophylaxis failure immediately after birth [90]. In addition, there was no significant difference in the risk of obstetric

complications observed across the various modes of delivery.

### Maternal and Foetal Outcomes

HBV infection, during pregnancy, does not appear to increase maternal or foetal morbidity and mortality in the absence of active liver disease. In a large study comparing 824 HBsAg-positive mothers to a control group of 6281 HBsAg-negative mothers, there were no significant differences in birthweight or the rates of pre-term delivery,

neonatal jaundice, congenital anomalies and perinatal mortality between the 2 groups [91]. In a case-control study [92] comparing the outcomes of 253 HBsAg-positive pregnant carriers to 253 matched controls, HBsAg carriers were found to have an increased risk of gestational diabetes mellitus, antepartum hemorrhage, and threatened pre-term labour, on multivariate analysis. There was no significant difference in mortality between the groups and the differences in outcomes may be attributable to the presence of active liver disease, which can increase the risk of obstetric complications.

Reddick and colleagues [93] looked through the National Inpatient Sample (a registry of discharge encounters from 1054 hospitals across 37 states in the USA) for all cases of pregnancy related discharges, pregnancy complications and viral hepatitis from 1999 to 2005. Logistic regression was then used to examine the association between HBV infection and pregnancy-related complications. It was found that women with HBV infection had an increased risk of pre-term delivery but, surprisingly, a decreased risk of delivery by Caesarean section. Of interest, it has also been recently discovered that there is a significant association between the presence of HBV DNA in cord blood and rates of spontaneous pre-term delivery in pregnant women with chronic HBV infection [94].

## Conclusion

Urgent strategies are required to address the global health burden that chronic HBV infection imposes. It is imperative for nations to formulate and implement consistent population-based screening and universal vaccination programs. Although immunoprophylaxis has been extremely successful and is the mainstay of therapy in pregnant women with low HBV DNA viral loads, there is a growing body of evidence strongly favouring the adjunct use of antiviral therapy during pregnancy in order to reduce the risk of perinatal transmission, especially as positive data accumulates regarding the safety profile and efficacy of medications such as lamivudine, telbivudine and tenofovir. However, there is a clear need for close monitoring of both pregnant women, with hepatitis B infection and their infants, both during and after pregnancy.

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