REVIEW

A pregnant patient with a positive hepatitis B surface antigen

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ABSTRACT

Hepatitis B is a major cause of liver disease worldwide. The highest rates of chronic infection occur in subjects who are infected early in life and these patients are also at the greatest risk of developing complications such as hepatocellular carcinoma and cirrhosis from the disease. There has been a concerted worldwide effort to immunise newborns that are at the highest risk of acquiring infection. In 1992, when WHO recommended global vaccination against hepatitis B, only 31 countries elected to participate in the programme. By 2009, 177 countries were part of WHO national infant immunisation programme. Consequently, maternal screening and infant immunoprophylaxis have significantly reduced vertical transmission of hepatitis B. In this paper, we will review the management of hepatitis B in the pregnant population and identify some of the challenges that are encountered in this specialised population.

CLINICAL SCENARIO

Mrs G, a 30-year-old G1P0 Asian American woman in the twelfth week of pregnancy, was recently seen for her first prenatal visit in the Obstetrics clinic and had routine prenatal testing, including screening for hepatitis B virus (HBV). These revealed that her hepatitis B surface antigen (HBsAg) was positive. Her serum hepatitis B DNA (HBV DNA) levels were subsequently checked and were found to be 7 log₁₀ copies/ml; hepatitis B e antigen (HBeAg) was positive and her Alanine aminotransferase (ALT) level was within the normal range. She has no other medical problems. There is no known family history of HBV; however, her parents have never been tested. She is a journalist and was born in China before moving to the USA at the age of three. She has been married for 3 years.

INTRODUCTION

The HBV is a double-stranded DNA virus belonging to the Hepadnavirus family.¹ According to WHO, approximately 2 billion people worldwide have been exposed to the virus and of these, 350–370 million people are chronic carriers of the virus.^{2–3} It is therefore a major global health concern and roughly 600 000 people die annually from complications of HBV infection.⁴ The prevalence of chronic hepatitis B (CHB) infection varies greatly globally. In high endemic areas such as China and other parts of Asia, sub-Saharan Africa and the Amazon Basin in South America, 8%–10% of the adult population are chronically infected. Most of the infections are acquired in the perinatal period or in early childhood. The Middle East and Indian subcontinent represent areas of intermediate endemicity and an estimated 2%–5% of the general population is chronically infected. Western Europe and the North America are areas of low endemicity and less than 1% of the population have CHB.⁴ However, the prevalence of CHB is much higher in immigrant populations and rates as high as 10%–17% have been reported in some groups of Asian American immigrants.⁵ Overall, it is estimated that 1 in 10 foreign born Asian Americans has CHB. As people born outside the USA from areas endemic for HBV are under-represented in epidemiological studies,⁶ it is estimated that 2–3 million people in the US have CHB compared with the often quoted 1.25 million Americans by the Centers for Disease Control.⁶

NATURAL HISTORY OF HBV INFECTION

At the time of acute hepatitis B infection in the adult, approximately 30% patients will

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develop jaundice while the remaining 70% will have subclinical disease.⁷ The incubation period lasts for 1–4 months and patients may be asymptomatic or present with generalised malaise, fatigue, fever, pruritus, arthralgia, nausea and jaundice. Fulminant hepatic failure in which there is massive immune-mediated necrosis of hepatocytes is unusual and only occurs in approximately 0.1%–0.5% of patients.^{7–8} In a typical case of acute infection, HBV DNA is usually detectable at low levels within 1 month. Subsequently, there is a rise in HBV DNA titres, secreted HBeAg levels as well as HBsAg levels. HBV core antigen specific IgG appears early followed by HB core antigen-specific IgG which is then present for life, regardless of the eventual outcome of infection. Approximately 3–4 months after the initial infection, serum ALT levels start to rise reflecting T cell-mediated liver injury. These patients seroconvert to anti-HBe and anti-HBs and clear HBV DNA, HBeAg and HBsAg from the circulation resulting in lifelong protection against hepatitis B infection.⁹ The risk for progression to chronic infection is related inversely to age at the time of infection. HBV infection becomes chronic in >90% of infants, approximately 25%–50% of children aged 1–5 years, and <5% of older children and adults.^{10–12} CHB infection is characterised by persistence of HBsAg for more than 6 months.

In contrast to HBV infection during adulthood, perinatal HBV infection typically results in chronic hepatitis. In perinatally acquired infection, there is an initial immune tolerant phase present which is associated with high levels of viral replication, high HBV DNA levels, positive HBeAg but minimal hepatic parenchymal damage and normal ALT levels.^{13–14} This phase can last for 10–30 years before progression to the immune clearance stage occurs. During this phase, immune-mediated lysis of infected hepatocytes occurs and is often associated with large elevations in serum ALT. There is spontaneous HBeAg clearance in 10%–20% of patients annually and this heralds the low or non-replicative stage.^{9–15} Patients are HBeAg negative and have HBeAg-specific antibodies in the serum and have very low or undetectable HBV DNA levels as well as normal ALT levels.¹⁶ The low replicative phase might last for life. However, some patients continue to have moderate levels of HBV replication and active liver disease as evidenced by elevated serum ALT and persistent inflammation on liver biopsies, but remain HBeAg negative. Mutations in the promoter region of the gene that encodes HBV core antigen result in the production of wild-type virus or HBV variants that cannot produce HBeAg and these patients are termed to have HBeAg-negative chronic hepatitis.^{17–18} Between 0.5% and 2% of patients with CHB infection become HBsAg negative annually and these patients usually have more favourable outcomes.⁹

Individuals infected with chronic HBV are at risk for liver cancer, cirrhosis and liver failure. Immunisation is the most effective way of preventing

HBV transmission, as reflected by the steep decline in incidence of acute hepatitis B after implementation of such programmes.¹⁹ Prenatal screening and appropriate management of at risk infants are also vital to disrupting HBV transmission. However, pregnancy is a unique time where the welfare of both mother and child must be considered.

HBV TRANSMISSION

The natural history of hepatitis B infection varies depending on the mode of transmission. Horizontal transmission can be the result of sexual or household contact or injection drug use and results in chronic infection in 5%–10% of cases. These account for the vast majority of new hepatitis B infections in the USA and Europe. However, mother to child transmission (MTCT, vertical transmission) in the perinatal stage is the most common and efficient method of HBV transmission worldwide. It is estimated that 50%–60% of chronically infected patients acquired the infection perinatally or in early childhood and up to a quarter of these will go on to die prematurely from hepatitis B related complications.^{20–21} In infants born to chronically infected HBsAg- and HBeAg-positive mothers, the rate of disease transmission is 70%–90% and the rate of chronic infection approaches 90%.²² In HBeAg-negative mothers, the risk of viral transmission is 40% and up to 70% of infants then go on to develop chronic infection.² Overall, the MTCT rate is reduced to 5%–10% with the appropriate administration of hepatitis B immunoglobulin (HBIG) and hepatitis B vaccination after birth. However, it is clear that despite appropriate active and passive immunoprophylaxis, the rates of viral transmission still remain high (up to 30%) in infants born to HBV infected mothers who have high serum viral loads.^{23–25}

RISK FACTORS FOR MTCT

HBV DNA and HBeAg

Serum HBV DNA levels and maternal HBeAg status have long been identified as the most important risk factors for MTCT. There are numerous studies highlighting that even after the institution of active and passive immunoprophylaxis, higher maternal viral load is associated with a higher rate of MTCT.^{23–27} Immunoprophylaxis failure rates of between 8% and 32%^{28–29} have been reported in various prospective trials around the world and the most important factors associated with MTCT were maternal HBeAg positivity and high HBV DNA levels^{23–24} (table 1). Significant viremia predisposing to immunoprophylaxis failure had been considered to be serum HBV DNA levels of >8 log₁₀ copies/ml. In the study by Wiseman *et al*, perinatal transmission despite immune prophylaxis only occurred in HBeAg-positive mothers with viral load of >8 log₁₀ copies/ml. Canho *et al* also reported that transmission occurred when the mother's viral load²⁶ was higher than 5.5 log₁₀ copies/ml. However,

Table 1 Risk factors for MTCT

Degree of risk	Causes
High risk	<ul style="list-style-type: none"> • HBV DNA >200 000 IU/ml (>6 log₁₀ copies/ml) • HbSAg and HBeAg positive • Threatened preterm labour • Prolonged first stage of labour (>9 h)
Moderate risk	<ul style="list-style-type: none"> • HBV DNA <200 000 IU/ml (<6 log₁₀ copies/ml) • HbSAg positive and HBeAg negative
No evidence of increased risk	<ul style="list-style-type: none"> • Amniocentesis • Assisted birth (forceps/ventouse delivery) • Breast feeding (currently recommended by American Academy of Pediatrics)

HBeAg, hepatitis B e antigen; HbSAg, hepatitis B surface antigen; HBV, hepatitis B virus; MTCT, mother to child transmission.

MTCT at lower viral titres has also been reported. In a retrospective case-control study of HBeAg-positive mothers, Ngui *et al* reported that although MTCT was more likely in the setting of a high viral load (>8 log₁₀ copies/ml), infection occurred in 5/12 cases with viral loads below this number.³⁰ Recently, in a retrospective single centre Chinese study, Zou *et al* divided patients into FOUR separate groups based on viral loads of <6, 6–6.99, 7–7.99 and ≥8 log₁₀ copies/ml.²⁵ The immunoprophylaxis failure rates in each group were 0%, 3.2%, 6.7% and 7.6%, respectively (p<0.001 for the trend). Therefore, all failures occurred in infants with HBV DNA levels ≥6 log₁₀ copies/ml and they were all born to HBeAg-positive mothers. More recently, in a large prospective study, Chen *et al* reported on 2356 children born to HBsAg-positive mothers who were enrolled in the universal HBV immunisation programme in Taiwan. In the study, HBV vaccines was given to all patients, HBIG was given to all infants with HBeAg-positive mothers and to 723 of 1773 infants with HBeAg-negative mothers. The authors reported that MTCT was significantly higher in infants with HBeAg-positive mothers than in HBeAg-negative mothers as measured by infant HBsAg and HBcAb levels (p<0.001 and p<0.0001, respectively).³¹ In addition, maternal HBeAg positivity also predisposed to increased rates of chronicity in the infant after MTCT (p=0.002). Very low immunoprophylaxis failure rates were seen in HBeAg-negative mothers (<1%) and no significant differences in MTCT were seen between patients receiving HBIG in this cohort.³¹ This study did show however that HBIG administration may prevent infantile fulminant hepatitis.

Modes of MTCT

MTCT of hepatitis B can occur in utero (ante-partum stage), during labour and delivery (intrapartum stage) and in the postpartum stage.

In utero transmission

This is defined as detectable HBV DNA in newborn peripheral blood within 24 h of delivery or detectable HBsAg within 30 days after birth³² and is thought to account for less than 2% of MTCT.³³ Risk factors include the presence of HBeAg and threatened preterm labour.³² A number of mechanisms have been postulated to result in intrauterine transmission. These include male germline and oocyte infections.^{34 35} In addition, transplacental spread is also implicated as evidenced by the presence of HBV DNA on placental cells closest to the fetus as well as possible placental leakage associated with threatened preterm labour.^{32 36} Amniocentesis theoretically disrupts the placenta but there is no convincing evidence that it is associated with increased antepartum HBV transmission.³⁷ Neonatal vaccination and HBIG administration do not protect against in utero MTCT and this partially explains immunoprophylaxis failures.

Intrapartum hepatitis B transmission

Intrapartum MTCT during labour and delivery may occur secondary to mixing of maternal and fetal blood during delivery.^{32 38} This can occur during partial placental leakage occurring during labour itself or at the time of threatened preterm labour. In addition, prolonged duration of first stage of labour is associated with increased presence of HBV antigens in cord blood³⁸ and all these factors confer a higher risk of HBV infection. HBsAg has been also been detected in cervicovaginal as well as in amniotic and vaginal fluid.^{38 39} Direct contact with the fluid in the maternal genital tract may result in ingestion of infected fluids and promote MTCT.^{38 39}

Postpartum hepatitis B transmission

Breast feeding was thought to be a major potential contributor to MTCT as HBsAg is abundant in the breast milk of infected mothers.³⁸ However, the high rate of HBsAg in breast milk does not seem to result in an increased risk of hepatitis B transmission and there are no differences in rates of infection between breastfed and formula-fed babies.^{40 41} Breast feeding is therefore not contraindicated for HBV-positive mothers and the American Academy of Pediatrics guidelines advocate breast feeding provided the infant has received HBIG and hepatitis B vaccine.

MANAGEMENT OF HEPATITIS B IN PREGNANT WOMEN

Hepatitis B screening in pregnancy

All pregnant women should be tested for hepatitis B by measuring HBsAg, ideally in the first trimester, or as soon as they come into contact with healthcare providers if this occurs at a later date.^{42 43} Subsequently, HBsAg positive mothers should be referred to a hepatologist and for counselling, and all close contacts

(household and sexual) of HBV infected patients should also be screened for hepatitis B.^{42 43}

Disease assessment

All individuals with HBsAg require further testing to assess for active infection and the presence of liver disease. Invasive procedures such as liver biopsy are generally avoided during pregnancy especially as the risk for advanced liver disease in most immune tolerant carriers younger than 30 is low. Subsequent studies should include liver enzymes, HBeAg and quantitative HBV DNA, the results of which help identify individuals who would benefit from antiviral therapy. Although elevated ALT or AST may offer indirect evidence of hepatic inflammation, haemodilution from increased plasma volume in pregnancy will reduce these values. Chronic HBV is typically well tolerated for several years, and thus the majority of women of childbearing age will not be appropriate candidates for antiviral therapy.⁴⁴ Most guidelines endorse therapy for individuals with increased ALT and HBV DNA greater than 2000 IU/ml. Yet, as most women of childbearing age are likely to have mild disease, maternal treatment decisions can usually be deferred until after delivery.

Prevention of transmission

There is no evidence that prenatal administration of HBIG affects MTCT. In a large Chinese randomised control study, Yuan *et al* demonstrated that in HBeAg positive women, monthly doses of HBIG in the 3 months preceding delivery did not result in any differences in MTCT between the control and treatment groups.⁴⁵

In the USA, routine screening for HBV infection of all pregnant women by testing for HBsAg regardless of previous immunisation status was introduced in 1988 by the Centers for Disease Control. This programme was instituted in conjunction with hepatitis B vaccination of all newborn infants as well as administration of HBIG in babies born to HBsAg positive mothers or in whom the mother's status is unknown. In the UK,

routine screening, immunisation and immunoprophylaxis were introduced in 2000. Passive-active immunoprophylaxis of the newborn after delivery is the main manner in which MTCT is prevented. It involves administration of HBIG and the first dose of the hepatitis B vaccine within 12 h of birth and is ideally done in the delivery room. Two additional doses of the hepatitis B vaccine are given at 1 and 6 months.⁴⁶ This protocol has been shown to dramatically reduce the risk of MTCT to under 10%.^{23 25}

However, it has long been recognised that immunoprophylaxis is less effective in patients who are HBeAg positive and have high titres of HBV DNA. Therefore, antiviral agents which suppress HBV DNA levels have been used for this purpose late in pregnancy. Based on efficacy and risk of viral resistance, treatment guidelines recommend only three first-line agents for management of chronic HBV: entecavir, tenofovir and pegylated interferon.⁴⁴ However, these agents may not be the optimal therapy to prevent MTCT for various reasons. There are currently no published clinical trials examining the use of tenofovir in HBV infected pregnant patients. There is one ongoing randomised, open label, prospective clinical trial which is recruiting patients and will examine the safety of tenofovir use in HBeAg-positive pregnant women with HBV DNA >6 log₁₀ copies/ml during late pregnancy as well as its efficacy in reducing MTCT (www.clinicaltrials.gov, Study NCT01488526). It has however been used extensively in pregnant patients with HIV alone or with HBV co-infection and it has been shown to be safe. The rates of birth defects do not differ significantly from patients who have never taken tenofovir (table 2). There are only scanty data on adefovir and entecavir in pregnant patients and their use is therefore not recommended in pregnant patients. Interferon therapy is also approved for the treatment of hepatitis B in the general population but its use is not recommended in pregnant patients.

As far back as 2000, van Nunen and colleagues showed that Lamivudine could be used to prevent MTCT in mothers with high viral loads.⁴⁷ More

Table 2 Antiviral agents for hepatitis B and birth defects by trimester when used in any antiretroviral therapy combination

Drug	FDA category	Birth defects/live births	Prevalence (95% CI)	Side effects
Lamivudine	C	1st trimester 122/3966 2nd/3rd trimester 178/6427	3.1% (95% CI 2.6% to 3.7%) 2.8% (2.4% to 3.2%)	Crosses placenta—possible association with mitochondrial toxicity in newborn
Telbivudine	B	1st trimester 0/8 2nd/3rd trimester 0/9	0 0	Crosses placenta—limited data
Tenofovir	B	1st trimester 27/1219 2nd/3rd trimester 15/714	2.2% (1.5% to 3.2%) 2.1% (1.2% to 3.4%)	Bone demineralisation in non-pregnant patients
Entecavir	C	1st trimester 1/30 2nd/3rd trimester 0/2	0 0	Limited data available
Adefovir	C	1st trimester 0/43 2nd/3rd trimester 0/0	0 0	Limited data—likely safe to use

Data adapted from Antiretroviral Pregnancy Steering Committee http://www.apregistry.com/forms/interim_report.pdf (1 January 1989 through 31 July 2011 (Issued: December 2011)).

FDA, Food and Drug Administration.

recently, Xu *et al* published a randomised, double-blind, placebo-controlled study examining whether lamivudine given from week 32 of pregnancy to 4 weeks after delivery could prevent perinatal HBV transmission in highly viremic mothers ($>9 \log_{10}/\text{ml}$).²⁴ Infants receiving lamivudine, HBV vaccine and HBIG had a significant decrease in incidence of HBsAg seropositivity (18% vs 39%; $p=0.014$) as well as detectable HBV DNA (20% vs 46%; $p=0.003$) compared with infants in the placebo, HBV vaccine and HBIG groups. A comprehensive meta-analysis analysed the efficacy of lamivudine in preventing MTCT and found that the use of lamivudine in patients with high viral loads late in pregnancy significantly reduced HBV intrauterine infection and MTCT.⁴⁸ No serious adverse effects were reported in either study.

Lamivudine is classified as a category C agent by the Food and Drug Administration and the other agents that are licensed for use in hepatitis B are summarised in table 2. The data shown are adapted from the Antiretroviral Pregnancy Register (www.apregistry.com), and demonstrate the associated birth defects seen with these agents when used alone or in combination with other antiviral agents. In the case of lamivudine, the infant birth defect rate is not statistically different from the rate seen in mothers who have never been exposed to the drug.

Telbivudine is an oral nucleoside analogue agent approved for the treatment of hepatitis B and has been shown to be more efficacious than lamivudine in patients with HBeAg-positive and HBeAg-negative CHB disease.^{49–50} In addition, in HBeAg-positive patients, it has been demonstrated to result in a higher rate of serum HBV DNA negativity and HBeAg loss and seroconversion than lamivudine.⁵⁰ There have been a number of prospective studies that have highlighted its effectiveness in preventing MTCT. Han *et al* studied a total of 229 patients who were HBeAg positive and had high viral titres ($>7 \log_{10}$ copies/ml).⁵¹ In all, 135 patients received Telbivudine starting between weeks 20 and 32 of gestation. Therapy was continued into the postpartum stage and telbivudine was stopped 1 month after delivery in mothers with immune tolerance (normal serum ALT at baseline) while other patients with elevated ALT levels at baseline continued to take telbivudine or another approved antiviral agent. A total of 94 patients were in the control arm of the study and did not receive telbivudine. All infants received HBIG within 12 h postpartum and the HBV vaccine. Telbivudine treatment was associated with a marked reduction in serum HBV DNA and HBeAg levels at postpartum week 28 as well as normalisation of elevated ALT levels before delivery. In addition, the incidence of perinatal transmission was significantly lower in telbivudine-treated mothers than controls (0% vs 8%; $p=0.002$). In all, 33% (44/135) of telbivudine-treated mothers and none (0%) of the control group had undetectable

HBV DNA levels. Importantly, no differences in adverse events were noted between the telbivudine-treated and control groups.

Another open label, prospective study enrolled HBeAg-positive patients with HBV DNA $>6 \log_{10}$ copies/ml and elevated ALT levels.⁵² Overall, 53 mothers received telbivudine starting in the second or third trimester, and 35 patients were in the non-telbivudine receiving control group. All patients were followed until postpartum week 28 and all infants received standard active and passive immunoprophylaxis after birth. After postpartum week 28, none of the infants whose mothers received telbivudine had immunoprophylaxis failure, whereas 8.6% of the infants born to mothers in the control group did ($p=0.029$). Added benefits of telbivudine therapy were that at postpartum week 28, significantly more patients had levels of HBV DNA below the lower limit of detection, normal ALT levels and higher HBeAg seroconversion compared with controls (58% vs none, $p<0.001$; 92% vs 71%; $p=0.008$; and 15% vs none; $p<0.001$, respectively). In addition, telbivudine therapy did not result in any adverse events in mothers or infants up to 28 weeks after delivery.

CHB in the peripartum and postpartum stages

Although pregnancy invokes a relatively immunosuppressed state, HBV reactivation during pregnancy has been reported but is very rare.⁵³ It is more often seen in patients with immunosuppression from cytotoxic chemotherapy, following organ transplantation and AIDS and occurs in a two-staged process.⁵⁴ Viral replication is enhanced when the immune system is depressed. Once the immune function is restored, there is a rapid immune-mediated destruction of HBV-positive cells. In pregnancy, increased oestrogen levels have been demonstrated to suppress HBV.⁵⁵ Additionally, cortisol levels rapidly return to the pre-pregnancy range. It has been hypothesised that this is analogous to immune reconstitution after therapeutic withdrawal of oral steroids and a combination of these factors may result in a flare in the postpartum phase.⁵⁶ It would seem prudent to treat HBV if the small chance of a clinically significant flare could be prevented. Unfortunately, the use of lamivudine in the third trimester does not prevent the risk of postpartum hepatitis⁵⁷ and up to a quarter of non-pregnant patients will experience clinical flare after stopping lamivudine although these are usually very well tolerated.⁵⁸

In the pregnant population, a retrospective study by ter Borg *et al* demonstrated that 62% of patients developed postpartum hepatitis after receiving lamivudine during the last 4 weeks of pregnancy compared with 36% in the control group.⁵⁷ In addition, the immune reconstitution that occurs in the first few months after pregnancy may also be responsible for the observation that 12.5%–17% of patients exhibit

HBeAg loss or seroconversion in the postpartum period.^{56–59} For this reason, women should be monitored closely after delivery for up to 6 months as an increase in ALT levels may precede HBeAg or HBsAg seroconversion. These flares in the postpartum phase are typically well tolerated, although there have been several reports of exacerbation of HBV after delivery and even cases of fulminant hepatitis.^{57–60}

MANAGEMENT OF CLINICAL SCENARIO

Hepatitis B infection in pregnancy presents many management challenges. Although there are defined guidelines about screening for hepatitis B in pregnancy and for the administration of active and passive immunoprophylaxis to infants born to HBsAg-positive mothers, there is an ongoing debate about the timing of initiation, duration and long term safety of antiviral therapies.

Despite the lack of consensus, it is possible to come up with an algorithm for the management of most patients with hepatitis B (see supplementary online figure S1) based on data that have been outlined in this review. Using this algorithm, our patient likely acquired hepatitis B by vertical transmission at the time of her birth as she is from an area of high endemicity. She is at a significant risk for failure of immune prophylaxis as she has a high viral load and is HBeAg positive. She would therefore be a good candidate for starting lamivudine or telbivudine in the third trimester of her pregnancy to prevent MTCT. This should only be done after extensive discussions about the risks and benefits of the medications and the rationale for initiating them is outlined to her. As she has normal ALT levels and no indication for long term therapy for her hepatitis B, her antiviral drug should be discontinued 4 weeks after delivery as per the clinical trials for these agents. However, she should be followed up closely in the postpartum period to monitor for any elevations in her transaminase levels after cessation of antiviral therapy. The newborn should receive HBIG and the first hepatitis B vaccine within 12 h of delivery. At follow-up, it should be ensured that the infant receives the full course of hepatitis B vaccine (administered at 1 and 6 months after delivery). In addition, the patient's husband, parents and close contacts should also be screened for hepatitis B.

SUMMARY

HBV infection during pregnancy represents a challenging clinical scenario with areas of uncertainty. Despite the low prevalence of birth defects seen with some antiviral agents, concerns remain about the long term safety of prolonged use of these drugs in pregnant patients. In addition, other side effects such as lactic acidosis and hepatic steatosis have been reported.⁶¹ The choice of antiviral agent should also be determined by the planned duration of therapy. In

situations where antiviral therapy is used in conjunction with immunoprophylaxis to reduce MTCT, lamivudine may be appropriate but if there is an indication to treat the mother for the long term, an alternative antiviral drug should be chosen due to the rapid development of drug-resistant HBV.⁶¹ There is also no consensus about the viral load at which antiviral therapy should be initiated to reduce the risk of MTCT. Historically, clinical trials used 8 log₁₀ copies/ml as the threshold for high viral titres but there is increasing evidence that there is a significant risk of MTCT in HBeAg-positive patients with viral loads of >6 log₁₀ copies/ml and using this as the cut-off for starting antiviral therapy results in decreased MTCT. Ultimately, physicians and pregnant patients with HBV infection need to agree on an individually tailored treatment plan after carefully evaluating the risks and benefits of therapy.

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Search strategy We searched PubMed (from January 1966 to the present) for publications containing the terms 'hepatitis B in pregnancy' in combination with 'liver disease' and 'vaccination'. We selected publications mainly from the past 10 years, but did not exclude important older publications.

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