**RESEARCH**

# Hepatitis B in pregnancy

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## ABSTRACT

**Objective** Vertical transmission of the hepatitis B virus (HBV) is the commonest mode of infection and can be prevented with immunoprophylaxis of the infant and antiviral therapy in the mother. Our aim was to review a cohort of subjects with HBV in pregnancy to determine the prevalence of active disease or high HBV-DNA levels that required treatment to prevent transmission, and to review the management of mothers and infants.

**Methods** A retrospective case-note review was conducted of all the HBV-infected pregnant women and their infants who attended the Newcastle obstetric services from 2007 to 2011.

**Results** There were 113 pregnancies in 81 women (median age 28 years; 15% hepatitis B e antigen (HBeAg) positive) during 2007–11. 71% of mothers were first diagnosed with HBV during pregnancy. The mothers were born in 28 different countries. 69% of mothers had an HBV-DNA level less than 2000 IU/mL and 13% had HBV-DNA levels greater than $1.0 \times 10^7$ IU/mL so would be eligible for antiviral therapy to prevent transmission to the infant. 9% had active eAg-positive HBV and 3% had active eAg-negative HBV requiring treatment. All infants born to HBeAg-positive mothers received hepatitis B immunoglobulin (HBIG) appropriately and 76% of infants received a full HBV vaccination course. One infant born to an HBeAg-negative mother was hepatitis B surface antigen positive 1 year post-delivery.

**Conclusions** One in six women had active HBV requiring treatment or high HBV-DNA levels that would benefit from antiviral treatment to reduce the transmission risk. HBIG was administered appropriately but completion of the vaccination course was suboptimal.

## INTRODUCTION

Chronic Hepatitis B virus (HBV) infection affects approximately 400 million individuals worldwide.[1–4] It is estimated that without therapy 15–40% of patients will develop serious complications related to chronic HBV including cirrhosis, liver failure and hepatocellular carcinoma,[5] and there are an estimated 620 000 HBV-related deaths each year worldwide.[6] The worldwide prevalence of chronic HBV infection varies widely, with 8–10% of the population being affected in high prevalence areas (China, other parts of Asia, sub-Saharan Africa and the Amazon basin). Overall, the UK is an area of low endemicity, with an estimated hepatitis B surface antigen (HBsAg) prevalence of 0.3%,[7] but prevalence rates are much higher in individuals migrating from endemic countries. A recent study found that 8.7% of the British-Chinese and 3.1% of the Pakistani community of the north east of England were chronically infected with HBV.[8]

Mother to infant (vertical) transmission from an HBV-infected mother is the commonest mode of transmission worldwide and accounts for 50–60% of chronically infected patients. It is estimated that up to 25% of these patients die prematurely from the complications of chronic HBV infection in later life (cirrhosis, liver failure, liver cancer).[9 10] The risk of perinatal transmission of HBV is related to maternal HBV-DNA levels and the hepatitis B e antigen (HBeAg) status of the mother. Without immunoprophylaxis, vertical transmission occurs in 70–90% if the mother is HBeAg positive.[11] This is reduced to 40% if the mother is HBeAg negative.[12] Overall, vertical transmission is reduced to 5–10% with appropriate active and passive immunoprophylaxis (hepatitis B vaccination for all plus hepatitis B immunoglobulin (HBIG) if the mother is HBeAg positive). However, in infants born to mothers with high HBV-DNA levels, despite immunoprophylaxis 8–32% of infants develop perinatal infection.[13–15]

In order to reduce perinatal transmission of chronic HBV, antenatal screening

for HBV was introduced in the UK in 2000 and immunoprophylaxis is given to infants born to HBV-infected mothers. It is recommended that all infants born to HBV-infected mothers should receive HBV vaccination at birth and complete a four-dose course.[16] Babies born to highly infectious mothers should receive HBIG within 24 h of delivery as well as active immunisation.

Recent studies have demonstrated that treatment with lamivudine[17] [18] or telbivudine[19] [20] in the third trimester significantly reduces the risk of transmission in mothers with a high HBV-DNA level. As a result, the British Viral Hepatitis Group (BVHG) and the National Institute for Health and Care Excellence (NICE) recommend treating mothers with an HBV-DNA level greater than $10^7$ IU/mL with oral antiviral agents in the third trimester to reduce further the risk of transmission.[21] [22]

Little is currently known about the demographics of patients with hepatitis B in pregnancy in the UK and what proportion of patients have active disease or who require antiviral treatment in pregnancy to reduce transmission risk. Our aim was to review our cohort of subjects with HBV in pregnancy to determine the prevalence of active disease or high HBV-DNA levels that require treatment. In addition, our aim was to review the management both of mothers during pregnancy and the mothers and infants postpartum.

## METHODS

This was a retrospective study reviewing the management for all HBV-infected pregnant women who attended the Newcastle obstetric services between 2007 and 2011. This patient review was registered and approved by the hospital clinical audit department. Patients were identified from the obstetric blood-borne virus database that keeps demographic data for all pregnant women who are infected with a blood-borne virus. The medical notes for all HBV-infected pregnant mothers were reviewed and data collected on: patient demographics; HBV, hepatitis C virus, hepatitis delta virus and HIV serology and virology results; biochemical results; management pre and post-delivery and antiviral treatment. When mothers had more than one pregnancy, data about the mothers were collected from the first pregnancy. Medical records of all infants born in 2008–11 (not just first pregnancies) were also reviewed to determine whether HBV vaccination and HBIG were administered appropriately.

The normal range for ALT in our centre is 0–40 IU/L for women.

HBV disease activity was defined into five groups based on European Association for the Study of the Liver (EASL) guidelines 2012:[3]

- The immunotolerant phase with HBeAg positivity, high HBV-DNA, ALT less than 40 IU/L and no/minimal liver necroinflammation or fibrosis.

- The immune active HBeAg-positive phase with HBV-DNA greater than 20 000 IU/mL, elevated or fluctuating aminotransferases (ALT >40 IU/L) and moderate or severe liver necroinflammation or fibrosis (METAVIR A2–3 and/or F2–4).
- The inactive carrier state with low or undetectable viral replication (HBV-DNA <2000 IU/mL), ALT <40 IU/L and no/minimal fibrosis.
- The active HBeAg-negative phase with fluctuating viral replication (HBV-DNA >2000 IU/mL) and aminotransferases (ALT >40 IU/L) with moderate/severe liver inflammation and or fibrosis (METAVIR A2–3 and/or F2–4).
- Indeterminate disease activity patients who had either HBV-DNA greater than 2000 IU/mL with ALT less than 40 IU/L or HBV-DNA less than 2000 IU/mL with ALT greater than 40 IU/L.

## RESULTS

### Demographics of the cohort
There was a total of 113 pregnancies in 81 HBsAg-positive women during the period studied. Eighty (99%) were referred to the viral hepatitis service. Twenty-one (26%) women did not attend more than one of their clinic appointments. The median age of the women at first pregnancy was 28 years (range 18–40 years). Fifty-eight (72%) mothers were first diagnosed with HBV through antenatal screening. The uptake of testing for HBV is 96% nationally in the UK, which means the majority of HBV-infected individuals are likely to be identified.[23] The mothers were born in a total of 28 different countries (figure 1).

### Virology and biochemical results
All women had their HBeAg/antibody status checked. Twelve subjects (15%) were HBeAg positive and anti-HBe negative, 69 (85%) were HBeAg negative and 64 (79%) were hepatitis B e antibody (HBeAb) positive. The median ALT level was 18 IU/mL (range 5–203, IQR 14). A breakdown of the serum ALT levels in the cohort is shown in table 1.
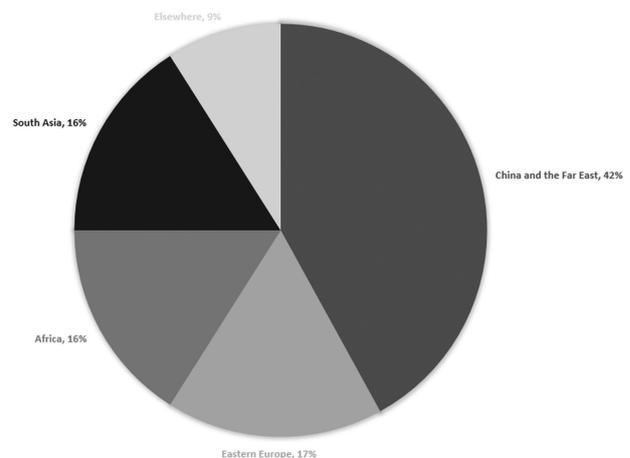


**Figure 1** Countries of birth.

## Table 1  Breakdown of the ALT values in the cohort

| | |
|---|---|
| <20 IU/mL | 42 (54%) |
| 20–40 IU/mL | 24 (31%) |
| 41–80 IU/mL (<2×ULN) | 5 (6%) |
| >80 IU/mL (>2×ULN) | 7 (9%) |

ULN, upper limit of normal.

Sixty-seven (92%) patients who attended clinic had their HBV-DNA levels tested during their first pregnancy including all the HBeAg-positive patients. The median HBV-DNA levels was 150 IU/mL (range <20 to >7.2×10$^8$ IU/mL, IQR 7879). Of the patients who had their HBV-DNA tested in pregnancy, 46 (69%) had an HBV-DNA level less than 2000 IU/mL, 12 (18%) had HBV-DNA levels between 2000 and 1.0×10$^7$ IU/mL and nine (13%) had HBV-DNA levels greater than 1.0×10$^7$ IU/mL. A breakdown of the patients by disease activity (based on EASL guidelines) is shown in table 2.[3] If the new 2013 NICE definitions of active HBV (using ALT cut-off of 19 IU/mL) were used, 11 (92%) of the HBeAg-positive patients and four (7%) of the HBeAg-negative patients would be characterised as having active HBV.

Two patients were co-infected with HIV. One patient was hepatitis C virus antibody positive but RNA negative and three patients were hepatitis delta antibody positive, but RNA negative. Nine (13%) women had HBV-DNA levels greater than 1.0×10$^7$ IU/mL so would have been eligible for antiviral treatment in the third trimester of pregnancy to reduce the risk of vertical transmission according to the BVHG and NICE guidelines.[21 22] If a lower threshold of 2×10$^5$ IU/mL was used for treatment to prevent transmission of HBV to the infant, 12 (18%) would have been eligible to receive antiviral therapy. Two patients received antiviral therapy with tenofovir during pregnancy. One woman co-infected with HIV was started on Truvada (emtricitabine and tenofovir) and Kaletra (lopinavir and ritonavir) at 24 weeks' gestation with a viral load of 1.7×10$^8$ IU/mL. The viral load dropped to 4.5×10$^5$ IU/mL on treatment but rose again due to poor compliance and treatment was stopped. One woman was started on tenofovir in the third trimester due to high viral load (1.8×10$^8$ IU/mL) to reduce the risk of transmission.

### Postpartum

Of those with inactive HBV, 23% had a postpartum flare in their ALT (defined as greater than or equal to doubling of baseline ALT or rise in ALT to >40 IU/mL). The highest ALT was 52 IU/mL. All patients settled spontaneously. There was no rise in the viral load associated with the increase in ALT for any of the women.

There were six women with eAg-positive immunoactive chronic HBV. Four were not treated as their ALT normalised (three genotype B, one genotype C). Two of them underwent a Fibroscan as a surrogate marker for fibrosis (results 3.8 and 5.1 kPa) (table 3).

### Care of infants

Data were available for infants born from 2008 to 2011. From a total of 99 pregnancies, data were available for 76 (77%) infants. All 15 infants born to HBeAg-positive mothers were given HBIG at birth. Fifty-eight (76%) infants received a full vaccination course and 14 (19%) received three doses. Only 35 (55%) of the 64 infants who should have had their post-vaccination status checked to date have had this completed. Thirty-four (97%) had an adequate response to vaccination with anti-HBs levels greater than 10 IU/mL. One infant (who only received three vaccinations) is HBsAg positive with a viral load of 5.4×10$^3$ IU/mL. The mother was HBeAg negative and HBeAb positive with a viral load of 1.7×10$^3$ IU/mL.

Of the nine infants born to women with HBV-DNA greater than 1×10$^7$ IU/mL, all received HBIG appropriately and a full four-dose course of vaccination. Eight infants had their post-vaccination serology testing and all of them had an adequate response to the vaccine.

### DISCUSSION

The present study represents a 'real life' experience of the management of patients with hepatitis B in pregnancy in the UK. A key finding of the study was that more than one in six of the patients seen had active HBV requiring treatment or had high HBV-DNA levels and would benefit from antiviral treatment to reduce the risk of transmission to the infant. This emphasises the importance of ensuring that all HBV-positive mothers are seen during the pregnancy by a team experienced in the management of patients with viral hepatitis. In our cohort, the majority (99%) of HBV-infected pregnant women are referred to tertiary hepatitis services. However, a high proportion did not attend appointments and efforts to improve attendance need to be intensified. In the present study, we did not explore the reason for non-attendance at appointments, but it is likely that a major reason is the language barrier as a high proportion of patients with HBV have

## Table 2  A breakdown of the mothers by HBV disease activity[3]

| Phase of disease | Number | eAg status | Viral load (IU/mL) | ALT (IU/mL) |
|---|---|---|---|---|
| Immunotolerant | 6 (9%) | +ve | High | <40 |
| Immune active HBeAg +ve | 6 (9%) | +ve | >20 000 | >40 |
| Inactive carrier | 42 (63%) | −ve | <2000 | <40 |
| Active HBeAg −ve | 2 (3%) | −ve | >2000 | >40 |
| Indeterminate | 11 (16%) | | Either viral load >2000 with ALT <40 or viral load <2000 with ALT >40 | |

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

**Table 3** Patients with active disease who received treatment

| Disease activity | Genotype | ALT (IU/mL) | Viral load (IU/mL) | Fibroscan result (kPa) | Liver biopsy (METAVIR) | Treatment |
|---|---|---|---|---|---|---|
| eAg +ve active CHB | C | 81 | $1.7 \times 10^8$ | 4.2 | A1 F1 | Pegasys IFN postpartum |
| eAg +ve active CHB | C | 119 | $1.7 \times 10^8$ | 16.3 | A3 F4 | Tenofovir postpartum |
| eAg −ve active CHB | C | 203 | $3.7 \times 10^5$ | 5.1 | A2 F1 | Tenofovir postpartum |
| eAg −ve active CHB | E | 122 | $1.9 \times 10^4$ | 9.1 | A1 F3 | Tenofovir postpartum |

CHB, ; eAg, e antigen; IFN, interferon.

migrated to the UK and English is not their native tongue. It is therefore essential that HBV-infected mothers receive appropriate education about HBV on diagnosis.

The WHO have recommended global vaccination against hepatitis B since 1992. In the UK there is no universal vaccination programme for HBV, but all mothers are offered screening for HBV (and HIV) during pregnancy. The risk of developing chronic HBV is related to age at the time of infection, with the highest rates in individuals acquiring the infection perinatally (up to 90% develop chronic infection).[24–27] High serum HBV-DNA levels and HBeAg positivity are the most important risk factors for perinatal transmission of HBV to an infant. UK guidelines recommend that all infants born to HBV-infected mothers are vaccinated against HBV at birth to reduce transmission risk. In addition, HBIG is given to HBeAg-positive mothers or HBeAg-negative mothers with HBV-DNA levels greater than $1.0 \times 10^6$ IU/mL as they are at highest risk of transmission.[16] However, immunoprophylaxis fails to prevent transmission of HBV to the infant in 8–32% of cases and the majority of these occur in mothers with high serum HBV-DNA levels.[13–15] Randomised controlled trials have demonstrated that perinatal transmission can be significantly reduced by treating mothers with a high viral load with oral antiviral agents (lamivudine or telbivudine) in pregnancy. The first study by Xu et al[28] showed that, in addition to immunoprophylaxis, treatment with lamivudine from week 32 of pregnancy to 4 weeks postpartum in mothers with HBV-DNA levels greater than $2 \times 10^8$ IU/mL significantly reduced infant HBsAg seropositivity rates compared with immunoprophylaxis alone (18% vs 39%, respectively). More recently Han et al[19] showed that telbivudine treatment starting between weeks 20 and 32 of pregnancy in mothers with HBV-DNA levels greater than $2 \times 10^6$ IU/mL reduced transmission from 8% to 0%. In that study all infants also received HBV vaccination and HBIG as is current practice in the UK. Currently, the BVHG recommend treating mothers with a HBV-DNA level of over $1.0 \times 10^7$ IU/mL with oral antiviral medications in the third trimester to reduce the risk of transmission to infants.[21] In the present study only two patients received treatment with tenofovir during pregnancy. This was mainly due to the fact that part of the study period pre-dated the BVHG recommendations being introduced in 2008. Five of the nine eligible women were pregnant before the implementation of the guidelines. The other two women who were eligible for treatment after the introduction of the guidelines were treated postpartum (one with interferon and one cirrhotic woman with tenofovir). Our study does indicate that 13% of mothers seen would be eligible to receive antiviral treatment for this indication. NICE guidelines recommend the use of tenofovir, over lamivudine and telbivudine in pregnancy as tenofovir is a more potent drug and has less propensity to cause resistance.[22 29–31] In addition, tenofovir has been used extensively in patients with HIV and a registry of over 1000 pregnant mothers exposed to tenofovir has demonstrated no increase in birth defects compared to a control population.[32]

The optimum maternal serum HBV level for the recommendation of antiviral treatment in pregnancy to prevent perinatal transmission is not yet clearly established. However, there is increasing evidence that the risk of vertical transmission remains high with viral loads greater than $2 \times 10^5$ IU/mL so it may be appropriate to institute treatment at lower HBV-DNA levels to prevent transmission.[33 34] A Chinese study retrospectively assessed a cohort of HBV mothers whose infants were all given immunoprophylaxis with vaccination and HBIG to determine immunoprophylaxis failure rates according to maternal serum HBV-DNA levels. In that study there was a significant positive relationship between immunoprophylaxis failure rates and maternal HBV-DNA levels (0%, 3.2%, 6.7% and 6.7% for viral loads of <6, 6–6.99, 7–7.99, >8 $\log_{10}$ copies/mL, respectively).[35] Therefore, all failures in that study were in mothers with HBV-DNA levels greater than $2 \times 10^5$ IU/mL (>6 $\log_{10}$ copies/mL), which suggests that a lower HBV-DNA threshold than is currently recommended by the BVHG and NICE guidelines for the treatment of pregnant mothers might be more appropriate, but this requires further evaluation in a controlled trial.[21 22] If the threshold of over $2 \times 10^5$ IU/mL was used to recommend antiviral treatment in pregnancy then 18% of our cohort would have been eligible for treatment. Interestingly though, the one immunoprophylaxis failure in our study occurred in a mother whose HBV-DNA level was $1.7 \times 10^3$ IU/mL, which is well below recommended thresholds for antiviral treatment. Clearly, transmission of HBV can occur in

utero, intrapartum or postpartum and the mechanism of transmission in this case is not known.[36]

In this study, four (5%) women were treated post-partum for active disease. Interestingly, this rate was higher than a previous study from Birmingham, UK, in which only 1% of postpartum women had active disease requiring treatment. The reason for this is not clear as the patient demographics in both studies were similar.[37] Of note, if the new NICE definitions of active disease were used (ALT >19 IU/mL) then more of our patients (92% of HBeAg positive and 7% of HBeAg negative) would be eligible for treatment if the ALT remained persistently elevated.

In the present study, 71% of the mothers were first diagnosed with HBV in pregnancy, which suggests that a large proportion of patients with HBV are undiag-nosed in our population. A recent case finding study of more than 1000 individuals in the north east of England using dry blood spot testing found that 8.7% of the British-Chinese and 3.1% of the Pakistani com-munity had undiagnosed HBV, including individuals with active disease requiring treatment.[8] In order to address this issue, recent NICE guidelines (UK) have recommended case finding in primary care for indivi-duals at increased risk of HBV,[38] which it is hoped will lead to the early diagnosis and treatment of HBV.

In the present study HBIG was administered appro-priately to the infants at highest risk of vertical trans-mission of HBV. However, completion of the four-dose HBV vaccination in infants was suboptimal postpartum (76% completed the full course) and post-vaccination testing was inadequate (55%). While we clearly need to improve these figures, they compare favourably with a study assessing HBV vaccination uptake in London, which found only 49% of infants received a full vaccination course and 33% of infants have post-vaccination testing.[39]

As a result of this review of our practice the Health Protection Agency is now collecting data prospectively on all infants born to HBV-positive mothers. This will improve the accuracy of the information recording for this patient group and ensure that administration of the complete vaccination course is given to all infants. Currently, family doctors are responsible for the administration of vaccinations and post-vaccination testing. A central 'reminder system' has now been introduced to advise family doctors 2 weeks before each vaccination dose is due. If infants still do not receive their vaccination a nominated health visitor will investigate further to ensure it is completed appropriately. Many infants do not have follow-up serology taken to determine whether they have acquired HBV and whether the vaccination has been successful in producing anti-HBsAb. In part this might be due to the need for a blood sample being drawn from the baby, which can be distressing for the infant, mother and phlebotomist. In order to address this, dry blood spot testing has been introduced, which we

think will be a more acceptable method of obtaining blood from the infant and should lead to increased testing rates. Dry blood spot testing is a well validated method for HBsAg, anti-hepatitis B core antibody and anti-HBsAb testing.[40 41]

In conclusion, the present study shows that a high proportion of mothers with HBV in pregnancy have high HBV-DNA levels or active disease and would therefore benefit from treatment to prevent transmission of HBV to their infant or disease progression. It is there-fore essential that all HBV-positive mothers are thor-oughly assessed during pregnancy to determine whether they need treatment.

## What is already known in this topic?

▶ Mother to infant (vertical) transmission is the com-monest mode of Hepatitis B transmission worldwide.
▶ The risk of transmission is highest in HBeAg positive mothers and those with high HBV DNA.
▶ The risk of vertical transmission is reduced to 5-10% with active and passive immunoprophylaxis.
▶ Antiviral therapy in the 3rd trimester reduces trans-mission risk in mothers with high HBV DNA levels (>1×107 IU/ML).

## What this study adds?

▶ More than 1 in 6 women had active disease or high HBV DNA levels and would benefit from antiviral treatment to reduce the transmission risk or treat active hepatitis.
▶ Hepatitis B Immunoglobulin was administered appro-priately to reduce transmission risk.
▶ There was suboptimal completion of the vaccination course and follow-up serology testing in infants.
▶ Attendance at hepatitis clinic appointments was poor.

## How might it impact on clinical practice in the fore-seeable future?

▶ All Hepatitis B positive pregnant women should be referred to viral hepatitis services for assessment.
▶ Efforts to improve attendance at hepatitis clinic appointments need to be intensified.
▶ Our procedure for delivering the vaccination course and post-vaccination testing of infants has changed to ensure this is completed.

patients. JW was instrumental in data collection. AT and EM assisted in patient identification and data collection. SM, MV, MH and MB reviewed the manuscript and managed the patients.

**Ethics approval** This patient review was registered and approved by the hospital clinical audit department.

**Patient consent** Not required.

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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