Ante-natal screening and post-natal follow-up of hepatitis B in the West Midlands of England

S. BHATTACHARYA, K. O’DONNELL, T. DUDLEY, A. KENNEFICK, H. OSMAN, E. BOXALL and D. MUTIMER

From the University Hospital Birmingham, Edgbaston, Birmingham B15 2TH, Birmingham, UK

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Summary

Background: We established at Queen Elizabeth Hospital in Birmingham a post-natal follow-up care service for hepatitis B virus (HBV) positive women diagnosed through ante-natal screening.

Aim: Virological and clinical follow-up of HBsAg positive mothers detected through ante-natal screening in Birmingham.

Design: Retrospective observational study.

Method: We evaluated 117 post-natal mothers with chronic HBV infection between April 2003 and December 2006. Patients were first seen at least 3 months post-delivery and followed up.

Results: Most of the women were of Asian or African origin (107 of 117 patients). Five out of 117 (4%) patients had undergone serum HBsAg clearance by the time of post-natal review, and 112 patients had persisting HBsAg-positivity (seven HBeAg positive and 105 HBeAg negative). HBeAg positive women were younger than HBeAg negative patients (median 21 vs 30-years old). Fifty percent of HBeAg negative women had detectable serum HBV DNA at the time of initial review. HBeAg positive women had higher serum HBV DNA titres than those negative for HBeAg (median 40 million copies/ml vs 4323 copies/ml). The majority of patients had normal serum transaminases. A single case of clinically significant liver disease was identified in a woman with HBV and delta virus infection.

Conclusion: Very few women who were diagnosed with chronic HBV infection at ante-natal screening have clinical evidence of liver disease. However, many have high levels of virus replication and remain at risk for the future development of liver disease.

Introduction

Hepatitis B virus (HBV) continues to be a major global public health problem. Recent analyses of the epidemiology of HBV in England and Wales highlighted the overwhelming contribution of migration to the prevalence of infection in the UK. Birmingham is the second largest city in the UK (population of approximately 1 million, 2001 census) and has an ethnically diverse population (29.6% of the City’s population are from an ethnic group other than white). Ante-natal screening for HBV (usually done between 11 and 20 weeks) is aimed at preventing mother to child transmission of the virus. Pregnant women are an essential target for screening when selective instead of universal infant vaccination is UK national policy. However, the implications of detecting an HBV-infected pregnant woman go beyond prevention of transmission of infection to the neonate. Follow-up has typically focused on the child, and the mother’s infection may be forgotten. The Liver Unit at the Queen Elizabeth Hospital in Birmingham introduced a service in April 2003 for post-natal follow-up and management of HBV positive women identified at routine ante-natal screening. Prior to the development of this service general practitioners (GPs) of the women were notified by the maternity unit and it was left to
the discretion of the GPs to arrange follow-up and referral of the women for specialist assessment.

In this article, we report the experience of this service from its establishment in April 2003 to December 2006. The objective of our study was to evaluate the post-natal follow-up service for HBV positive women diagnosed through the ante-natal screening programme. The women were screened for HBV at ante-natal clinics in five Birmingham hospitals.

**Patients and methods**

**Public health management**

This was principally the responsibility of the Community Hepatitis B Nurse Specialist (CHNS). Link midwives in each ante-natal clinic would notify the CHNS when a diagnosis of HBV infection was made. The CHNS then contacts with the patient and arranged to see her at home or in the ante-natal clinic. The purpose of the home visit was to counsel the patient and family about HBV, and to offer contact screening and vaccination of household members (if the patient agreed). Blood was taken from children older than 5 years, and younger children were referred to relevant paediatric departments for HBV screening. The CHNS was also responsible for reviewing the HBV serology results and for GP liaison to establish a plan of action for subsequent management of the family (vaccination of non-immune at-risk contacts and referral of contacts with established HBV infection). In addition, GPs were advised that direct referral of the index case (the HBV-positive pregnant woman) had been made to the Liver Unit, and that an outpatient appointment was scheduled for ~3 months post-delivery. The CHNS maintained a database of all HBsAg-positive women. In addition to those women identified and then referred to the Liver Unit via the CHNS, a few referrals were made to the Liver Unit by GPs and consultant obstetricians from hospitals in the West Midlands other than the five covered by the remit of ante-natal link nurses and CHNS.

**Post-natal management of the HBV positive women at Liver Clinic**

Patients were referred to the Consultant Hepatologist by the CHNS. The initial hospital consultation was with the Hepatitis Nurse Specialist (HNS). The specialist nurse saw the patients at their first Liver Unit appointment (3 months post-delivery), took a structured history, provided further education and counselling (with the help of an interpreter if needed), and organized blood tests (full blood count, liver function tests and hepatitis B serology—HBsAg, HBeAb, HBeAg, HBcAb, HBV DNA titre). The patients included in our study were not routinely tested for HCV antibodies either during the ante-natal screening programme or during the post-natal follow-up. HCV testing was done selectively in a few patients and only if clinically indicated. Antibody testing for delta virus (HDV) infection was also done selectively in few patients (unexplained liver function abnormality and previous residence in a high endemic area for HDV, i.e. Central Africa or Eastern Mediterranean region). Patients were reviewed 6 weeks later with these results by the Consultant Hepatologist.

**Laboratory methods**

Liver biochemistry including serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by standard methods. Viral serology for HBV was done by AxSYM automated immuno-assay system (Abbott Diagnostics, Berkshire, UK). All sera positive for HBsAg were confirmed by repeat testing at a reference laboratory. HBV quantitative PCR was done using Cobas Amplicor HBV monitor test (Roche Diagnostics, UK) or Cobas Ampliprep/Cobas Taqman HBV test (Roche Diagnostics, UK). Up to May 2005, HBV viral load results were expressed as copies/ml. Subsequently results were changed to IU/ml. To maintain uniformity of results all HBV quantitative PCR reported in IU/ml were converted into copies/ml per millilitre using appropriate conversion factor (1 IU/ml = 5.26 copies/ml in the Cobas Amplicor assay and 5.82 copies/ml in the Taqman assay). For patients having viral load above the upper limit of detection of the assay (7.6 x 10^6 IU/ml in the Cobas Amplicor assay and 1.1 x 10^9 IU/ml in the Taqman assay) the upper limit of the assay was taken as the viral load. The lower limit of the quantitative HBV PCR assays has changed with time. It was 1000 copies/ml in early 2003, then 300 copies/ml until May 2005 when the units were changed to IU/ml. With the current Taqman assay it is 54.2 IU/ml, whereas it was 60 IU/ml with the Cobas Amplicor assay.

**Statistical tests**

The mean and median were calculated using the free online software from www.graphpad.com

**Results**

The HBsAg positivity rate among ante-natal population in the five Birmingham hospitals during the
period of evaluation was 0.59% (390 patients out of 66,422 women from July 2003 to June 2006). Among them a total of 205 women patients were referred to the Liver Unit (Figure 1). Those patients who were already seen by specialists or were difficult to contact (usually through changes to accommodation, as many are new to the UK) were not referred. Altogether, 281 children lived in the households of the 205 mothers. Of 205 identified, only 117 (57%) had attended the Liver Unit at the time of this analysis—37 patients (18%) were awaiting an appointment and 51 (25%) patients did not attend the clinic despite being offered appointment and sent reminders. The drop out rate was therefore 51 out of 168 patients (30%). Despite this drop out rate the home visits by the community hepatitis B nurse specialist (CHNS) compensated to some extent the public health consequences of HBV infection in terms of screening of contacts and vaccination of susceptible contacts. The majority of the patients were of Asian (including South Asian and Chinese Asian) or African origin (Asian 74, African 33, Afro-Caribbean 3, and Eastern European 7). The mean age of the 117 women was 29.5 years (median 29 years; range 18–51 years). The mean number of children among the 117 mothers who attended the liver clinic was 2.4 (median 2) (Table 1).

Five of 117 (4%) patients had undergone HBsAg seroconversion by the time of first outpatient review. Of 112 patients with persistent serum HBsAg positivity, seven patients were HBeAg positive and 105 HBeAg negative. HBeAg positive women tended to be younger (median age 21 years; range 19–29 years) than those who were HBeAg negative (median 30 years; range 18–51 years).

A significant proportion (50%) of HBeAg-negative women had detectable serum HBV DNA at the time of their first appointment. HBeAg positive women had higher serum HBV DNA titres (median 40 million copies/ml; range $5.6 \times 10^5$ to $6.4 \times 10^8$ copies/ml) than those negative for HBeAg (median 4323 copies/ml; range 262 to $7.5 \times 10^5$ copies/ml).

At first Liver Unit appointment, 13 patients had serum HBV DNA titres greater than 100,000 copies/ml—eight from the Indian subcontinent (South Asian) and four were from the Far East (China and Vietnam) and one from Middle East (Yemen). Seven of 13 were HBeAg positive and six HBeAg negative. Only 2/13 had elevated serum ALT (one of these patients also had coarse echo-texture of the liver on ultrasound scan). Most of the patients with HBeAg positive infection (five out of seven) and none with HBeAg negative infection had HBV DNA titres in excess of 1 million copies/ml in their first visit.

Serum transaminases (ALT and AST) were normal in most women. Only 15 of 112 patients had ALT greater than the upper limit of normal (ALT > 41 U/l) at the first visit (mean ALT of those patients with abnormal ALT 67 U/l). AST was abnormal (>41 U/l) in only 5/15 with elevated ALT (mean AST of those patients with abnormal AST 45 U/l). Most of the patients with raised serum ALT (13/15) were HBeAg negative. Five of 15 underwent ultrasound scan (USS) of the liver (three normal and two abnormal) and one of these consented to liver biopsy (this patient from the Congo was found to have cirrhosis due to HBV and delta virus infection). Eight of 15 had undetectable DNA. The median serum HBV DNA titre of the remaining seven patients was 7710 copies/ml (range 2300 to $6.4 \times 10^5$ copies/ml).
Figure 2 plots serum ALT versus serum HBV DNA titre at time of first outpatient consultation. There was no correlation of DNA titre with serum ALT in HBeAg-positive or HBeAg-negative infection. Of 15 patients with elevated serum ALT, eight were serum HBV DNA negative (below the detection threshold of the PCR assay). None of the HBeAg-negative patients with serum HBV DNA >10^4 copies/ml had an elevated serum ALT. Thus, serum ALT had a poor correlation with HBV DNA titre in this population.

In total, 15 women underwent USS of the liver (principally for raised ALT and/or high or increasing serum HBV DNA). Five were found to be abnormal (described as coarse echo texture in four, nodular echo texture in one, irregular edge in one). Liver biopsy was recommended but only two patients underwent biopsy—mild chronic inflammatory change without fibrosis was present in one, and the other had established cirrhosis (see above, confirmed delta virus infection).

Following the initial assessment and review, annual or biannual follow-up was recommended for all patients. Routine liver function tests and serum HBV DNA titres were measured at each review. Figures 3 and 4 demonstrate the serum HBV titres measured for women who have attended for second and third outpatient reviews (and for each DNA measurement compares the value with that measured for the same patient at the time of initial outpatient assessment). The figures demonstrate the significant fluctuation of viral titre for patients with HBeAg-negative infection. For a given patient, greater than 2 log variation was commonly observed. For three patients, HBV DNA was undetectable on one occasion but as high as 10^4 or 10^5 copies/ml on another occasion. There was a tendency of HBV titres to decrease with time (Figure 4).

Discussion

Notifications for hepatitis B have been steadily increasing in England and Wales (435 in 1990 and 1151 in 2003) and in the West Midlands region (30 in 1990 and 80 in 2003). In England and Wales, notification among females has risen from 175 in 1990 to 469 in 2003. In England, in 2005, 383 antenatal women (0.26%) were found to be HBsAg-positive.5,6

At our clinic for HBsAg-positive women identified at ante-natal screening, we saw 11 patients in 2003, 16 in 2004, 46 in 2005 and 45 in 2006. The largest number of referrals was directly via the Community Nurse Specialist (105 women), and an additional 12 referrals came from GPs and local consultant obstetricians.

In the UK, ante-natal screening for HBV has become the standard of care.3 All babies born to
HBV-positive mothers are vaccinated. In addition, babies of highly infectious mothers (HBeAg positive) also receive Hepatitis B immunoglobulin (HBIG). This is because the transmission rate from mother to babies depends on HBeAg status and HBV DNA positivity. In a study by Song et al., the rate of HBV immunoprophylaxis failure was 0%, 21% among the children born to HBeAg-seronegative, HBeAg-seropositive mothers, respectively. Immunoprophylaxis failure was significantly associated with detectable maternal HBV DNA.

The guidelines from the UK’s Department of Health uses HBeAg and HBeAb status of the mother to determine the immunization schedule for the baby (HBV vaccine only, or vaccine with immunoglobulin). Currently, HBIG is only indicated if HBeAg is positive or HBeAg and HBeAb are negative—there were three such patients in our cohort. However, HBeAg is a surrogate marker of infectivity that has good positive predictive value, but poor sensitivity for identification of patients with high serum titres. For example, in our study population, six HBeAg negative mothers had HBV DNA titres in excess of 100,000 copies/ml and 14 had titres >10,000 copies/ml.

Although some countries like the United States recommend administration of vaccine and HBIG to the offspring of all mothers who are HBsAg positive, there is little evidence at the moment to support the use of this combination in preventing perinatal transmission from HBeAg negative mothers. A study in Taiwan showed that when combined vaccine and HBIG is used in babies of HBeAg negative mothers there is higher geometric mean titre (GMT) of antibody to HBsAg (anti-HBs) at 2 months post-immunization but a lower GMT of anti-HBs at 7 months compared to those babies who received vaccine only. There was also no difference in the breakthrough infection in the two groups. The loss of immunological memory is more likely in those given HBIG.

We have previously reported the occurrence of fulminant hepatic failure in the infants born to highly infectious mothers with HBeAg-negativity. It has been postulated that transplacental transmission of HBeAg may be responsible for neonatal immune tolerance with subsequent susceptibility to chronic HBV infection. Perinatal infection, occurring in the absence of immune tolerance (as might be observed when the HBeAg is absent), may be more likely to cause significant hepatitis, occasionally acute liver failure. Under these circumstances, the use of HBIG with vaccination may be justified to further reduce the risk for neonatal infection. Further randomized studies in HBeAg negative mothers using vaccine with or without immunoglobulin would be useful. Neonatal hepatitis B is very unusual and would require a huge study to establish effective outcome.

All HBsAg-positive pregnant women were seen by the CHNS. This nursing role was established to improve the care offered to HBV-positive mothers and to their families. Many women were recent migrants to this country and few had been diagnosed with HBV before the ante-natal visit. Many had young children that were born in the country of origin before migration to the UK. Many lived within extended families. The CHNS was able to offer appropriate counselling, screening for HBV and vaccination of susceptible household members. Patients were offered direct referral to the specialist Liver Unit, and the majority came to clinic. The CHNS was able to provide advanced notice about the need for and nature of translation services that would be required in clinic. This was arranged prospectively, and enabled the clinic HNS to provide additional counselling and explanation to the patient and family. In addition, the plan of investigation and purpose of blood tests could be adequately explained to the patient.

Guidelines for the management of patients with chronic HBV infection have been published by a number of learned societies and associations.

### Table 1  Liver function and virological profile of 112 post-natal women attending liver unit

<table>
<thead>
<tr>
<th></th>
<th>HBeAg Pos (n=7)</th>
<th>HBeAg Neg (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Median (Range)</td>
<td>21 (19–29) years</td>
<td>30 (18–51) years</td>
</tr>
<tr>
<td>ALT: Median (Range)</td>
<td>27 (15–66) U/l</td>
<td>23 (9–116) U/l</td>
</tr>
<tr>
<td>Normal</td>
<td>5 patients</td>
<td>92 patients</td>
</tr>
<tr>
<td>AST: Median (Range)</td>
<td>24 (16–42) U/l</td>
<td>23 (15–102) U/l</td>
</tr>
<tr>
<td>Normal</td>
<td>7 patients</td>
<td>100 patients</td>
</tr>
<tr>
<td>HBV DNA titre: Median (Range)</td>
<td>39 976 000 (562 820–640 200 000) copies/ml</td>
<td>4323 (262–746 920) copies/ml</td>
</tr>
<tr>
<td>HBV DNA undetectable by PCR</td>
<td>Nil</td>
<td>53 patients</td>
</tr>
</tbody>
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*aOn 52 patients with detectable DNA in plasma.*
For instance, recommendations from the American Association for the Study of Liver Diseases suggest that patients chronically infected with HBV should be monitored (clinically, biochemically and virologically) on a regular basis (6–12 monthly) for HBeAg seroconversion, and considered for liver biopsy in case of persistent or intermittent elevation of transaminases. These guidelines are basically in agreement with the recommendations of the European Viral Hepatitis Educational Initiative (EVHEI). None of the HBeAg-positive women underwent HBeAg seroconversion during follow-up. Increased aminotransferase concentrations have been associated with mortality from liver disease. In the population that we report, there was a dissociation of serum ALT and serum HBV DNA titre. Most patients with elevated HBV DNA had normal serum transaminases, and most with elevated serum transaminases had low serum HBV titre. Hence, liver biopsy was recommended for few. For many patients, the serum HBV DNA titres fluctuated, sometimes by as much as 3 logs. The association of serum HBV titre with later complications of liver disease, including cirrhosis and liver cancer, has been reported in a number of studies. Clearly, these patients require ongoing review and periodic re-evaluation for evidence of viral replication and liver disease.

It is predicted that some of these will eventually develop complications of chronic HBV infection. Unfortunately, it is difficult to identify with accuracy those patients within the cohort who may eventually die of liver complications. Lifelong surveillance will be necessary for all.

Conflict of interest: None declared.

References