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ARTICLE

Lamivudine treatment and outcome in pregnant women with high hepatitis B viral loads

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Abstract Perinatal transmission is the most common mode of hepatitis B virus (HBV) transmission and is a leading cause of chronic infection worldwide. Maternal treatment with lamivudine (LAM) can result in a rapid and significant reduction in HBV viral load (VL) and, thus, mitigate the risk of mother-to-child transmission (MTCT). The aim of this study was to retrospectively evaluate the safety of LAM treatment administered in the third trimester of pregnancy and determine the influence, if any, on infant outcome. The medical charts of all HBV surface antigen (HBsAg)-positive women eligible for treatment with LAM and who registered for antenatal care between 2007 and 2012 were retrospectively reviewed. During the 6-year period, 45 women met the criteria for LAM treatment. Thirty-six women (80 %) accepted treatment; the remaining women declined treatment (5), defaulted from care (3) or transferred to another maternity unit (1). The median duration of treatment was 11.4 weeks (range 5.3–17.4) and the median baseline VL was 1.4×10^8 IU/mL (range 1.8×10^7–1.7×10^8). The median VL at delivery was 2.3×10^5 IU/mL and 60 % of women achieved a VL reduction >2 log10 IU/mL before delivery. No cases of perinatal transmission occurred in the infants born to mothers who received treatment; however, one infant, born to a mother who defaulted from care, was HBV-infected at 8 months. The results suggest that LAM therapy in highly viraemic HBV-infected pregnant women could lower the rate of vertical transmission.

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Introduction

Chronic hepatitis B (CHB) affects 350 million people worldwide [1]. Perinatal transmission of hepatitis B virus (HBV) is a major problem in endemic areas, including Asia and Africa [2], and approximately 85–95 % of vertically infected infants will become chronic HBV carriers [3]. Increased migration of populations from countries of high prevalence into low-prevalence countries means that the prevention of perinatal transmission is now a global concern. Transmission can be prevented by the vaccination of at-risk infants. However, despite this, perinatal transmission still occurs in a small proportion (5–10 %) of infants who have received complete active–passive immunisation [4, 5]. High maternal viral load (VL), intrauterine transmission and escape mutants have been associated with vaccine breakthrough [6, 7]. It has also been suggested that maternal infection with HBV genotype C may confer a greater risk of immunoprophylaxis failure [8].

Treatment with lamivudine (LAM), a nucleoside analogue and reverse transcriptase inhibitor, can result in a rapid and significant reduction in HBV VL [9–11]. A randomised trial of LAM versus placebo showed a reduction in HBV vertical transmission from mothers who received LAM and had a decrease in VL of 2 logs or greater [5]. LAM is considered a pregnancy Category C medication by the U.S. Food and Drug Administration (FDA) and, therefore, there was no evidence of teratogenicity in animal studies. A recently published analysis of more than 10,000 cases from the US Antiretroviral Pregnancy Registry (APR) concluded that LAM use in pregnancy was not associated with an increased risk of birth defects [12]. Furthermore, LAM use in pregnancy has been shown to be cost-effective in the prevention of vertical transmission of HBV [13].

The Rotunda Hospital, located in Dublin's inner city, is one of the three largest maternity hospitals in Ireland. In addition to providing routine antenatal care, the Rotunda serves as a referral centre for high-risk pregnancies. With over 9,000 deliveries per year, the Rotunda accounts for 31–33 % of deliveries in Ireland in a given year, hence maternal infections in pregnancy are well represented. During a 10-year period (2001–2011), 89,571 women registered for their antenatal care at the Rotunda. In this time, 788 women were HBV surface antigen (HBsAg)-positive, giving a seroprevalence rate of 0.88 % in the antenatal population.

Based on the association between higher HBV VL and risk of perinatal transmission, in 2007, a treatment protocol was initiated to offer LAM to women with high HBV VL (>17 million IU/mL). Treatment with LAM commenced in the third trimester (~32 weeks gestation) and was discontinued after delivery. The aim of this study was to retrospectively evaluate the safety of LAM treatment administered in the third trimester of pregnancy and determine the influence, if any, on infant outcome.

Materials and methods

Patients

For this study, data were analysed for 6 years from January 2007 to December 2012, inclusively. Case notes were retrospectively reviewed for all HBsAg-positive women eligible for treatment with LAM, defined as: patients with VL >17 million IU/mL (the upper limit of detection at the start of the study period), no hepatitis co-morbidities identified and no evidence of decompensated liver disease. LAM therapy (100–150 mg/day) was commenced at 32 weeks gestation and discontinued immediately following delivery. All infants received hepatitis B immunoglobulin (Hepatect) 0.4 mL/kg IV over ~5–10 mins immediately after delivery, along with the first dose of HBV vaccine. Subsequent HBV vaccines were administered with the routine infant immunisation schedule by the infants' primary healthcare provider at 2, 4 and 6 months of age. Infants were followed up at 8 months of age (2 months post final vaccine) to assess HBV serology.

Biochemical and virological assessments

HBsAg, anti-HBs, HBeAg and anti-HBe titres were measured with the Abbott ARCHITECT i4000SR system (Abbott Diagnostic Laboratories). HBV VL was measured by real-time polymerase chain reaction (PCR; COBAS AmpliPrep/COBAS TaqMan 48, Roche Diagnostics or RealTime HBV, Abbott Molecular Diagnostics). The HBV genotype and LAM drug resistance were determined using the INNO-LIA HBV Genotyping and Multi-DR (Innogenetics) assays, respectively.

Liver function tests and HBV VL determinations were conducted on all patients at baseline, monthly during treatment and during follow-up postpartum following discontinuation of LAM. Genotypic anti-viral resistance investigations were performed on 28 of 36 women who received treatment to identify the emergence of resistance, which could impact on future treatment regimes. The complications of CHB and adverse effects of LAM treatment were also recorded, along with delivery outcome.

Results

Baseline patient characteristics

During the six years from 2007 to 2012, 452 hepatitis B-infected women registered at the Rotunda Hospital for their antenatal care and 45 women (10 %) met the criteria for LAM treatment as described. Thirty-six women (80 %) accepted LAM therapy. Of the remaining nine women, five declined treatment, three failed to attend the hepatology/infectious diseases clinic for treatment before 32 weeks gestation (i.e. defaulted from care) and one woman transferred to another maternity unit.

The median age of those in receipt of treatment was 26 years and the majority of these women were of Asian descent (Table 1). One-third of the treated women were newly diagnosed HBV infections and all women tested were HBeAg-positive. In addition, six women were anti-HB core IgM-positive, suggestive of active infection. The median baseline VL was 1.4×10^8 IU/mL (range 1.8×10^7–1.7×10^8). HBV genotypes B and C were the predominant genotypes, accounting for over 70 % of cases, and women infected with HBV genotype B had a significantly higher baseline VL compared to those infected with genotype C ($1.1 \times 10^8 \pm 2.2$ vs. $4.4 \times 10^7 \pm 3.0$ IU/mL, $p=0.03$).

Table 1 Patient characteristics at baseline

Characteristic	Treated women (n=36)
Age, years	26 (16–40)
Ethnic origin	
Asian	26 (72)
Gestation at booking (weeks)	14 (9.7–23.6)
HBV newly diagnosed	12 (33)
HBeAg-positive	36 (100)
Anti-HB core IgM	6/28 (21)[a]
HBV DNA (log10 IU/mL)	8.15 (7.25–8.23)
Alanine aminotransferase (ALT), IU/mL	30.5 (7–174)
ALT × ULN	0.71 (0.16–4.05)
HBV genotype	
B	14 (38.9)
C	12 (33.3)
D	4 (11.1)
E	1 (2.8)
N/A	5 (13.9)

Data are shown as number (%) or median (range), as appropriate

ULN= upper limit of normal; 43 IU/mL

[a] Results not available in all cases, revised *n* given as denominator in table

The median serum alanine aminotransferase (ALT) level was 30.5 IU/mL (range 7–174). There was no association between ALT levels and HBV genotype. The median duration of LAM treatment was 11.4 weeks (range 5.3–17.4) and all women ceased treatment at or just before delivery.

Impact of third trimester LAM treatment on VL, ALT and viral resistance

Delivery and postpartum VL was available for 35/36 and 21/36 women who received LAM therapy, respectively. The median HBV DNA level closest to delivery was 2.3×10^5 IU/mL (range 2.5×10^3–1.3×10^8), which represented a significant decrease from baseline values ($p<0.001$). The mean decrease was 2.3 log10 IU/mL (range 0.12–4.48). Sixty percent of the women achieved a greater than 2 log decrease (median treatment duration of 13 weeks; range 6–17 weeks). There was no association between genotype and the reduction in VL. After cessation of treatment postpartum, the median VL increased to 9×10^7 IU/mL (range 4.0×10^4–9.0×10^9) (Fig. 1).

The median serum ALT decreased from a baseline of 30.5 IU/mL (range 7–174) to 16.5 IU/mL (range 8–99) at delivery and then increased to 34.5 IU/mL (18–574) postpartum. Eight women who received LAM treatment had elevated ALT levels at baseline (>43 IU/mL), of whom five and four remained above the upper limit of normal (ULN) at delivery and postpartum, respectively. Two women with normal serum ALT levels at baseline increased to 60 and 64 IU/mL at delivery, respectively, while four women with normal ALT at both baseline and delivery developed elevated serum ALT levels postpartum (48, 49, 260 and 371 IU/mL, respectively). In total, 5 of the 26 women who had liver function testing postpartum experienced an "ALT flare" (defined as 3× ULN) (range 3.14–13.35 ×ULN).

LAM was well tolerated and no adverse effects due to treatment or complications due to HBV infection were experienced during this period. Good compliance was reported in all but one patient, who misunderstood medical instruction and ceased LAM therapy two days prior to delivery. Genotypic anti-viral resistance testing was carried out on 28/36 women at their postpartum visit. In all cases, wild-type strains were identified.

Neonatal outcome

Table 2 summarises the neonatal outcome. There were 34 live births to 34 treated women and two women transferred to another maternity unit prior to delivery. All 34 infants were born at term (>37 weeks gestation) and 26 % (n=9) were delivered by Caesarean section. The median birth weight of infants born to treated mothers was 3.5 kg (range 2.3–4.7). Follow-up serology at 8 months was not available for all infants in the cohort—this was mainly due to mothers returning to their country of origin after delivery. Of 34 treated mothers, 21 had serology following completion of immunisations and no infant was infected.

In contrast, amongst the nine women who also met the criteria for LAM treatment at registration but did not receive treatment for reasons outlined previously, one infant out of six followed up at 8 months was HBV-infected. This infant was born to a mother who defaulted from care for most of her pregnancy.

Discussion

The risk of perinatal transmission is largely dependent on the maternal VL. A study of 313 chronically infected women and their infants showed a transmission rate of 9 % to infants born to mothers with HBV VL>10^8 copies/mL [14]. Indeed, Zou et al. reported a linear correlation between immunoprophylaxis failure rate and maternal VL. In their evaluation of 1,043 mother–infant pairs, the highest rate of transmission (7.6 %) was noted when the maternal VL pre-delivery was >10^8 copies/mL. The corresponding transmission rate was 0 % when the maternal VL was <10^6 copies/mL [15]. In the present study, LAM was found to be effective in reducing HBV DNA in all patients and no adverse effects or complications caused by LAM therapy were observed in either mothers or infants. The median VL at delivery was

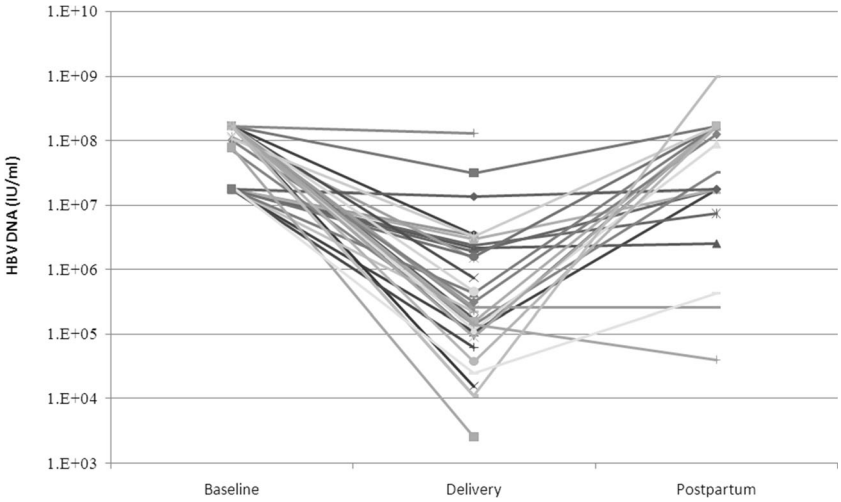

Fig. 1 Hepatitis B virus (HBV) DNA levels at baseline, delivery and postpartum for women (n= 36) treated with lamivudine (LAM)

2.3×10^5 IU/mL, with 60 % of women achieving a VL reduction >2 log10 IU/mL before delivery. This compares favourably to a recently published meta-analysis of 15 randomised controlled trials in which LAM was administered to pregnant women. This analysis identified maximal benefit when LAM was administered in the third trimester of pregnancy and when the maternal VL decreased to $<10^6$ copies/mL [16]. In our study, treatment was offered to all HBV-infected women with an HBV DNA VL >17 million IU/mL. While this achieved satisfactory results in our cohort, a review of 63 articles and abstracts by Pan et al. on the prevention of mother-to-child transmission (MTCT) of HBV recommends initiating third trimester treatment in all HBsAg-positive mothers with HBV DNA levels above 200,000 IU/mL [6].

There have been conflicting reports on the influence of genotype on virologic response to LAM, with some studies reporting a superior response against HBV genotype B compared to genotype C [17, 18], while other research has shown no difference between the two [19, 20]. In the current study, although patients infected with HBV genotype B had a significantly higher baseline VL, there was no association between genotype and the relative reduction in VL achieved with treatment.

The emergence of resistance is a well-documented problem with longer term administration of LAM [21, 22]. This concern is minimised with our protocol due to the short duration of the treatment in the third trimester of pregnancy and no LAM resistance was identified postpartum in our cohort. Despite this, it is essential to monitor the development of resistant mutants postpartum to inform treatment options in subsequent pregnancies.

To determine the extent of liver inflammation, serum ALT was determined at baseline, delivery and postpartum. Elevations >3× ULN in serum ALT or "ALT flares" at initiation (treatment flares) and cessation (withdrawal flares) of LAM therapy are not uncommon [23, 24]. Treatment flares are generally asymptomatic and occur during the first weeks of treatment as VL rapidly decreases. Withdrawal flares usually occur 4 to 12 weeks post therapy and can be severe, symptomatic and lead to liver decompensation. In our cohort, the ALT levels had declined at delivery versus baseline. Serum ALT increased in >90 % of cases postpartum and 20 % of the cohort experienced an ALT flare. This is less than the incidence reported by yer Borg et al., where postpartum ALT flares were observed in 62 % of LAM-treated women [25]. The lower incidence observed in our study may be due to the shorter follow-up period, but also serves to highlight the importance of continuity of care from maternity to adult hepatology or infectious diseases services.

Since July 2008, HBV vaccination has become part of the national immunisation schedule for all babies born in Ireland. This incorporates hepatitis B vaccination into the routine schedule given at 2, 4 and 6 months. In this study, all infants followed up at 8 months had completed the active–passive immunisation schedule. No cases of MTCT occurred in the infants born to mothers who received treatment; however, one

Table 2 Neonatal outcome

	Infants born to mothers who received LAM therapy (n=34)
Gestation at delivery (weeks)	39.7 (37.4–41.4)
Gender: male	18 (53)
Weight (kg)	3.5 (2.3–4.7)
Caesarean delivery	9 (26.5)
Infant HBsAg-positive at 8 months	0/21 (0)[a]

Data are shown as number (%) or median (range), as appropriate

[a] Results not available in all cases (six babies were lost to follow-up, seven babies had moved to China); revised n given as denominator in table

infant, born to a mother who did not receive LAM therapy, was HBV-infected at 8 months. This HBV-positive baby was born to a mother who, despite meeting the criteria for treatment at initial registration, defaulted from antenatal care for much of the third trimester of pregnancy and, so, LAM therapy could not be offered or commenced at 32 weeks gestation.

There are some limitations of the present study. Firstly, not all infants had follow-up at 8 months to ascertain their HBV serology. As this was mainly due to emigration out of Ireland, there is little we could have done to improve the infant follow-up rate. Secondly, the follow-up period of mothers post delivery is shorter than the follow-up period presented elsewhere. Future studies may extend this follow-up period to provide long-term safety data on LAM use in pregnancy.

The results of this study are especially salient in light of recent publications which propose the selective use of antiviral prophylaxis in hepatitis B-infected pregnant women, especially those with high VL [26, 27]. Short-course treatment with LAM is safe and efficacious, with no development of resistance. Such a strategy might be optimal for women with high VL, as well as those who are deemed to be at risk of defaulting postpartum from infant follow-up for necessary HBV vaccination.

In conclusion, the results presented here suggest that LAM therapy in highly viraemic HBV-infected pregnant women could lower the rate of vertical transmission. In addition, treatment was well tolerated and no adverse events or outcomes were reported. The development of resistance to LAM is a potential risk and, although no mutant strains were identified, where available, testing should be done upon cessation of treatment to inform future therapeutic strategies.

Conflict of interest The authors declare they have no conflict of interest.

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