Perinatal management of hepatitis B virus: Clinical implementation of updated Australasian management guidelines

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Abstract

Objective: To evaluate the implementation of the 2013 Royal Australian and New Zealand College of Obstetricians and Gynaecologists 'Management of Hepatitis B in Pregnancy' guideline.

Methods: Retrospective cohort study of the clinical management and obstetric outcomes among hepatitis B virus-positive women in a single tertiary maternity hospital. Women with viral load $>200,000$ IU/ml were referred to a specialised clinic for consideration of tenofovir disoproxil fumarate therapy to reduce mother to child transmission.

Results: A total of 11,496 women gave birth during the study period, of which 101 (0.9%) women were hepatitis B virus positive. Viral load was measured in 99 (98%) of 101 hepatitis B virus-positive women; 30 (30%) had a viral load $>200,000$ IU/ml. Twenty-six women accepted tenofovir disoproxil fumarate; of these, 23 had a successful virological response (viral load $<200,000$ IU/ml before delivery).

Conclusions: Adherence to updated management guidelines and patient acceptance of tenofovir disoproxil fumarate in our Australian population were high when provided in the context of a dedicated perinatal service.

Keywords

Hepatology, perinatal medicine, infectious diseases, gastroenterology, drugs (medication)

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Introduction

Mother to child transmission (MTCT) of hepatitis B virus (HBV) is a major contributor to the global healthcare burden of chronic HBV infection. The risk of becoming chronically infected is inversely proportional to the age of exposure with 90% of perinatal transmissions leading to chronic HBV infection. Approximately half of the 350 million people infected worldwide acquired HBV through MTCT.^{1,2} In Australia, 0.4%–1.3% of pregnant women are chronically infected with HBV.³ Despite the current measures to prevent perinatal transmission – active and passive immunisation of the newborn – the rates of perinatal transmission in Australia remain in the order of 7%–9%.⁴

Standard immunoprophylaxis for babies born to HBV-positive mothers consists of hepatitis B immunoglobulins (HBIGs) and HBV vaccine around the time of birth. However, failure of newborn immunoprophylaxis – defined as persistent infant infection at 9–12 months despite HBIG and completed HBV vaccination⁵ – occurs in up to 30% of infants born to mothers with a highly infective HBV profile.⁶

The two greatest risk factors for MTCT of HBV are (i) high maternal viral load (VL; HBV DNA $\geq 200,000$ IU/ml) and (ii) HBV e-antigen (HBeAg) positivity.^{1,4,7–12} There appears to be considerable scope for improvement in the antenatal care of women with HBV in Australia. A report on clinical practice during the period 2006–2011 revealed rates of HBeAg and VL testing of only 33% and 20%, respectively.³ In 2013, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) issued an updated statement on the management of HBV in pregnancy, with a new recommendation for VL testing of all HBV-positive women.¹³ It recommended that women identified as high risk of newborn prophylaxis failure due to high VL be considered for third trimester anti-viral therapy (AVT) for the prevention of MTCT. Recent evidence from a well-conducted randomised controlled trial now supports the practice of third trimester maternal treatment with tenofovir disoproxil

fumarate (TDF) for the reduction of MTCT for women with a VL $>200,000$ IU/ml.¹²

The aims of this study were (i) to evaluate the clinical implementation of the updated 2013 RANZCOG recommendations in an Australian tertiary maternity hospital, (ii) to determine the proportion of HBV-positive women who met indications for AVT and (iii) to assess the acceptability and compliance with AVT in our antenatal population.

Patients and methods

A tertiary maternity hospital in Melbourne, Australia, introduced a comprehensive antenatal and postpartum care plan for HBV-positive pregnancies in late 2013 to comply with Australasian guidelines published by RANZCOG.¹³ Under this protocol, all antenatal women are screened for HBV surface antigen (HBsAg) as per traditional practice. HBsAg-positive women are then assessed with liver function tests (LFTs), and HBeAg, HBV e-antibody, hepatitis D virus (HDV), hepatitis C virus (HCV), hepatitis A virus (HAV) and human immunodeficiency virus (HIV) testing. The HBV DNA threshold for offering AVT treatment is $>200,000$ IU/ml (6 log copies/ml).¹³ Women with HBV DNA above this threshold were referred to a perinatal infectious

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diseases clinic to discuss AVT in the third trimester. Women who were eligible for AVT had antenatal care provided by an infectious disease specialist and a maternal fetal medicine specialist for the remainder of their pregnancy. The women who accepted AVT were given (i) 300 mg TDF daily commencing at 30–32 weeks (ii) repeat HBV VL tested at 4–6 weeks post commencement of AVT and (iii) repeat VL around the time of delivery. TDF was continued until six to eight weeks postpartum, and cessation was medically supervised in the perinatal clinic with LFT monitoring.¹⁴ At each review, women were asked about any side effects experienced since commencement of TDF, and these were recorded in their antenatal history. A severe adverse drug event was defined according the Therapeutic Goods Administration of Australia: inability to work, death, birth defects, danger to life, hospital admission/prolonged hospitalisation or increased investigation/treatment costs.¹⁵

In line with recent literature, ALT levels five times the upper limit of normal constituted a hepatic flare.¹⁶ Local laboratory thresholds determined that >33 U/L were considered abnormal, with >165 U/L constituting hepatic flare.

Neonates continued to received the standard full post-exposure prophylaxis protocol (100 IU HBIG and H-B-VAX II 5 µg within 12 h of birth) prior to discharge. Women were given a hospital-developed written patient information pamphlet about TDF and were supported to breastfeed whilst on AVT.

Patient data were extracted from the Birthing Outcomes System (BOS), a confidential electronic hospital database, for all deliveries ≥20 weeks' gestation for the 24 months from January 2014 to December 2015 inclusive. Confinements were analysed according to maternal HBsAg status as recorded in BOS. Manual review of patient medical records was performed on all women coded as "HBsAg-positive", "HBsAg unknown" or with no recorded HBsAg status in BOS.

Detailed maternal and newborn outcomes were collected on all HBV-positive women, including HBV viral replicative status. In line with recent literature, we defined high VL as >200,000 IU/ml, and effective AVT was defined as VL <200,000 IU/ml prior to delivery.

Infant birth weights were adjusted for gestational age (GA) at delivery using the hospital customised growth chart. Birth weights were grouped as small for GA (<10th centile), appropriate for GA (10th–90th centiles) and large for GA (>90th centile).

Descriptive statistics, including percentages, medians and means with standard deviations were generated for maternal demographics and birth outcomes. Chi-squared analyses and Fisher's exact test were used as appropriate. Statistical analysis was completed using SPSS software (version 22.0) with a *p* value of significance <0.05. Human Research Ethics Committee approval for this study was obtained from Mercy Health (ref. R15/48).

Results

Over the two-year study period, 11,496 women gave birth from 20 weeks' gestation, of which 11,409 (99.2%) had a recorded HBV screening result. There were 101 HBsAg-positive women, giving an overall prevalence of 0.9% (95% CI: 0.7%–1.1%).

Demographic characteristics

The demographic characteristics of the HBV-positive women and the general antenatal population are shown in Table 1. Compared with HBsAg-negative women, women who were HBsAg-positive were significantly younger, leaner, more likely to be born overseas and more likely to be cared for in a public rather than a private antenatal care model. The majority of HBV-positive women were non-Australian born (89%, *n* = 90). Most HBV-positive women were South-East Asian born (74%, *n* = 75), with China (50%, *n* = 50) and Vietnam

Table 1. Maternal demographic characteristics according to HBsAg status.

Maternal demographics	HBV negative	HBV positive	<i>p</i> value
Total confinements (<i>n</i>)	11,308	101	–
Age, mean (±SD), years	32.1 (±4.9)	30.7 (±5.2)	0.004
Ethnicity <i>n</i> (%)			<0.001
Australian born	7013/11,308 (62%)	11/101 (10.9%)	
Non-Australian born	4295/11,308 (38%)	90/101 (89.1%)	
Gravida, median (IQR)	2 (1–3)	2 (1–3)	0.08
Parity, Median (IQR)	0 (0–1)	0 (0–1)	0.14
BMI, mean kg/m ² (±SD)	25.3 (±5.6)	22.4 (±4.3)	<0.001
Mode of delivery <i>n</i> (%)			0.054
Caesarean	<i>N</i> = 3947 (34.9%)	<i>N</i> = 26 (25.7%)	
Elective	2047	17	
Emergency	1900	9	
Vaginal	<i>N</i> = 7361 (65.1%)	<i>N</i> = 75 (74.3%)	
Normal	5751	65	
Breech	18	0	
Instrumental			
Forceps	951	7	
Vacuum	641	3	
Care model <i>n</i> (%)	11,134 ^a	101	0.002
Any public care model	10,036 (90.4%)	100 (99.0%)	
Obstetric unit	2963	45	
Sharecare	1961	8	
Midwife	3805	34	
Perinatal medicine	566	13	
Maternity group practice	570	0	
Family birth centre	171	0	
Private obstetrician	1094	1	
No antenatal care	4	0	

^aData only available for 11,134 women.

(15%, *n* = 15) being the most frequently nominated countries of birth. Mandarin was the most commonly reported primary language (38%), with English, Vietnamese and Cantonese representing the other most frequently reported languages, 26%, 10% and 8%, respectively.

Of the available data regarding years since migration (*n* = 83), 37% had migrated within the last five years and 16% within the last year before delivery. Obstetric complications in the HBV-positive population included diabetes mellitus (*n* = 1), gestational diabetes (*n* = 9), obstetric cholestasis (*n* = 1), pregnancy induced hypertension (*n* = 2) and pre-eclampsia (*n* = 1).

The investigation and management of HBsAg-positive women are shown in Figure 1. An antenatal assessment of hepatic inflammation, using ALT, was performed in 100% of HBsAg-positive women. Thirteen women had mild ALT elevations and one had clinically relevant ALT warranting referral to specialist liver services. This patient had a low HBV VL, was HBeAg negative, and did not have obstetric cholestasis. Seven HBV-positive patients were on AVT pre-pregnancy with suppressed VL and continued their regular medication throughout pregnancy (five on TDF and two on lamivudine). These women were included in the HBsAg-positive with low VL cohort.

Among the 101 HBsAg-positive women, HCV, HIV, HAV and HDV testing was performed in 100, 99, 51 and 33 women, respectively. There were no co-infections recorded.

Figure 1. Flowchart of HBV management. *Two cases with no recorded HBV VL: (i) one was a private patient with incomplete antenatal records at this public facility and (ii) temporary visitor to Australia who delivered prematurely at 26 weeks prior to an infectious diseases evaluation. †Seven of these HBV-positive patients on tenofovir pre-pregnancy and continued throughout: five on tenofovir and two on lamivudine. All of these patients on anti-viral therapy pre-pregnancy had VL <200,000 IU/ml. ‡Declined tenofovir due to concerns about potential adverse fetal effects, secondary to seeking gastroenterology opinion. ¶Not offered due to (i) spontaneous reduction in VL below treatment threshold before third trimester, (ii) ongoing clinical input from partner hepatology unit with patient failure to adhere to recommendations for tenofovir and (iii) inappropriate risk stratification due to VL threshold misinterpretation. HBV: hepatitis B virus; MTCT: mother to child transmission; VL: viral load.

Women with high VL

Thirty (30%) patients of HBsAg-positive women had a VL >200,000 IU/ml, meeting criteria for AVT. Twenty-seven patients were offered third trimester AVT with TDF.

All 26 women treated with TDF began treatment at the commencement of the third trimester, mean GA 30.1 weeks (± 1.8). Twenty-four treated women had HBV DNA VL recorded after initiation of therapy, prior to delivery, and all but one had a successful treatment response by the time of delivery, (96%, 95% CI: 80%–99%; Figure 2). The patient who did not meet treatment target nevertheless demonstrated a reduction in VL reduction on AVT: 19,952,623 IU/ml (pre-treatment), 1,584,893 IU/ml (four weeks post-treatment) and 758,578 IU/ml (pre-delivery). Twenty-one women had successful virological response after four weeks of treatment.

AVT side effects

Approximately half ($n = 13$) of treated women experienced mild side effects (54%, 95% CI: 35%–72%), but there were no premature cessations prior to delivery due to severe adverse drug events. The most common side effects included nausea/vomiting, epigastric discomfort, dizziness/headache and fatigue. All of these except fatigue are documented as potential side effects in the pharmaceutical product

information. Most symptoms resolved within two weeks of commencing treatment. One patient ceased treatment at two weeks postpartum due to side effects, but AVT compliance had been consistent throughout until delivery.

Neonatal outcomes

Neonatal outcomes for infants born to HBsAg-positive and HBsAg-negative women are presented in Table 2. Compliance with HBV vaccination and immunoglobulin was high among all HBsAg-positive women. Ninety-eight (98%) of the 99 live-born infants completed post-exposure prophylaxis (PEP). The one infant without recorded PEP was delivered prematurely and transferred to another tertiary maternity hospital. All infants received PEP the same day as birth (<24 h), however, due to poor recording of administration time it is unknown how many received PEP within the recommended 12 h of birth. Among the HBsAg-positive women, TDF treatment was not associated with any significant difference in infant outcomes including mean birth weight ($p = 0.08$) or prevalence of small for gestational age (SGA) infant ($p = 0.3$).

The majority of infants born to HBsAg-positive mothers were discharged with a feed regime including breast milk ($n = 89$, 88%). There was no significant difference in the rate of breastfeeding between the HBsAg-positive women on TDF (21/26, 81%) and those not on TDF (68/73, 93%; $p = 0.15$).

Figure 2. Virological response to antiviral treatment in pregnancy ($n = 24$). Pre-Rx, Before antiviral treatment VL, viral load. One patient demonstrated a reduction in VL on tenofovir but still remained above 200,000 IU/ml at the time of delivery. Upper limit of VL assay was 7.3 log IU/ml, and most patients with high VL exceeded this upper limit; hence, the common pre-treatment VL is depicted in the figure. Only 19 data points are evident as six patients had results that overlay each other graphically. VL: viral load.

Table 2. Neonatal outcomes according to maternal HBsAg status.

Neonatal outcomes	HBV negative	HBV positive	<i>p</i> value
Mean gestational age, weeks ($\pm$ SD)	38.7 ($\pm$ 2.6)	38.4 ($\pm$ 3.4)	0.36
Mean birth weight, g ($\pm$ SD)	3289 ($\pm$ 678)	3188 ($\pm$ 686)	0.11
Birth status	<i>N</i> = 11,569	<i>N</i> = 102	0.12
Live born	11,518 (99.6%)	100 (98%)	
Stillborn during labour	43 (0.4%)	1 (1%)	
Stillborn prelabour	8 (0.1%)	1 (1%)	
Infant sex (<i>n</i>)			
Male	6018 (52%)	51 (50%)	0.9
Female	5545 (47.9%)	51 (50%)	
Indeterminate	6 (0.1%)	0 (0%)	
Discharge feed type	<i>N</i> = 11,423 ^a	<i>N</i> = 99 ^b	0.05
Breast only	10,792 (94.5%)	89 (89.9%)	
Formula only	631 (5.5%)	10 (10.1%)	

^aData only available for 11,423 neonates.

^bOnly 99 live infants at discharge.

Postpartum flare

Twenty-four of the 26 TDF-treated women returned to the hospital for a postpartum visit between six and eight weeks postpartum. Seven women had mildly elevated ALT (>33 U/L) and one had ALT levels meeting the definition of a hepatic flare (>165 U/L). This asymptomatic flare occurred in the setting of continued AVT until eight weeks postpartum, settled spontaneously and was of no clinical significance. For the small number of women who did not have a postpartum ALT performed by our hospital laboratory, all had a follow-up plan with their general practitioner or a gastroenterology service documented in their patient file.

Discussion

Our results show the effective implementation of new Australasian guidelines into practice, with VL testing being performed in 98% of HBV-positive women. This contrasts starkly with a prior study including our institution that showed that VL testing occurred in only 20% of HBV-positive pregnancies.³

While the 2014–2015 prevalence of HBV in our patient population (0.9%) was in keeping with that of the wider Australian population,³ a substantial proportion meet clinical criteria for AVT (30%), highlighting the importance of VL testing in all HBV-positive women. AVT was appropriately offered to, and accepted by, the vast majority of eligible women resulting in good virological response rates, no severe adverse drug events and no negative impact on breast-feeding rates. We attribute these excellent results to the support of a dedicated perinatal infectious diseases clinic, which provided continuity of care and expert advice on the use of AVT in pregnancy for these women.

TDF is the current first-line AVT for prevention of MTCT of HBV. Whilst several other agents have also been shown to reduce HBV VL,^{1,17,18} these agents vary in their potency, postulated long-term safety and propensity for inducing viral resistance. Extensive reassurance clinical experience with TDF for maternal HIV infection has been reported by the Antiretroviral Pregnancy Registry (www.apregistry.com).¹² One of the limitations of our study was our fixed study period, which did not contain sufficient numbers of women on TDF to assess its safety. While we observed no significant difference in SGA infants or formula-only feeding in HBV-positive women on TDF, compared to those not on TDF, our sample size only had sufficient power to detect an odds ratio of ≥ 10 in either outcome. We therefore cannot exclude a difference in fetal growth or breast-feeding rates in women on TDF.

As expected, our HBV-positive women were mostly of East/South-Eastern Asian origin. Recognition of the cultural and linguistic background of these women has prompted translation of the TDF patient information into Mandarin. The demographic characteristics of this population underscore the responsibility of maternity carers to ensure women are appropriately triaged and referred to long-term care postpartum. A recent position paper on HBV management in pregnancy emphasises the importance of interdisciplinary care for the provision of ongoing education and patient support in this chronic disease.¹⁹ Our local protocol sought to standardise this process through (i) referral to partner institution hepatology clinic, (ii) standardised letter to the general practitioner outlining diagnosis and treatment provided antenatally and (iii) translation of patient information into common languages. Despite all efforts, two patients on TDF did not attend for postnatal review at the hospital – highlighting the need to ensure adequate patient education and reliable follow-up arrangements prior to commencing women on therapy.

There was also some evidence of clinician confusion when interpreting various units of VL. Much of the early literature references HBV VL in copies per millilitre (copies/ml). The WHO has, however, standardised reporting to international units per millilitre (IU/ml).²⁰ These units can then be reported in a linear scale or in a log scale. The conversion between copies and IU, and linear and log units is the postulated reason that one patient with VL $>200,000$ IU/ml was not offered AVT. Standardisation in laboratory and research reporting should be addressed to minimise confusion in implementing research findings into clinical practice.

TDF therapy produced a positive virological response in $>90\%$ of cases. However, one of the limitations of our study was that we were unable to determine the actual rates of MTCT as long-term follow-up of the infants was not performed. Instead, for reasons of feasibility, we used viral suppression to $<200,000$ IU/ml as a surrogate measure of reducing MTCT risk.

Future areas for research include (i) surveillance for long-term effects on infants exposed to TDF in utero, (ii) maternal and infant engagement in long-term hepatology care and (iii) determination of the ideal duration

of AVT treatment postpartum. Recent studies have demonstrated that the extension of AVT into the postpartum period does not protect against hepatic flare, nor is this peak in hepatic inflammation of high clinical significance.^{16,21} Due to the incidence of side effects and very low incidence of hepatic inflammation postpartum, the current AVT regime lasting up to eight weeks postpartum may come into review in the future.

Our current practice of universal neonatal HBV vaccination is expected to greatly reduce the rate of chronic HBV in the Australian community. However, immigration patterns and our close proximity to areas of endemic HBV infection mean that chronic HBV infection in women of reproductive age will continue to be an important public health issue in obstetric medicine and neonatal care.

Conclusion

Updated Australasian guidelines on the management of HBV in pregnancy were readily implemented in a tertiary hospital setting with dedicated resources. The results of this study demonstrate that 30% of HBsAg-positive pregnant women in an Australian metropolitan population meet recommended criteria for AVT in third trimester, underscoring the importance of VL testing. AVT during pregnancy had high patient uptake and compliance rates with no negative impact on breast-feeding rates. The acceptability of AVT for reducing MTCT of HBV among our Australian metropolitan population is high when provided in the context of a specialist perinatal infectious diseases service.

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Ethical approval

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Guarantor

LH

Contributorship

All authors contributed to the intellectual planning and design of the study. HB collected and analysed the data and wrote the manuscript. LH supervised the data collection and analysis and assisted with the manuscript. LH, SW and GW reviewed the final manuscript for style and intellectual content.

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