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Mother to Child Transmission of Hepatitis B: Examining Viral Cut Offs, Maternal HBsAg Serology and Infant Testing

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Abbreviations:

HBV- Hepatitis B virus

CHB- Chronic hepatitis B

MTCT- Mother to child transmission

AVT- Anti-viral therapy

TDF- Tenofovir disoproxil fumarate

ROC- Receiver operating characteristic

NESB- Non-English speaking backgrounds

PPV- Positive predictive value

NPV- Negative predictive value

EASL- European Association for the Study of the Liver

AASLD- American association for the study of Liver Diseases

APASL- Asian Pacific Association for the Study of the Liver

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Abstract

Background/Aims: Anti-partum antiviral therapy in the setting of high viral load is recommended to prevent mother-to-child transmission of hepatitis B although recommended viral load cut-offs vary. Quantitative HBsAg has been proposed as an alternative screening strategy to identify high viral load in this setting. Guidelines suggest testing all infants for vaccine response and infection. We set out to re-examine viral load cut-offs; the predictive value of quantitative HBsAg and the need for follow-up infant testing in our cohort.

Methods: A retrospective cohort study of 469 HBsAg positive mother-baby pairs from two tertiary hospitals in Sydney was performed. Antiviral therapy (lamivudine or tenofovir disoproxil fumarate) was offered to women with viral load $\geq 6 \log_{10}$ IU/mL (high) from 32 weeks gestation. Transmission and vaccine response was analysed according to viral load. The utility of quantitative HBsAg in identifying high viral load was examined.

Results: Mother-to-child transmission only occurred in setting of high viral load, in 0.85% (1/117) of those who received antiviral therapy and in 8.66% (2/23) of those who chose not to. Quantitative HBsAg did not accurately identify high risk mothers $\geq 6 \log_{10}$ IU/mL. Infant vaccine response was 98.7% overall, and 99.4% when viral load was $< 6 \log_{10}$ IU/mL.

Conclusion: Antiviral therapy initiated at 32 weeks when maternal viral load is $\geq 6 \log_{10}$ IU/mL almost completely abrogates transmission. Quantitative HBsAg does not reliably predict high viral load. When maternal viral load is $< 6 \log_{10}$ IU/mL, high vaccine efficacy and zero transmission suggests testing infants is of little value.

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Keywords: Mother to child transmission; perinatal transmission, Antiviral therapy; Quantitative HBsAg; Maternal viral load, tenofovir, HBV, pregnancy

Key Points

- There were no MTCT when maternal viral load was $<6 \log_{10}$ IU/mL; AVT is not required.
- An effective cut off for AVT to prevent MTCT is $\geq 6 \log_{10}$ IU/mL when using standardised HBV DNA assays. For centres relying on in-house PCR, cut offs may vary.
- Quantitative HBsAg correlates weakly with viral load; there is no titre that can reliably identify HVL mothers.
- In view of excellent vaccine response and absence of MTCT, testing infants born to low risk mothers ($<6 \log_{10}$ IU/mL) appears unnecessary.

Introduction

Worldwide, there are 257 million people with chronic hepatitis B (CHB).¹ Untreated infection may lead to hepatocellular carcinoma or death from liver related sequelae in 15-45% of those affected. CHB is usually the result of mother to child transmission (MTCT) due to impaired immunological response and clearance.²⁻⁸ Despite immune-prophylaxis, up to 10% of babies from mothers with high viral loads (HVL) acquire HBV thus ante-partum anti-viral therapy (AVT) is recommended to reduce this.^{2, 4, 5, 9, 11-16}

The risk to the infant from AVT is expected to be small, although decreased bone mineral density in Tenofovir Disoproxil Fumarate (TDF) exposed infants (of HIV positive mothers) has been reported, and longer term follow-up of exposed infants is limited.¹⁷ In

addition there may be risks to mothers receiving AVT, with the possibility that maternal flare post-partum may be exacerbated. In addition, selection of drug resistant variants has been described following short term lamivudine treatment in this setting.^{14, 18-20}

The maternal viral load at which AVT is recommended is controversial. A large retrospective study by Zou et al of 869 infants from a single centre in Beijing reported MTCT to be 3.2%, 6.7% and 7.6% at viral loads of 6-6.99, 7-7.99 and $>8 \log_{10}$ copies/mL respectively (which using standard conversion factors approximate 5-5.9, 6-6.9 and $>7 \log_{10}$ IU/ml respectively).^{21, 22} Thus guidelines recommended consideration of AVT when viral load is above 200,000 IU/ml (approximately $5 \log_{10}$ IU/mL).²³⁻²⁵ Not all data supports such a low threshold. Yin et al reported transmission rates of 0%, 0.56% and 6.01% with maternal viral load of $<3 \log_{10}$ IU/mL, $3-6 \log_{10}$ IU/mL and $>7 \log_{10}$ IU/mL, respectively in a cohort of 1355 Chinese mother-baby pairs.²⁶ Similarly, Liu et al (reporting on 256 mother-baby pairs) found all HBV infected infants were from HBeAg positive mothers with a HBV DNA level $>6.75 \log_{10}$ IU/mL.²⁷ Reporting on 138 babies in a western setting, Wiseman et al found that MTCT was only seen when the viral load was above $\geq 7 \log_{10}$ IU/mL.¹⁰ This variation in reported threshold explains some variations in clinical guideline.

HBV DNA quantification may be the optimal method to predict transmission risk, yet the cost of performing the assay is high (estimated \$150 AU) and laboratory expertise may not always be available. HBsAg quantitation is a cheaper (\$15 AU) alternative to HBV DNA. In a large cohort from Taiwan, Wen et al reported a strong positive correlation between quantitative HBsAg levels and maternal viral load, and with MTCT. In that study, a HBsAg value $>4.1 \log_{10}$ IU/mL had sensitivity 100% and specificity 71.3% for predicting transmission.²⁸ Quantitative HBsAg levels have thus been proposed as an alternative to identifying women with a high risk for MTCT in recent EASL guidelines.^{3, 25} Data remains limited for such firm conclusions. The correlation is imperfect in other settings for reasons that may include variation with HBV genotype.^{3, 29}

The presence of HBeAg is a marker of high viral replication, and may have a role in predicting risk of MTCT and need for AVT.^{3, 11, 28-31} Mechanistically, HBeAg is transferred across the placenta and may influence fetal immunotolerance.^{2, 4, 29} Some

studies report transmission only when HBeAg is positive, although others have reported transmission from HBeAg negative mothers.^{4, 26, 29}

In this study we aim to clarify the HBV DNA threshold for MTCT by examination of a large western cohort. We determine the utility of serological assays in predicting HVL and thus who should be considered for AVT. Current CDC, NICE and NHMRC (Australian) guidelines recommend infants of HBsAg positive mothers be tested for HBsAg and anti-HBs between 9 to 18 months of age. The relevance of this recommendation, given current strategies to prevent MTCT, is examined.^{23, 32-37}

Method

A retrospective cohort study was performed examining all HBsAg positive mothers identified at routine antenatal screening and referred to two tertiary hospital Hepatitis Clinics in Sydney, Australia between 2008 and 2015.²⁴ The study was approved by the South Western Sydney Area Health Service Human Research Ethics Committee (HREC) at Royal Prince Alfred Hospital (RPAH) (Reference X14-0213 & HREC/09/RPAH/624). All mothers had given informed consent.

All mothers with viral load (second trimester testing) $\geq 6 \log_{10}$ IU/mL were offered AVT from 32 weeks gestation, based on our previous data of $7 \log_{10}$ IU/mL plus allowance down to 6 acknowledging variability in laboratory testing and/or patient preference after discussion of risk and benefit. The AVT regimen varied over the study period, initially using lamivudine 100mg from 2008 to 2010 and then TDF 300mg from late 2010 to 2015.

At birth, babies received HBV immunoglobulin (*Hepatitis B Immunoglobulin-VF – CSL Limited*) within 12 hours of delivery followed by the standard Australian Hepatitis B virus vaccination schedule (*either H-B-VAX II [thiomersal-free, 5 μ g recombinant HBsAg protein; CSL Biotherapies/Merk Sharp and Dohme] or ENERGIX-B [10 μ g recombinant HBsAg protein; Glaxo Smithkline]*) at 0, 2, 4 and 6 months of age. A majority of the babies received HBIG and the first vaccine within 4 hours prior to leaving the birthing unit (personal communication head of unit). Infants were tested for HBsAg and anti-HBs at least 3 months after completion of vaccination schedule. A negative HBsAg in

conjunction with an anti-HBs titre of >10 IU/L was considered a successful vaccine response. Immunocompetent persons who achieve anti-HBs concentrations >10 mIU/mL after preexposure vaccination have virtually complete protection against both acute disease and chronic infection even if anti HBs concentrations subsequently decline to <10mIU/mL.^{38, 39}

Maternal HBV DNA level was measured in real time by the COBAS Ampliprep/COBAS Taqman HBV Test (Roche Diagnostics GmbH, Mannheim, Germany) between 2008 and September 2009, and COBAS Ampliprep/COBAS Taqman HBV Test, v2.0 from October 2009. The dynamic range of the assay varied over the study period with lower limits of detection of 12 IU/mL and 20 IU/mL; lower limit of quantitation of 55 IU/mL and 20 IU/mL; and upper limit of quantitation from 110 million to 170 million IU/mL for the respective assays. For the purposes of logarithmic conversion, <20 IU/mL and <55 IU/mL were assigned values of 20 IU/mL and 55 IU/ml respectively, and undetectable was assigned a value of 10 IU/mL. Similarly, >110 million IU/mL and >170 million IU/mL were assigned values of 110 million IU/mL and 170 million IU/mL, prior to logarithmic conversion.

Quantitative HBsAg

Levels of HBsAg were quantified with the Roche Elecsys HBsAg II Quant test (Roche Diagnostics GmbH, Mannheim, Germany) in blood that had been stored at -20°C according to manufacturer's instructions by experienced and accredited laboratory staff.

Statistics

Statistical analyses were performed using Microsoft Excel (2013) and Graph Pad Prism 7 (2017). Fisher's Exact test (two-tailed) was used to analyse categorical values with p value ≤ 0.05 considered statistically significant.

Correlation between quantitative HBsAg levels and HBV DNA viral load was determined using Pearson's coefficient. The optimal quantitative HBsAg cut-off value to predict viral load was determined using the receiver operating characteristic (ROC) curve.

Results

Baseline Characteristics of HbsAg positive pregnant women

Five hundred and fifty-eight HBsAg positive women and their 642 babies were included in the study (Table 1). Seventy-four women gave birth twice during the study period, 4 women gave birth 3 times and two women gave birth to a set of twins. The median age was 30 years (range 15-44) and a majority were born in South East Asian countries with 62.6% (n=402) from non-English speaking backgrounds. Birth route was normal vaginal in 72.3% (n=464), by caesarean section in 20.6% (n=132), by instrumental delivery in 6.5% (n=42), and unknown for 4 pregnancies.

The majority had normal liver function with median ALT 19 (interquartile range 12). Thirty percent (n=192) were HBeAg positive. Viral load was $< 3 \log_{10}$ IU/mL in 55% (n=352) of women, $3-6 \log_{10}$ IU/mL in 19% (n=122), and $>6 \log_{10}$ IU/mL (high viral load) in 26% (n=168) (Figure 1.) Only 17(2.6%) of pregnant women had a viral load between 5 and $5.9 \log_{10}$ IU/mL, the zone of controversy regarding the need for AVT.

Mother-To-Child Transmission according to Viral load

Samples to determine MTCT was available in 469 of 642 infants. Loss to follow-up occurred in 142 (31%) infants from mothers with viral load $<5 \log_{10}$ IU/mL, 3 (17%) from viral load $5-5.9 \log_{10}$ IU/mL; 28 (16.7%) from viral load $>6 \log_{10}$ IU/mL. There was one infant death (Figure 2).

The majority of mothers with HVL were reported in the safety and efficacy study of TDF.⁹ Here we report MTCT in the entire cohort. Of the HVL mother, 117/140 (83.6%) elected to take AVT. MTCT occurred in 1/ 117 (0.85%) from an HBeAg positive mother whose baseline HBV DNA was $>8 \log_{10}$ IU/mL and despite reduction to $4.42 \log_{10}$ IU/mL at delivery, indicating compliance and effective AVT. The mode of delivery in this case was vacuum extraction. There was no fetal injury/abrasion documented.

Of the 23 HVL women who chose not to take AVT, there were two cases of MTCT (8.66%) (p=0.07). Baseline maternal viral load was $>8 \log_{10}$ IU/mL in both cases and both mothers were HBeAg positive. Mode of delivery was vacuum extraction in one and normal vaginal in the other. Transmissions occurred despite protocol compliant passive-

active HBV immune prophylaxis. Sequencing confirmed maternal origin with no vaccine escape mutations detected.

There was no transmission from any mother with viral load was $<6 \log_{10}$ IU/mL (one received AVT for a maternal indication). In particular, there was no MTCT in the contentious $5-6 \log_{10}$ IU/mL range in the absence of AVT.

Thus only viral load $\geq 6 \log_{10}$ IU/ml presented a risk of transmission ($p < 0.05$).

Relationship of Quantitative HBsAg to Viral Load

There were 523 mothers with serum samples sufficient for qHBsAg testing and correlation with maternal viral load from same collection time point. Applying the suggested quantitative HBsAg $\geq 4 \log_{10}$ IU/mL threshold in our cohort, HVL was identified with sensitivity 70.5%, specificity 91.0%, positive predictive value (PPV) 70.5% and negative predictive value (NPV) 91.0%. The correlation between quantitative HBsAg levels and maternal viral load was weak ($R=0.536$) (Figure 3.), Seventy two women would have been misclassified, thirty-six (6.9%) incorrectly placed into the HVL group (false positives) and 36 (6.9%) missed despite having HVL. In the HVL subgroup, quantitative HBsAg $> 4.0 \log_{10}$ IU/mL had better correlation ($R=0.69$) (Fisher-exact (two-tailed), $p = 0.001$).

A ROC curve analysis in our cohort identifies the optimal HBsAg cut-off to predict HVL of $3.0 \log_{10}$ IU/mL. The high NPV of 95.3% is at the cost of much lower specificity (41.2%) and sensitivity (66.7%).

We cannot establish the utility of quantitative serology to predict MTCT as events were almost entirely prevented by AVT. Nevertheless, the antepartum HBsAg levels when MTCT occurred was $3.3 \log_{10}$ IU/mL and $5.2 \log_{10}$ IU/mL, also suggesting poor utility for risk assessment (serum not available in one case).

HBeAg positive serology did significantly correlate with HBV DNA (p value Fisher-exact test (two-tailed), 0.0001). Positive HBeAg predicted HVL with a sensitivity of 93.4%, specificity of 92.3%, PPV of 78.6% and NPV of 97.9% and fewer patients misclassified

than quantitative HBsAg > 4.0 log₁₀ IU/mL; with 31 (5.9%) false positives and 8 (1.5%) false negatives.

Vaccine Efficacy

Four hundred and sixty nine infants received passive-active HBV immunoprophylaxis as per protocol and underwent subsequent serological follow up. Of these, 6 could not be tested as there was insufficient serum for anti-HBs testing although their HBsAg was negative. These six were from 5 mothers with viral load <6 log₁₀ IU/mL and 1 with >6 log₁₀ IU/mL. Vaccine response could thus be assessed in remaining 463. Successful serological vaccine response (SSVR) (HBsAb >10IU/L) was seen in 98.7% (457/463). In the subgroup with maternal HBV DNA < 6 log₁₀ IU/mL, 99.4% (322/324) had a SSVR (Table 2.). Two who failed to respond were HBsAg negative. From the subgroup with maternal HVL, infant SSVR was 97.1% (135/139), with non-responders including 3 infected (HBsAg positive) and one HBsAg negative.

Discussion

Guidelines recommend AVT in the third trimester of pregnancy in addition to routine AVT reduces the risk of HBV MTCT in mother with HVL.^{2, 9-14, 20} The exact viral threshold at which AVT should be administered is somewhat controversial with both the European Association for the Study of the Liver (EASL) 2017 and the American association for the study of Liver Diseases (AASLD) 2015 recommending a low level of >200, 000 IU/mL and the Asian Pacific Association for the Study of the Liver (APASL) 2016 recommending viral load above 6-7 log₁₀ IU/mL, although when below 6 log₁₀ IU/mL, AVT can be considered.^{2, 10-12, 15, 21, 23-25, 40-42} Our study describes the effective prevention of MTCT with AVT in addition to routine immunoprophylaxis in mothers with viral load ≥6 log₁₀ IU/ml.

We previously reported MTCT when viral load was ≥8 log₁₀ copies/mL (established without standardized assays at that time, but extrapolated to approximately >7 log₁₀ IU/ml). The controversy around the best cut-off results from reports of transmissions at lower viral loads. For example in the Zou cohort, transmission occurred below 7 log₁₀ IU/mL, yet we note that few (7.6%) mothers had HBV DNA above 7 log₁₀ IU/mL

(extrapolated) despite 55.8% being HBeAg positive.²¹ This is surprising as in our cohort, 22.7% had viral load above 7 log₁₀ IU/mL even though fewer (30%) were HBeAg positive. We suspect assay variation may explain this, due to viral loads reported from in-house PCR methodologies with variation in amplification efficiency leading to imprecise extrapolation to international units. Genotypic or host variation is unlikely to explain the difference between the Zou and our cohort as both have a dominant populations of South East Asians. Generalization of data from studies using non standardized assays should be done with caution. In our study, the number of samples in the area of controversy (5-5.9 log₁₀ IU/mL) was small, thereby limiting the conclusions, yet this likely reflects the biology of HBV; most patients falling into the low or high viral load groups when tested with standardized assays. Other explanations for transmission at the lower viral load thresholds in other cohorts could include quality or timing of HBIG administration, with consequent reduced efficacy of immunoprophylaxis.

With lower cost and reported reliability, quantitative HBsAg has been proposed to identify pregnant women at risk of MTCT as an alternative to viral load in the EASL 2017 guidelines.^{34, 40} This is surprising as outside of pregnancy the relationship between viral load and quantitative serology is not close. In the setting of pregnancy, Sun et al reported a sensitivity of 85.1%, specificity of 96.5%, PPV of 98.8% and NPV of 65.9% in using qHBsAg >4.1 log IU/mL to predict viral load >7.0 log IU/mL.¹¹ Wen et al reported that in 526 mother-infant pairs that a quantitative HBsAg could be used to predict a significant risk of immune-prophylaxis failure as well as high maternal viral load.²⁸ A quantitative HBsAg of 4.1 log₁₀ IU/ml predicted maternal viral load of 5.95 log₁₀ IU/mL with sensitivity of 100% and specificity of 71%..²⁸ We found only a weak correlation (r=0.531) between quantitative HBsAg and maternal viral load. A cut-off of qHBsAg >4 log₁₀ IU/mL for AVT would have missed 36 of 122 (29.5%) mothers with HVL and AVT prescribed to 36 of 401 (9.0%) mothers whose viral load was < 6 log₁₀ IU/mL. In order to predict HVL in all cases in our cohort, we would need a qHBsAg cut-off level of ≥ 2.2 log₁₀ IU/mL which would inflict a high false positive rate. A two-step process, testing HBV DNA only in those with quant HBsAg above this level, would allow avoidance of viral load testing in 24% although cost saving would be offset by increasing complexity of decision making.²⁸

Our samples were taken in the second trimester of pregnancy, however in the Wen cohort, serology was tested from 2 days and up to 2 months post-partum. If qHBsAg is a potential screening tool for consideration of AVT to prevent MTCT, our second trimester data is a more appropriate time point to investigate this question.

The Wen study did not address the comparative utility of HBeAg status with qHBsAg to predict maternal viral load. This was justified because of statistical limitation of “separation”, when independent variables perfectly predicted the outcome variable.²⁸ We noted that a positive HBeAg provided better sensitivity at 93.4% specificity (92.3%), PPV (78.6%) and NPV (97.9%) than qHBsAg $>4 \log_{10}$ IU/mL for detection of HVL. However HBeAg would have missed HVL in 6.6%. The specificity of qHBsAg and HBeAg was similar with approximately 9% and 8% of low risk mothers respectively being incorrectly identified for AVT.

Our study provides reassuring post vaccination data. We found that 99.4% of infants from mothers without HVL had a SSVR and no MTCT. Testing infants in this circumstance seems of little value. Whilst HBsAb titres would be expected to fall as these children grow older, an anamnestic response has been shown to preserve protection in most cases and boosters are not generally recommended.⁴³⁻⁴⁹ Testing should be prioritized to infants of mothers with HVL. We do not know the impact of maternal antiviral treatment on the duration of induced immunity against HBV in the longer term, thus further research may be required to address this question. Limitations of our study include loss-to-follow up in 27%, although the size of the study remains valuable. Loss to follow up is a shared problem for investigations in this field.

To summarise, MTCT is prevented successfully with immune prophylaxis alone when maternal viral load is $<6 \log_{10}$ IU/mL and in combination with AVT when maternal viral load is $\geq 6 \log_{10}$ IU/mL. Quantitative HBsAg is an unreliable test to predict HVL. HBeAg may be more useful although neither is able to perfectly predict HVL. Where resources allow quantitative HBV DNA, using standardized assays reported in IU/mL, remains gold standard. When maternal viral load is $< 6 \log_{10}$ IU/mL, high vaccine efficacy and absence of MTCT suggest universal testing of infants is of limited value, when considering costs and inconvenience. Guidelines could be reconsidered.

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Figure Legends

Figure 1. Distribution of Maternal Viral Load and HBeAg Status

Figure 2. Mother to Child Transmission According to Maternal Viral Load

Figure 3. Correlation between Quantitative HBsAg and Maternal Viral Load

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Table 1. Cohort Characteristics According to Viral Load.

		Maternal Viral Load Log ₁₀ IU/mL		
		<5*	5-5.9*	>6*
Number of mother/baby pairs		457	17	168
Median Age		31	31	29
HB eAg positive (%)		24(5.3%)	10 (58.8%)	158 (94%)
Median ALT (Interquartile range)		17 (10)	22 (19)	24 (17)
Mode of Delivery:	Normal Vaginal	326 (71.3%)	12 (70.6%)	126 (75%)
	Caesarian Section	99 (21.7%)	5 (29.4%)	28 (16.7%)
	Instrumental	29 (6.3%)	0	13 (7.7%)
	Unknown	3 (0.7%)	0	1 (0.6%)

* 5 log₁₀ IU/mL (low risk, AVT not indicated), 5-5.9 log₁₀ IU/mL (intermediate risk, AVT controversial), > 6 log₁₀ IU/mL (high risk, AVT recommended)

Table 2. Vaccine Efficacy by Viral Load.

Maternal Viral Load	<6 log ₁₀ IU/mL	≥6 log ₁₀ IU/mL ¹	Overall
% Vaccine Efficacy (HBsAb >10 IU/L)	99.4% (322/324)	97.1% (135/139)	98.7% (457/463)

¹ Three non-responders in the maternal viral load group ≥6 log₁₀IU/mL were HBsAg positive children

Figure 1. Distribution of Maternal viral load and HBeAg status

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Figure 2. Mother to Child Transmission According to Maternal Viral Load

¹ Including one death

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Figure 3. Correlation between Quantitative HBsAg and Maternal Viral Load

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