ORIGINAL ARTICLE

Prevention of mother-to-child transmission (MTCT) of hepatitis B virus: An observation of routine practice in a tertiary liver centre before and after the introduction of the Global Health Sector Strategy on Viral Hepatitis (GHSSVH)

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ABSTRACT

Introduction: Worldwide, around 296 million people have hepatitis B virus (HBV) infection, most commonly transmitted from mother-to-child. Global Health Sector Strategy on Viral Hepatitis (GHSSVH) was introduced in May 2016, calling for elimination of viral hepatitis by 2030. This study aims to compare practice in a tertiary liver centre before and after GHSSVH introduction for prevention of mother-to-child transmission (MTCT).

Materials and Methods: This retrospective cohort study was performed in a tertiary referral liver centre in Malaysia, using data from electronic medical record from January 2015 to December 2019. A total of 1457 medical records of female with HBV infection were screened. The inclusion criteria of the study were pregnant women with HBsAg positive or known to have HBV infection during the study period. We excluded patients with co-infections of other types of viral hepatitis or human immunodeficiency virus, concurrent liver diseases (e.g.: autoimmune hepatitis, Wilson's disease), previous organ transplant and malignancy—except for hepatocellular carcinoma (HCC).

Results: This study included 117 pregnancies and 21/117 (17.9%) were on antiviral therapy (AVT) for HBV. In 2017–2019, 13/18 (72.2%) of those with HBV DNA >200,000IU/ml were on AVT, compared to 5/9 (55.6%) for 2015–2016, indicating 58% (95% CI −63% to 568%) higher odds of being on AVT in post GHSSVH group after accounting for HBV DNA.

Conclusion: Uptake of maternal AVT for the prevention of MTCT shows an increased trend since the introduction of GHSSVH, with room for improvement.

KEYWORDS:
Antiviral therapy, Global Health Sector Strategy on Viral Hepatitis (GHSSVH), hepatitis B virus, mother-to-child transmission, neonatal immunoprophylaxis failure, prevention

INTRODUCTION

Worldwide, it is estimated that there are around 296 million people living with chronic hepatitis B infection. Malaysia is one of the countries in World Health Organisation (WHO) Western Pacific Region, which has the highest burden of infection, where 116 million people are infected.[1] It is a major global health problem as approximately 15–40% of patients with hepatitis B virus (HBV) infection may develop complications like liver cirrhosis, hepatocellular carcinoma or liver failure.[2] As such, WHO aims to eliminate viral hepatitis by 2030.

Each year, there are about 1.5 million new hepatitis B infections, most commonly transmitted from mother to child in highly endemic areas like Malaysia. Unlike infection acquired in adulthood, which leads to chronic infection in less than 5% of cases, infection acquired in infancy and early childhood resulted in chronic hepatitis in about 95% of cases,[1] which is the main contributor to the morbidity and mortality related to HBV infection.[3] Therefore, efforts should be focused on the prevention of new hepatitis B infection among the infants by prevention of mother-to-child transmission (MTCT) with various strategies.[4]

Studies have shown that HBV transmission, despite adequate neonatal immunoprophylaxis, can still occur in highly viraemic mothers, with HBV DNA >6 $\log_{10}$ copies/ml,[5] prompting additional measures to further reduce this form of vertical transmission. Immunoprophylaxis with HBV vaccines and Hepatitis B Immunoglobulin (HBIG), which were developed in the 1980s, have been estimated to prevent approximately 90% of new infections among infants. Causes of immunoprophylaxis failure include intrauterine infection, which cannot be prevented by prophylaxis administered at birth, peripartum infection resulting from breakthrough infection that occurred at delivery and postnatal infection occurring in small proportion of children who failed to mount an adequate immune response to the immunoprophylaxis given.[6]

Despite the abundance of data available for hepatitis treatment and prevention, viral hepatitis as a public health threat remained neglected and made little progress compared to diseases like human immunodeficiency virus (HIV) or malaria. Lack of international investments in viral hepatitis programmes especially in low-income and middle-income countries, as well as the paucity of global guidance on

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strategies framework are the main hurdles in achieving hepatitis elimination.[7] Consequently, in 2016, the WHO Global Health Sector Strategy on Viral Hepatitis (GHSSVH) provided the initial guidance for the elimination of viral hepatitis as a public health problem by 2030.[8] It provides countries with a range of options for measurements of targets in assessing progress towards elimination, depending on available surveillance data and capacity. Gaps can then be identified and guide decisive actions towards achieving the goal.[8] Prevention of MTCT of HBV is among the core intervention areas documented in this guidance[9] whereby the use of perinatal antiviral therapy (AVT) when indicated is advocated.[10]

Closer to home in Malaysia, the targets set by National Strategic Plan for Hepatitis B and C 2019–2023 with regards to the prevention of MTCT of HBV only cover antenatal hepatitis B screening and hepatitis B vaccination program by active immunisation for infants.[11] This program for infants was introduced in 1989, even before the introduction of GHSSVH. The three doses of vaccination are given within 24 hours of birth, 1month and 6months of age. Although a seroprevalence study showed that the prevalence of hepatitis B surface antigen (HBsAg) in children born after the implementation of the program was lower than those born before (0.2% versus 1.08%),[12] there is still room for improvement as elimination of HBV infection as a public health threat requires a decrease in prevalence of HBsAg to below 0.1%.[3] This further reinforces the need for prophylactic AVT for HBsAg positive pregnant women with high viral load. Our study aims to compare the practice of prevention of MTCT of HBV in a tertiary referral liver centre before and after GHSSVH introduction.

MATERIALS AND METHODS

Study Design

This is a retrospective study performed in a tertiary referral liver centre in Malaysia. Total 1457 medical records of female with HBV infection from 1st January 2015 to 31st December 2019 were screened and patients fulfilling inclusion criteria were included. The inclusion criteria of the study were pregnant women with HBsAg positive or known to have HBV infection during the study period. We excluded patients with co-infections of other types of viral hepatitis or human immunodeficiency virus, concurrent liver diseases (e.g. autoimmune hepatitis, Wilson's disease), previous organ transplant and malignancy—except for hepatocellular carcinoma.

Data Collection

Electronic medical records were used to systematically identify patients using the diagnosis keyword "Hepatitis B" or "HBsAg positive" then filtered by gender and pregnancy status. Patients' demographics (age, ethnicity, parity and number of previous miscarriages) were recorded. Clinical features of patients during follow-up in outpatient clinic or inpatient reviews in ward were also recorded and divided into three parts: laboratory data, pregnancy-related comorbidities and HBV therapy. Laboratory data included platelet count, highest serum alanine aminotransferase (ALT) levels (normal value ≤33 U/L, abnormal value >33 U/L), highest serum aspartate aminotransferase (AST) levels (normal value ≤31 U/L, abnormal value >31 U/L), HBeAg status, HBeAb status and HBV DNA viral load. Prognostic scores of liver fibrosis via Fibrosis-4 (Fib-4) Score and AST to Platelet Ratio Index (APRI) Score were calculated.

Outcome Measurements and Endpoints

As GHSSVH was introduced in 2016, data collected were divided into two time epochs, 2015-2016 and 2017-2019. Primary outcomes were the percentage of pregnant mothers with HBV DNA > 200, 000 IU/ml on antiviral prophylaxis, with comparison being made between the two-time epochs. The secondary outcomes were to look at percentage of HBeAg-positive and HBeAg-negative patients with HBV DNA > 200, 000 IU/ml in this study population. This is to explore the possibility of initiation of antiviral prophylaxis based on HBeAg positive status as HBV DNA is a more cumbersome investigation.

Data Analysis

Statistical analyses were performed using IBM® Statistical Package for Social Sciences version 23.0 (SPSS, Chicago, IL). Numerical variables were presented using mean and standard deviation (SD) for normally distributed data while median and interquartile ranges (IQR) were additionally presented for non-normally distributed data. Comparison of data between 2015-2016 and 2017–2019 was determined using Pearson's chi-square test or Fischer's exact test for categorical data and Mann Whitney test for continuous data. The odds ratio (OR) and 95% confidence interval (CI) of pregnant women being on AVT when HBV DNA > 200, 000 IU/ml is derived using logistic regression analyses. All tests were two-sided and a $p<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of HBsAg positive Pregnant Women

This study included 117 HBsAg positive pregnancies (Table I). The median age was 32 years (interquartile range (IQR) 31 to 35). In the study population, 53.8% were Malay, 42.7% were Chinese while 3.4% were of other races including foreigners. Majority are Para 1 and primigravida.

During the follow-up, median highest ALT was 16 U/L (IQR 12–27) while median highest AST was 25 U/L (IQR 20 – 35). Among the pregnant women studied, 30.8% (n=36) were HBeAg positive while 23.1% (n=27) had HBV DNA > 200, 000 IU/ml. The median Fibrosis-4 (Fib-4) Score was 0.76 (IQR 0.59 to 1.15) while the median AST to Platelet Ratio Index (APRI) Score was 0.32 (IQR 0.24 to 0.47). None of the patients had liver cirrhosis or varices. One patient had both hepatocellular carcinoma and ascites.

Pregnancy-Related Comorbidities and Outcomes

Among the patients studied, 14 (12%) had anaemia in pregnancy, 24 (20.5%) had gestational diabetes, 6 (5.1%) had pre-eclampsia and 1 (0.9%) had placenta previa. Regarding pregnancy outcomes, 35 (29.9%) had lower segment caesarean section, 13 (11.1%) had pre-term delivery, 10 (8.5%) had low birth weight and 1 (0.9%) had birth defect (Table II).

Table I : Baseline characteristics of the study population (n = 117), 2015–2019

Characteristics	Value
Age in years, median (IQR)	32 (31–35)
Ethnicity, n (%)	
Malay	63 (53.8)
Chinese	50 (42.7)
Indian	0
Others	4 (3.4)
Parity, n (%)	
Missing data	1 (0.9)
0	27 (23.1)
1	30 (25.6)
2	20 (17.1)
3	24 (20.5)
4	7 (6.0)
≥5	8 (6.9)
Highest ALT during pregnancy	
Median (IQR)	16 (12–27)
Highest AST during pregnancy	
Median (IQR)	25 (20–35)
HBeAg status, n (%)	
Missing data	10 (8.5)
Negative	71 (60.7)
Positive	36 (30.8)
HBeAb status, n (%)	
Missing data	13 (11.1)
Negative	44 (37.6)
Positive	60 (51.3)
HBV DNA in IU/ml	
Missing data, N (%)	31 (26.5)
≤200,000, N (%)	59 (50.4)
>200,000, N (%)	27 (23.1)
Median (IQR)	566 (53 to 1,085,437)
Fibrosis-4 (Fib-4) Score	
Missing data, N (%)	27 (23.1%)
Median (IQR)	0.76 (0.59–1.15)
AST to Platelet Ratio Index (APRI) Score	
Missing data, N (%)	27 (23.1%)
Median (IQR)	0.32 (0.24–0.47)
Cirrhosis, n (%)	
Missing data	1 (0.9)
Not present	116 (99.1)
Present	0
Hepatocellular carcinoma, n (%)	
Missing data	9 (7.7)
Not present	107 (91.5)
Presents	1 (0.9)
Varices, n (%)	
Missing data	10 (8.5)
Not present	107 (91.5)
Present	0
Ascites, n (%)	
Missing data	3 (2.6)
Not present	113 (96.6)
Present	1 (0.9)

Table II: Pregnancy-related comorbidities and outcomes in study population (n = 117), 2015–2019

Comorbidities or Outcomes	Number (%)
Anaemia [a]	
Missing data	7 (6.0)
Not present	96 (82.1)
Present	14 (12.0)
Gestational diabetes	
Missing data	28 (23.9)
Not present	65 (55.6)
Present	24 (20.5)
Pre-eclampsia	
Missing data	27 (23.1)
Not present	84 (71.8)
Present	6 (5.1)
Placenta previa	
Missing data	26 (22.2)
Not present	90 (76.9)
Present	1 (0.9)
Lower segment C-section	
Missing data	33 (28.2)
No	49 (41.9)
Yes	35 (29.9)
Pre-term Delivery[b]	
Missing data	33 (28.2)
No	71 (60.7)
Yes	13 (11.1)
Low birth weight[c]	
Missing data	35 (29.9)
No	72 (61.5)
Yes	10 (8.5)
Birth defect	
Missing data	35 (29.9)
No	81 (69.2)
Yes	1 (0.9)

[a] Haemoglobin (Hb) <11 g/dl 1st trimester, Hb <10.5 g/dl 2nd trimester, Hb<10g/dL 3rd trimester [13]
[b] Delivery before 37weeks period of gestation[14]
[c] Birth weight < 2500g [15]

Table III: Cross-tabulation of HBV DNA level and HBeAg status versus AVT

	AVT during pregnancy	
	No	Yes
HBV DNA ≤200,000 IU/ml	56 (94.9%)	3 (5.1%)
HBV DNA >200,000 IU/ml	9 (33.3%)	18 (66.7%)
HBeAg Negative	66 (93.0%)	5 (7.0%)
HBeAg Positive	21 (58.3%)	15 (41.7%)

Table IV: Cross-tabulation of HBeAg status versus HBV DNA level ∧

HBeAg status:	HBV DNA level in IU/ml	
	≤200,000	>200,000
Negative	50 (92.6%)	4 (7.4%)
Positive	8 (27.6%)	21 (72.4%)

∧ Diagnostic accuracy values with HBV DNA level as the reference standard:
Sensitivity = 84.0% (63.1 to 94.7%)
Specificity = 86.2% (74.1% to 93.4%)
Positive predictive value = 72.4% (52.5 to 86.6%)
Negative predictive value = 92.6% (81.3 to 97.6%)
Positive likelihood ratio = 6.09 (3.12 to 11.85)
Negative likelihood ratio = 0.19 (0.08 to 0.46)

AVT for Hepatitis B

Majority, 95 (81.2%) had no AVT during pregnancy. One woman (0.9%) had AVT pre-pregnancy, but stopped during pregnancy while 3 (2.6%) had AVT before and during pregnancy. There were 18 (15.4%) patients who were newly started on AVT during pregnancy as prophylaxis.

About two-third, 18/27 (66.7%) of those with HBV DNA > 200, 000 IU/ml were on AVT during pregnancy. (Table III) The odds ratio of being on AVT for patients who had HBV DNA > 200, 000 IU/ml was 37.3 (95% CI 9.1 to 153.0). On the other hand, 3/59 (5.1%) of those whose HBV DNA ≤ 200, 000 IU/ml were on AVT. All of them were already on AVT prior to pregnancy, and the treatment was continued during pregnancy.

Table V: Comparison of 2015–2016 vs 2017–2019

Variables	2015–2016 (N = 39)	2017–2019 (N = 78)	*p* value
Age in years, median (IQR)	31 (29 to 33)	33 (31 to 36)	<0.001 [a]
Race, n (%)			1.000 b
Malay	21 (53.8)	42 (53.8)	
Chinese	17 (43.6)	33 (42.3)	
Indian	0	0	
Others	1 (2.6)	3 (3.8)	
Parity, n (%)			0.020 [b]
Missing data	1 (2.6)	0	
0	12 (30.8)	15 (19.2)	
1	4 (10.3)	26 (25.6)	
2	9 (23.1)	20 (17.2)	
3	10 (25.6)	24 (20.7)	
4	0	7 (9.0)	
≥5	3 (7.7)	5 (6.4)	
Number of miscarriages, n (%)			0.444 [b]
Missing data	1 (2.6)	0	
0	27 (69.2)	52 (66.7)	
1	8 (20.5)	17 (21.8)	
2	2 (5.1)	9 (11.5)	
5	1 (2.6)	0	
HBeAg status, n (%)			0.954 [b]
Missing data	3 (7.7)	7 (9.0)	
Negative	23 (59.0)	48 (61.5)	
Positive	13 (33.3)	23 (29.5)	
HBV DNA in IU/ml			0.801 [c]
Missing data, n (%)	13 (33.3)	18 (23.1)	
≤200,000, n (%)	17 (43.6)	42 (53.8)	
>200,000, n (%)	9 (23.1)	18 (23.1)	
Median (IQR)	1653 (115 to 12,434,917)	277 (22 to 461,895)	0.056 [a]
AVT during pregnancy, n (%)			0.799 [c]
No	33 (84.6)	63 (80.8)	
Yes	6 (15.4)	15 (19.2)	

p values are based on the following tests.
[a] Mann–Whitney test; [b] Fisher's exact test; [c] Chi-square test.

Among those with HBeAg positive status,15/36 (41.7%) were on AVT during pregnancy (Table III). On the other hand, 5/71 (7.0%) of those whose HBeAg-negative were on AVT. The odds ratio of being on AVT for patients who were HBeAg positive was 9.4 (95% CI 3.1 to 29.0).

Relationship of HBeAg Status to Hepatitis B Viral Load

Positive HBeAg predicted HBV DNA > 200, 000 IU/ml with a sensitivity of 84.0%, specificity of 86.2%, positive predictive value (PPV) of 72.4%, negative predictive value (NPV) of 92.6%, positive likelihood ratio of 6.09 and negative likelihood ratio of 0.19 (Table IV).

Comparison Between 2015–2016 and 2017–2019

There were 39 HBsAg positive pregnancies between 2015 and 2016 and 78 between 2017 and 2019 (Table V). The median age was 31 in the former group and 33 in the latter group. Thirteen (33.3%) in 2015–2016 group and 23 (29.5%) in 2017–2019 had HBeAg positive while 9 (23.1%) in 2015–2016 group and 18 (23.1%) in 2017–2019 had HBV DNA > 200,000 IU/ml. In 2015–2016, 5/9 (55.6%) of those with HBV DNA >200,000 IU/ml were on AVT during pregnancy, compared to 13/18 (72.2%) for 2017–2019, indicating that a patient has 58% higher odds (95% CI –63% to 568%) of being on AVT in 2017–2019 compared to 2015-2016 after accounting for HBV DNA level.

DISCUSSION

Our study found that HBsAg positive pregnant women with HBV DNA > 200,000 IU/ml have 58% higher odds of being on AVT in 2017–2019 compared to 2015–2016, although it is not statistically significant. This likely reflects changes in practice as increasing evidence is available regarding benefits and safety of short-term antiviral treatment to pregnant women with high viral load, in order to bring down the HBV DNA level for active and passive immunisation to be effective.

In parallel with this, many international guidelines are advocating perinatal antiviral prophylaxis as an additional measure to prevent MTCT of HBV. However, there are some variations in their recommendations. European Association for the Study of the Liver (EASL) 2017 Clinical Practice Guideline recommends that all HBsAg positive pregnant women with HBV DNA > 200, 000 IU/ml or HBsAg > 4 $\log_{10}$ IU/ml should receive antiviral prophylaxis starting at 24–28 weeks of gestation.[16] The American Association for the Study of Liver Diseases (AASLD) 2018 and WHO (2020) recommend antiviral prophylaxis at a similar HBV DNA level, starting at 28 weeks of gestation.[3,17] On the other hand, the Asian Pacific Association for the Study of the Liver (APASL) 2016 recommends short term antiviral treatment to pregnant women at higher HBV DNA level threshold, at above above 6–7 $\log_{10}$ IU/ml from 28 to 32 weeks of gestation although it acknowledges that HBV infection can be transmitted even at

a lower HBV DNA level and that antiviral prophylaxis can be given after discussion with the patient.[18]

GHSSVH also provides doctors with an initial framework and goals to work on in order to attain WHO aim of achieving viral hepatitis elimination by 2030. It sets targets such as to achieve 50% coverage of prevention of MTCT of HBV by 2020 and 90% by 2030 as well as <1% prevalence of HBsAg positive among children by 2020 and <0.1% by 2030.[8] The availability of multiple guidelines which advocate antiviral prophylaxis in high viral load pregnant women likely increases the awareness of treating doctors to convince this group of patients for treatment and at the same time, pregnant women are more confident to accept antiviral prophylaxis.

However, it is worth pointing out that HBV DNA had 26.5% missing data while HBeAg status had 8.5% missing data in this study population. A possible explanation for this is HBeAg has shorter turn-around time and will be available earlier. Apart from that, HBV DNA is a more cumbersome test compared to HBeAg because HBV DNA is a quantitative virologic marker. Quantitative assaying of HBV requires expensive equipment and a contamination-free facility, and it cannot be routinely done in smaller hospitals serving rural communities.[19] Patients were referred to the tertiary referral liver centre from all over the country, which have different laboratory investigation capacity, and some may not have the availability of HBV DNA testing.

As such, this study also looks at the feasibility of using HBeAg positivity status for antiviral prophylaxis rather than high HBV DNA viral load. It was known that HBeAg positivity is a marker of high viral replication and may have a role in predicting risk of MTCT and the need for antenatal AVT.[20] In a retrospective study looking at predictive factors of high HBV DNA levels among women of reproductive-age group with Chronic Hepatitis B infection done by Khoo et al., it was found that HBeAg positive women had a 9.99-fold higher risk of showing HBV DNA > 200, 000 IU/ml compared to those who were HBeAg negative (AOR=9.99; 95% CI=5.50 to 18.13; p<0.001).[21] WHO also recommends that in low-income settings in which antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for antiviral prophylaxis in order to reduce MTCT of HBV.[3]

In this cohort of patients studied, a positive HBeAg predicted HBV DNA > 200,000 IU/ml with a sensitivity of 84.0%, specificity of 86.2%, positive predictive value (PPV) of 72.4%, negative predictive value (NPV) of 92.6%, positive likelihood ratio of 6.09 and negative likelihood ratio of 0.19. In a resource-limited setting, these values are acceptable, considering only 7.4% of those with negative HBeAg status have HBV DNA > 200,000 IU/ml. Similar results were obtained in a study by Thilakanathan et al., whereby a positive HBeAg provided sensitivity at 93.4% specificity at 92.3%, PPV at 78.6% and NPV at 97.9% for detection of HBV DNA ≥6 $\log_{10}$IU/mL.[22]

Alternatively, HBV DNA can be sent only for pregnant women who have positive HBeAg, which is estimated to account for about 20–55% of all HBsAg-positive women at child-bearing age. Such a testing protocol needs to be done earlier in pregnancy to ensure adequate time for subsequent HBV DNA level testing and initiation of AVT to achieve significant viral suppression before delivery.[5]

Based on our study, we recommend clear guidance and policy-driven care pathway for hepatitis B in pregnant women, starting with antenatal HBsAg screening, then further evaluation of HBsAg positive pregnant women for appropriate prophylaxis with antiviral and addition of passive hepatitis B immunisation to the babies born, in order to optimise prevention of MTCT of HBV. Detection of HBsAg positive pregnant woman is also an opportunity for contact tracing and bring to care other infected family or household members. Apart from that, our study found HBeAg positivity has high sensitivity, specificity and negative predictive value for HBV DNA > 200,000 IU/ml, making it possible to use HBeAg positivity status as guidance for antiviral prophylaxis to prevent MTCT of HBV, especially in healthcare set-up which has poor accessibilities for molecular testing laboratory.

Limitations of our study include the proportion of missing data in the study population, especially HBV DNA level, possibly due to late referral and this can be a potential bias. Although there is an increase in the percentage of pregnant women with HBV DNA > 200,000 IU/ml on prophylactic AVT after the introduction of GHSSVH, this study did not have adequate statistical power to show that it is statistically significant due to the small sample size. As this is a retrospective study, such limitations could not be avoided. Therefore, the generalisation of the study should be done with caution. However, these findings are useful preliminary data to show that as a tertiary referral liver centre, we have achieved WHO target of 50% coverage of prevention of MTCT by 2020. The information gathered may also guide future research on larger sample sizes and better study designs.

CONCLUSION

In conclusion, the introduction of GHSSVH and availability of vast evidence and guidelines advocating use of prophylactic AVT for HBsAg positive pregnant women with high viral load had positively affected the practice. HBeAg status can also serve as a potential alternative test in guiding antiviral prophylaxis for MTCT prevention. Nevertheless, a protocol on HBV management in pregnant women and education may enhance care in order to achieve WHO target of 90% coverage of prevention of MTCT of HBV and 0.1% prevalence on HBsAg among children by 2030.

ETHICAL APPROVAL

Ethical approval was obtained from the Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR ID-22-00620-51E). An informed consent waiver was approved in view of a non-intervention, retrospective study.

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