ORIGINAL ARTICLE

Hepatitis B virus infection among children of hepatitis B surface antigen positive mothers in a Malaysian hospital

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ABSTRACT

Introduction: There have been no published data on the transmission of hepatitis B virus (HBV) infection among children of hepatitis B surface antigen (HBsAg) positive mothers in Malaysia.

Methods: This is a cross-sectional study of all the children of HBsAg-positive mothers who delivered at the University of Malaya Medical Centre between 1993 and 2000.

Results: A total of 60 HBsAg-positive mothers and their 154 children participated in the study. HBsAg was detected in four children (2.6%) while IgG antibody to the hepatitis B core antigen (anti-HBc IgG) was detected in seventeen children (11.0%). The mother's age at childbirth was significantly lower in the children with detectable HBsAg (22.5±6.1 years vs. 29.7±4.5 years, p=0.043) and anti-HBc IgG (26.6±6.1 years vs. 30.0±4.3 years, p=0.004). Children born in the 1980s were significantly more likely to have detectable HBsAg (18.8% vs. 0.7%, p=0.004) and anti-HBc IgG (37.5% vs. 8.0%, p=0.000) compared with those born later. All children with detectable HBsAg were born via spontaneous vaginal delivery, and hepatitis B immunoglobulin was either not given or the administration status was unknown. The majority of mothers with chronic HBV infection (70.4%) were not under any regular follow-up for their chronic HBV infection and the main reason was the lack of awareness of the need to do so (47.4%).

Conclusion: Transmission of HBV infection among children of HBsAg-positive mothers in Malaysia is low. However, attention needs to be given to the high rate of HBsAg-positive mothers who are not on any regular follow-up.

KEY WORDS:
HBV; vertical transmission; Malaysia

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a major public health issue that is affecting an estimated 240 million people worldwide and results in more than 780,000 deaths annually from complications such as cirrhosis and hepatocellular carcinoma.[1] It is most endemic in countries of the African region and the Western Pacific region with prevalence estimated at 8.8% and 5.3%, respectively.[2] In areas of high endemicity, vertical transmission (from exposure to maternal blood and secretions at delivery) is the major mode of transmission and perpetuation of the infection. The risk of a child developing chronic HBV infection is about 90% when infected perinatally. Furthermore, children younger than 5 years of age living with HBV-infected persons may acquire the infection via horizontal transmission. The World Health Organization recommends that all infants receive the hepatitis B vaccine as soon as possible (<24 hours) after birth followed by 2 or 3 doses (with minimum interval of 4 weeks between the doses) to complete the series. The complete vaccine series confers protective antibody level in more than 95% of infants, children and young adults, and helps prevent both vertical and horizontal transmission. Infants born to hepatitis B surface antigen (HBsAg) positive mothers should in addition receive hepatitis B immunoglobulin (HBIG) immediately after birth especially if the mother is also hepatitis B envelope antigen (HBeAg) positive.[3]

In Malaysia, the prevalence of chronic HBV infection varies according to the ethnic group studied with the highest prevalence among the Chinese (4-7%), followed by the Malays (2-4%) and the Indians (<1%).[4] Routine hepatitis B vaccination was introduced in Malaysia in 1989. In addition, HBIG is given to infants born to HBsAg-positive mothers.[5] The transmission rate of HBV infection to children in family of HBsAg-positive mothers has never been studied before in Malaysia although it is assumed that the rate will be low with a preventive program in place in the form of routine hepatitis B vaccination and the administration of HBIG to infants born to HBsAg-positive mothers. The primary objective of this study is to determine the transmission rate of HBV infection to children in family of HBsAg-positive mothers. The secondary objectives include to study the factors associated with the transmission of HBV infection, and to determine the proportion of HBsAg-positive mothers who are under regular follow-up for their chronic HBV infection and the reason if they are not doing so.

METHODOLOGY

This is a cross-sectional study of all the children of HBsAg-positive mothers who delivered at the University of Malaya Medical Centre between 1993 and 2000. The mothers were identified from the delivery book and contacted by telephone call to participate in the study. After three unsuccessful telephone calls, a letter was sent to the last available home address in the hospital computer system. For mothers who

This article was accepted: 19 April 2018
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Table I: Characteristics of children with detectable and non-detectable HBsAg

	HBsAg detected, n = 4	HBsAg not detected, n = 150	p
Mother's age at childbirth, years	22.5 ± 6.1	29.7 ± 4.5	0.043
Year of delivery			
1980-1989	75.0	8.7	0.000
1990-1999	25.0	60.0	
2000-2009	0	31.3	
Gender, %			
Male	50.0	45.3	1.000
Female	50.0	54.7	
Ethnicity, %			
Malay	75.0	48.7	0.771
Chinese	25.0	47.3	
Indian	0	2.0	
Others	0	2.0	
Mode of delivery, %			
Vaginal	100	84.0	1.000
Caesarean	0	16.0	
Immunoglobulin, %			
Given	0	66.0	0.015
Not given / Unknown	100	34.0	
Vaccination, %			
Given	100	91.3	1.000
Not given / Unknown	0	8.7	
Breastfeeding, %			
Yes	75.0	88.7	0.395
No	25.0	11.3	

Table I: Characteristics of children with detectable and non-detectable anti-HBc IgG

	Anti-HBc IgG detected, n = 17	Anti-HBc IgG not detected, n = 137	p
Mother's age at childbirth, years	26.6 ± 6.1	30.0 ± 4.3	0.004
Year of delivery			
1980-1989	35.3	7.3	0.001
1990-1999	35.3	62.0	
2000-2009	29.4	30.7	
Gender, %			
Male	47.1	45.3	0.888
Female	52.9	54.7	
Ethnicity, %			
Malay	64.7	47.4	0.533
Chinese	35.3	48.2	
Indian	0	2.2	
Others	0	2.2	
Mode of delivery, %			
Vaginal	11.8	16.1	1.000
Caesarean	88.2	83.9	
Immunoglobulin, %			
Given	52.9	65.7	0.301
Not given / Unknown	47.1	34.3	
Vaccination, %			
Given	94.1	91.2	1.000
Not given / Unknown	5.9	8.8	
Breastfeeding, %			
Yes	94.1	87.6	0.695
No	5.9	12.4	

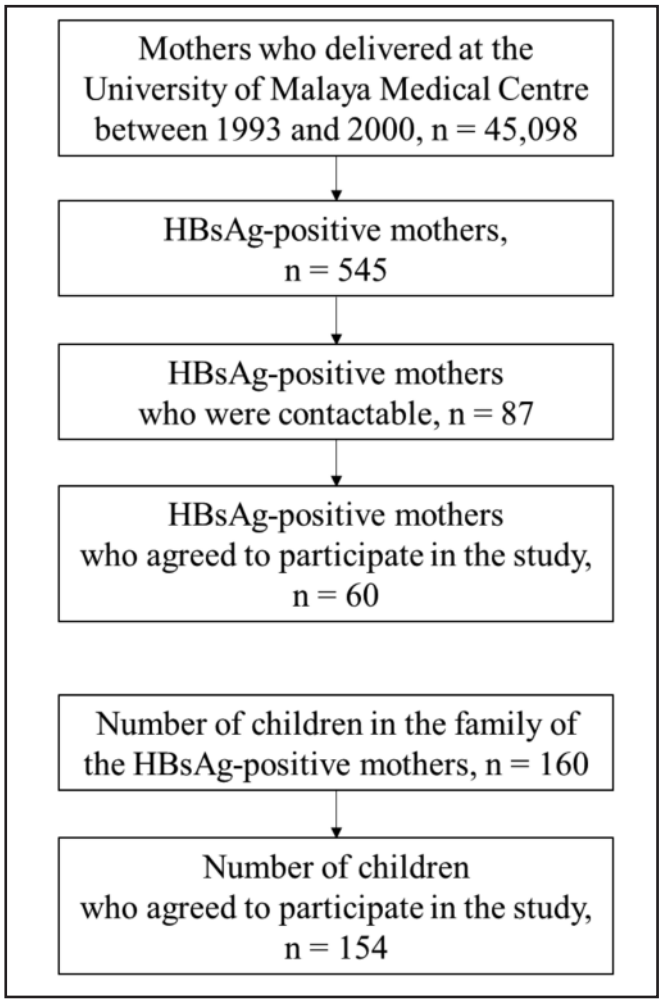

Fig. 1: Study profile.

were not contactable by telephone calls and the initial letter, a search for their latest home address was carried out at the National Registration Department of Malaysia, Ministry of Home Affairs, and a second letter was sent to the latest home address. The mothers who were interested to participate in the study brought all their children to the University of Malaya Medical Centre. A standard questionnaire was completed for each of the children. The birth certificate and vaccination record for each of the children were reviewed for hepatitis B vaccination status. Blood was drawn to test for the HBsAg, the hepatitis B surface antibody (anti-HBs), and the IgG antibody to the hepatitis B core antigen (anti-HBc IgG). In addition, a standard questionnaire was completed for the mothers who participated in the study. The study was approved by the Medical Ethics Committee of the University of Malaya Medical Centre and conformed to the Declaration of Helsinki 1975. Written informed consent was obtained from subjects who were ≥ 18 years old, or their parents if they were < 18 years old.

With an estimated prevalence of 10% based on previous studies,[6,7] a sample size of 139 subjects was needed to estimate the prevalence with 95% confidence and 5% precision. Data were analysed using a standard statistical software program (SPSS 15.0, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means with standard deviation or medians with interquartile ranges, and analyzed using t-test or Mann-Whitney test, where appropriate. Categorical variables were expressed as percentages and analyzed using chi-square test or Fisher exact test, where appropriate.

RESULTS

A total of 60 mothers with chronic hepatitis B and their 154 children participated in the study (Figure 1). HBsAg was detected in four children (2.6%) while anti-HBc IgG was detected in seventeen children (11.0%). Characteristics of children with detectable and undetectable HBsAg, and detectable and undetectable anti-HBc IgG are shown in Tables 1 and 2, respectively. The mother's age at childbirth was significantly lower in the children with detectable HBsAg (22.5±6.1 years vs. 29.7±4.5 years, p=0.043) and anti-HBc IgG (26.6±6.1 years vs. 30.0±4.3 years, p=0.004). Children born in the 1980s were significantly more likely to have detectable HBsAg (18.8% vs. 0.7%, p=0.004) and anti-HBc IgG (37.5% vs. 8.0%, p=0.000) compared with those born later. All the children with detectable HBsAg were born via spontaneous vaginal delivery, and HBIG was either not given or the administration status was unknown. The majority of mothers with chronic HBV infection (70.4%) were not under any regular follow-up for their chronic HBV infection despite knowing that they have the infection. The reasons were the lack of awareness of the need to do so (50.0%), the lack of time (36.8%), cost (7.9%), and inconvenience (5.3%).

DISCUSSION

This is the first study on HBV infection among children in family of HBsAg-positive mothers in Malaysia. Chronic hepatitis B as reflected by a detectable HBsAg was observed in 2.6% of the children. The presence of anti-HBc IgG which suggest previous HBV infection was observed in an additional 11.0% of the children. The mother's age at childbirth was significantly lower in the children with detectable HBsAg and anti-HBc IgG. This is consistent with the natural history of chronic HBV infection whereby younger mothers tend to be in the immune tolerant phase when they are positive for the HBeAg and have high HBV DNA levels making perinatal transmission of the virus more likely. In a study on 303 mother-infant pairs[6], all 10 HBV-infected infants were born to HBeAg-positive mothers who were significantly younger and had significantly higher HBV DNA levels compared with HBeAg-negative mothers. In the study, maternal viral load was the only factor significantly associated with transmission after adjusting for various other potential factors. Moreover, maternal viral load appeared to have a dose-response effect on transmission with predictive rates of infection at maternal viral load levels of 7, 8 and 9 log10 copies/ml being 6.6%, 14.6% and 27.7%, respectively.

In our study, children born in the 1980s were also significantly more likely to have detectable HBsAg and anti-HBc IgG. This is likely a reflection of the absence of a preventive program in the form of routine hepatitis B vaccination and the administration of HBIG to infants born to HBsAg-positive mothers which only came into effect in 1989 in Malaysia. Furthermore, HBIG was either not given or

the administration status was unknown in all the children who had detectable HBsAg in our study. Compared with hepatitis B vaccination alone, the administration of HBIG to infants born to HBsAg-positive mothers has been shown to further reduce the risk of HBV transmission from 21% to 6.8%.[8] Although the percentage of children with detectable HBsAg who was ethnic Malay appeared much greater than the percentage of children with detectable HBsAg who was ethnic Chinese (75% vs. 25%), the percentage of Malay and Chinese children who had detectable HBsAg was 3.9% and 1.4%, respectively. The percentages were not significantly different between the two ethnic groups. It is true that the prevalence of HBsAg positivity is higher among the Chinese compared with the Malays, but this is due to infection that is already present in the Chinese population rather than a higher perinatal transmission rate.

Prenatal screening for HBV infection does not only allow appropriate intervention to be carried out to reduce transmission to the infant but also provides an opportunity to detect previously undiagnosed and asymptomatic women with chronic HBV infection. Regular follow-ups allow patients with chronic HBV infection who require antiviral treatment to be identified early thus preventing them from progressing to cirrhosis and hepatocellular carcinoma. Unfortunately, over two thirds of the HBsAg-positive mothers in our study were not on regular follow-up for their chronic HBV infection despite knowing that they have the infection and nearly half of them were not aware that they require follow-up in the first place. This reflects a lack of proper education and represents a missing link in the delivery of care for this special group of people with chronic HBV infection. Training of healthcare provider to disseminate information and create awareness among HBsAg-positive mothers that they require regular follow-ups is crucial to overcome this problem. Further studies should be conducted to determine any clinical or socio-economic factors that could have contributed to the high rate of HBsAg-positive mothers not on regular follow-up for their chronic HBV infection.

This was a single-centre study conducted in a tertiary hospital and the results may not be generalizable to other populations. The retrospective nature of the study results in several important limitations in this study. First, the mother's responses to the questionnaire may be subjected to recall bias. Secondly, a large proportion of the HBsAg-positive mothers were not contactable despite using all available means. Thirdly, the influence of factors such as maternal HBeAg status and HBV DNA level could not be studied. Nevertheless, this study provided an estimate of detectable HBsAg and anti-HBc IgG among children in the family of a cohort of HBsAg-positive mothers from a tertiary hospital in Malaysia where such data is not available. It also provided a glimpse into the high rate of HBsAg-positive mothers who are not on any regular follow-up for their chronic HBV infection and showed that lack of awareness was the main underlying reason.

In conclusion, transmission of HBV infection in family of HBsAg-positive mothers from a tertiary hospital in Malaysia is low and within the range expected in a country where a preventive program is in place. However, attention needs to be given to the high rate of HBsAg-positive mothers who are not on any regular follow-up for their chronic HBV infection and the lack of awareness among them of the need to do so.

ACKNOWLEDGEMENT

The authors would like to thank Ms. Wan Noor Hidayu for her assistance in the research project.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859): 2095-128.
2. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015; 386(10003): 1546-55.
3. In: Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. Geneva, 2015.
4. Yap SF. Chronic hepatitis B infection in Malaysians. Malays J Pathol 1994; 16(1): 3-6.
5. Tan KK, Wong SL, Kuan GL, Shaik Hedra Z, Lee JK, Hung LC, et al. Childhood Immunisation. Malaysia: Ministry of Health Malaysia and the Academy of Medicine Malaysia, 2004.
6. Wen WH, Chang MH, Zhao LL, Ni YH, Hsu HY, Wu JF, et al. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. J Hepatol 2013; 59(1): 24-30.
7. Chen HL, Lin LH, Hu FC, Lee JT, Lin WT, Yang YJ, et al. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterology 2012; 142(4): 773-81.
8. Wong VC, Ip HM, Reesink HW, Lelie PN, Reerink-Brongers EE, Yeung CY,et al. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. Double-blind randomised placebo-controlled study. Lancet 1984; 1(8383): 921-6.