THE INTRAUTERINE INFECTION OF HEPATITIS B VIRUS

Kuei-Hsia Liu, MSN, RN.

To understand the intrauterine hepatitis B virus infection among pregnant women, and to determine the need of establishing programs for prevention of maternal transmission.

Venous blood samples of 273 pregnant women were collected and screened for HBsAg, HBeAg, Anti-HBs, Anti-HBe and Anti-HBc using ELISA method. All infants born to mothers who were positive for HBsAg alone or positive for both HBsAg and HBeAg were screened for HBsAg using the radioimmunoassay method at birth, 1 month and 6 months after birth.

Twenty-seven apparently healthy pregnant women (9.89%) were HBsAg-positive. Among Those, 9(3.3%) were HBsAg-positive along and 18(6.59%) were positive for HBsAg and HBeAg. Two of the women were Anti-HBs-positive (0.73%), 13 (4.76%) were Anti-HBe-positive, and 14 (5.13%) were Anti-HBc-positive. Nine infants born to mothers positive for HBsAg alone showed negative of HBsAg within six months after births. Among 18 infants born to women positive for both HBsAg and HBeAg, 3(16.67%) were HBsAg seropositive six months after their births. An overall rate of HBsAg carrier was estimated as 1.1% (3/273) in infants born to all pregnant women studied.

Couples are recommended to receive HBV test before marriage and pregnancy, as well as at their early pregnancies. Immunization of infants born to HBsAg/HBeAg-positive mothers with hepatitis B immunoglobulin within 24 hours after delivery and with hepatitis B vaccine later were suggested.

Keywords: Intrauterine infection, Hepatitis B, Pregnant women

Reprints and Corresponding Author:
Kuei-Hsia Liu,
Associate Professor
School of Nursing,
Chung Shan Medical and Dental College,
110, Section 1, Chien Kuo North Road,
Taichung,(402), Taiwan, R.O.C.
Tel.: +886- 4- 4730022 ext 1731
Fax: +886-4-3890964
E-mail: hsia@mercury.csmc.edu.tw.

中山醫學院護理學系

Introduction

Perinatal transmission is one of the most common modes of hepatitis B virus infection and often leads to long-term health consequences. Infants born to women positive for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) have a 70-90 percent chance of becoming infected in south Asia. Eighty to ninety of those infected infants will become chronic carriers (1).

Petermann and Ernest (2) believed that, in pregnancy, the hepatitis B virus is transmitted primarily at the time of delivery. Vertical transmission is an effective route for neonatal infection, and approximately 10% to 85% of infants born to hepatitis B surface antigen (HBsAg)-positive mothers will be infected, depending on the hepatitis B e antigen (HBeAg) status of the mother.

Roingeard et al. (3). indicated that postnatal transmission has been documented in infants from HBsAg-positive mothers. There are three potential modes for HBV transmission from mothers to their infants; in utero, during delivery, and postnatally.

Prenatal transmission of HBV to neonates born to HBsAg-positive carrier mothers has been reported by a number of investigators (1-4). Transmission during delivery may occur via contamination of maternal blood into the infant's circulation during the tearing of the placenta at birth, or by contact with blood or vaginal secretion while passing through the vaginal canal. Therefore, One way to eliminate HBV propagation of the disease is the prevention of intrauterine infection.

Intrauterine hepatitis B viral infection is one of the major factors that lead to HBsAg chronic carrier and failure of the HBV vaccine after birth (5). Humans are the only natural host of hepatitis B virus (6). The majority of infected newborns or children are asymptomatic, however they may become carriers with life-long and may have the complications of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (7-12). In order to learn more about the intrauterine hepatitis B infection, pregnant women from Wu Han area were selected for the present study. Hopefully, the study will shed more light on the issue concerning the prevention of maternal transmission from carrier mother to the fetus or newborn during perinatal period.

Materials and Methods

From December, 1992 to June, 1994, a total of 273 pregnant women from Jin Men First Public Hospital in Wu Han region in Hu Peh province, China were included in our screening program. Fasting venous blood from pregnant women were collected and sera were screened for hepatitis B virus surface antigen (HBsAg), hepatitis Be antigen (HBeAg), Anti-HBs, Anti-HBe and Anti-HBc using ELISA (Enzyme Linked Immunosorbent Assay) Kits (Abbott, North Chicago, IL.). Those seropositive in the screening underwent further screening of their infants using similar radioimmuno-assay.

Blood samples from those infants were screened for HBsAg at birth, and one month and six months after their births (triple tests). Infants who demonstrated HBsAg-positive in the triple tests were classified as having hepatitis B viral infections.

Results

A total of 273 apparently healthy pregnant women underwent the present study. Among those , 27 (9.89%) were HBsAg-positive. In this group, 9 were positive for HBsAg alone and 18 were positive for both HBsAg and HBeAg (double positive). Two of the women in this study (0.73%) were found to be Anti-HBs-positive. Thirteen

(4.76%) women were Anti-HBe-positive and 14 (5.13%) were Anti-HBc-positive.

Results of the screening for these HBV serological markers among 273 pregnant women are shown in Table 1.

Nine infants born to HBsAg-positive and HBeAg-negative mothers, were also found to be HBsAg-Positive, However, those infants showed no sign of HBsAg positive within six months after their births. Eighteen infants born to women positive for both HBsAg and HBeAg (double positive), also tested positive for HBsAg.

Three (16.67%) of those infants remained HBsAg seropositive six months after their births. Thus an overall rate of HBsAg carrier was estimated as 1.1% (3/273) in infants born to all pregnant women studied. The results of the screening for HBsAg serological markers in infants at birth, 1 months and 6 months after birth for HBsAg-positive or HBsAg/HBeAg double positive mothers are shown in Table 2.

Discussion

In this study, about 10% pregnant women from a sample obtained Wu Han region in Hu Peh province were found to be positive for HB surface antigen (Table 1). This rate of HBsAg-positive was higher than that reported in Stockholm (8) and in Ankara (9). Present study showed that pregnant women positive for both HBsAg and HBeAg were 6.59% (18/273) (Table1), which were also higher than that found in Senegal (3). Those women were considered as a high-risk group possibly carried highly infective hepatitis B virus that encouraged intrauterine infection. Among infants born to 18 HBsAg/HBeAg-positive mothers, three were HBsAg-positive at 6 months of age. Thus the HBsAg carrier rate of those infants were 16.67% (Table 2). The over all HBsAg-positive rate were 1.10% among 273 infants studied, which fitted well with the 0.53%-2.47% reported by Shu (13) and did not exceed the 3% reported by Wu & Chang (14). These three infected infants were likely the victims of intrauterine infection and thus the prevalence of intrauterine infection was 16.67% (3/18) among infants born to HBsAg/HBeAg-positive mothers. However, all infants born to HBsAg single positive mothers demonstrated HBsAg-negative at 6 months of age. (Table 2).

The ultimate way to control and prevent the propagation of hepatitis B virus is vaccination. Although vaccination had good response in post-exposure prophylaxis, it failed in some cases mainly due to intrauterine infection. Interestingly, the three cases as mentioned above were actually those who failed in hepatitis B vaccination. Therefore, what preventive procedure should be taken in this high-risk group and block the intrauterine hepatitis B infection is an important issue. Rosenthal et al. (7) indicated that 90% of infected infants and 30 to 60% of infected children between 1 and 5 years old develop chronic infection.

Comparing our results to those studies done by Obi et al. (15) and other investigators (3,8,9). as showed in Table 3, it is found that the HBeAg seropositives or HBsAg/HBeAg-positive rate was higher in present study than those in other studies. However, the Anti-HBc-positive among pregnant women from Wu Han region were much lower than those reported by Roingeard et al. (3) from Senegal West Africa. This results shows that pregnant women in our study had elevated level of antigens but poor titer of antibodies. This indicated that pregnant women from Wu Han region were more susceptible to hepatitis B.

In this study, 66.67%(18/27) of pregnant women tested positive for HBsAg were also found to be positive for HBsAg/HBeAg, which was much higher than 20%(8/40) reported by Chien et al. (16). The rate of 16.67%(3/18) of HBsAg carrier infants born to HBsAg/HBeAg (Double positive) mothers 6 months after they birth was higher than

those studies of Chien et al. (16) and Shu. (13) with a HBsAg carrier rate of 5.88% and 0.53%-2.47% respectively. Base on this finding, the prevalence of intrauterine hepatitis B infection appeared to be high in Wu Han region. Thus it is necessary to look for the possible causes and preventive actions.

Reece (17) pointed out that to eliminate hepatitis B virus, the first priority is to screen all pregnant women and follow-up vaccination of all infants. The second is the immunization of at-risk adolescents and adults. Additional education program concerned with hepatitis B virus infection should be enhanced and promoted. Ikeda et al. (1) and Rosenthal et al. (7) indicated that perinatal transmission of hepatitis B is largely preventable. Through perinatal screening of HBsAg-positive mothers and treating their infants with hepatitis B immune globulin(HBIg) and hepatitis B vaccine, a regimen that is 85-95 percent effective in preventing the carrier state. Petermann et al. (2) and Grosheide et al. (18) also thought that 90% of infections can be prevented if HBsAg-positive mothers are identified early and their offsprings are treated promptly after delivery with hepatitis B immune globulin and the HBV vaccine. Greenberg et al. (19) recommended universal immunizations to infants born to HBV non-carrier mothers with three doses of hepatitis B vaccine, at ages birth to 2 months, 1 to 4 months and 6 to 18 months (with $\geqq$ 1 month interval between the first and second doses) to increase their immunities towards infections.Lin et al. (20) suggested that the control of HBV infection can be achieved in two ways: first, by prevention of HBV perinatal transmission; and second, by reducing horizontal infection, such as reduction of HBeAg-positive carriers, screening of blood donors, and education. Those authors also suggested that the best way to prevent HBV infection is vaccination (21). It was recommended that infants born to HBsAg/HBeAg-positive mothers should receive HBIg within 24 hours after delivery and also hepatitis B vaccine should be given later. Healthy infants should also receive inoculation of three doses of hepatitis B vaccine at ages 3 to 5 days, 1 month and 6 months, respectively to block HBV infection (22). Sangfelt et al. (8) reported that hepatitis B immunoprophylaxis of newborns is highly effective in preventing a chronic carrier state. Hepatitis B vaccine in combination with HBIg gave good protection to infants born to HBeAg-positive mothers. In the study of Chan et al. (23), two hundred and seventy-seven infants born to (HBsAg)-negative non-carrier mothers had received hepatitis B vaccine inoculation and were followed up annually to the age of six. No infants in their study became HBsAg-positive. In other words, HBV infection could be blocked and prevented by conducting HBV screening among mothers and newborns as well as via treatment of hepatitis B immune globulin (HBIg) and inoculation of hepatitis B vaccine.

In conclusion, we recommend couples to take HBV test before marriage and at early pregnancy. Proper treatment will be recommended for those with positive result for HBsAg or HBeAg and their newborn infants to limit the spreading of hepatitis B virus.

ACKNOWLEDGMENTS

The author greatly appreciate the help of professor Guo-Ping Liang of Hu-Bei Medical University, China. for sample collection. And thank to the following colleagues, Dr. C.C. Lin, Dr. Shuan-Yow Li and Dr. Kan-Jen Tsai. for their valuable commends and advises in the preparation of the manuscript. I also like to thank Dr. Ming-Young Chow for his encouragement and help through out the study.

REFERENCES

1. Ikeda, R.M. , Birkhead, G.S:, Flynn, M.K., et al.: Use of multiple reporting sources for perinatal hepatitis B surveillance and follow-up. Amreican Journal of Epidemiology 1995; 142(7): 765-770.
2. Petermann, S., & Ernest, J.M.: Intrapartum hepatitis B screening. Amreican Journal of Obstetric and Gynecology 1995; 173(2): 369-374.
3. Roingeard, P., Diouf, A., Sankale, J.L., et al.: Perinatal transmission of hepatitis B virus in Senegal, West Africa. Viral Immunology 1993; 6(1): 65-73.
4. Pao, C.C., Yao, D.S., Lin, C.Y., et al.: Prenatal transmission of hepatitis B virus to neonates born to serum hepatitis B virus DNA-positive mothers. American Journal of Perinatology, 1992; 9(1): 61-65.
5. Chu, C.J., Tuan, S.C., Hsu, H.F., et al.: Prenatal transmission of hepatitis B virus from mother to infant. Chinese Journal of Infection 1989; 7(13): 159-161.
6. Lu, C.L., & Chen, T.y. : The Prevention and therapy for hepatitis B. Clinical Medicine 1994; 34(2): 99-109.
7. Rosenthal, P., Wood, D.L., Greenspoon, J.S., et al.: Hepatitis B virus serology in pregnant women : transmittal of results from obstetricians to pediatricians in California. The pediatric Infectious Disease Journal 1995; 14(11): 927-931.
8. Sangfelt, P., Reichard, O., Lidman, K., et al.: Prevention of hepatitis B by immunization of the newborn infant a long-term follow-up study in Stockholm, Sweden. Scandinavian Journal Infectious Disease 1995; 27: 3-7.
9. Erdem, M., Sahin, I., Erdem, A., et al.: Prevalence of hepatitis B surface antigen among pregnant women in a low-risk population. International Journal Gynecology and Obstetrics 1994; 44: 125-128.
10. Paquet, C., Babes, V.T., Drucker, J., et al.: Viral hepatitis B in Bucharest. Bulletin of the World Health Organization 1992; 71(6): 781-786.
11. Murnane, A., Evertson, L., & Helmchen, R. Maternal hepatitis B screening at a private hospital. The Journal of Reproductive Medicine 1992; 37(10): 841-844.
12. Ko, T.M., Tseng, L.H., Chang, M.H., et al.: Amniocentesis in mothers who are hepatitis B virus carriers does not expose the infant to an increased risk of hepatitis B virus infection. Archives of Gynecology and Obstetrics 1994; 255: 25-30.
13. Shu, C.I. : Epidemiological study on the efficiency of HBV vaccination in China. The national symposium of viral hepatitis held by Chinese Medical Association, 1996;11-14.
14. Wu, H.H., & Chang, C.C.: Study of immune tolerance of chronic hepatitis B infection and the strategy of resolution. The national symposium of viral Hepatitis held by Chinese Medical Association1996; 23-29.
15. Obi, C.L., Anyiwo, C.E., Nnatu, S.N., et al.: A comparison of human immunodeficiency virus (HIV) seropositivity and hepatitis B surface antigenemia (HBsAg) among the same group of apparently healthy pregnant women in Lagos, Nigeria: A preliminary report. Viral Immunology 1993; 6(1), 43-47.
16. Chien, H.H., Wen, L.C., Ma, T.Y., et al.: Monitoring transmission of hepatitis B virus from mother to infant using molecular hybridization. Chinese Journal Obstetrics and Gynecology 1992; 27(5): 259-262.
17. Reece, S.M. : Immunization strategies for the elimination of hepatitis B. Nurse Practitioner 1993; 18(2): 42-50.
18. Grosheide, P.M., Quartero, H.W.P., Schaim, S.W., et al.: Early invasive prenatal diagnosis in HBsAg-positive women. Prenatal Diagnosis 1994; 14: 553-558.
19. Greenberg, D.P., Vadheim, C.M., Wong, V.K.,

et al.: Comparative safety and Immunogenicity of two recombinant hepatitis B vaccines given to infants at two, four and six months of age. Pediatric Infectious Disease Journal, 1996; 15(7): 590-596.

20. Lin, H.H., Hsu, H.Y., Lee, T.Y., et al.: Age-specific prevalence of hepatitis B surface and e antigenemia in pregnant women in Taiwan. Asia-Oceania Journal Obstetrics Gynecology 1994; 20(2): 141-145.
21. Lin, H.H., Huang, L.C., & Lin, D.Y.: Hepatitis B virus infection in eastern Taiwar from a regional general hospital. Medical Journal 1992; 4(2): 94-99.
22. Department of Health, Executive Yuai Manual of preventive vaccination Department of Health, Executive Yuai . 1997
23. Chan, C.Y., Lee, S.D., Tsai, Y.T., et a term follow-up of hepatitis B Vacci infant born to non-carrier mothers ir China Medical Journal 1992; 50: 83-8.

Table 1. Primarily screening for HBV markers among 273 pregnant women.

Item	HBsAg	HBsAg HBeAg	Anti-HBs	Anti-HBe	Anti-H
Number of	9(3.3%)	18(6.59%)			
Seropositive	27(9.89%)		2	13	14
(%)			(0.73%)	(4.76%)	(5.13

Table 2. Carrier rate of HBsAg in all studied infants at birth, at 1 month and 6 months

Mothers	Infants					
	Number of infants	HBsAg(+)			At 6 months HBsAg Carrier rate (%)	At 6 months HBsAg carrier among 273 Pregnant (%)
		At birth	1 month	6 months		
Double positive HBsAg (+) HBeAg (+)	18	2	2	3	3/18=16.67	3/273=1.10
Single positive HBsAg (+)	9	1	1	0	0	0

Table 3. Distribution of HBV serological markers among pregnant women

Region	Total number of samples	Number of sero-positive (%)					
		HBsAg*	Anti-HBs	HBeAg**	Anti-HBe	Anti-HBc	HBsAg HBeAg
Wu Han	273	27 (9.89%)	2 (0.73%)	18 (6.59%)	13 (4.76%)	14 (5.13%)	18 (6.59%)
Stockholm	10519	416 (3.96%)		58 (0.55%)	331 (3.15%)		
Ankara	1224	53 (4.33%)		4 (0.33%)	28 (2.29%)		
Senegal	152	21 (13.8%)		2 (1.32%)		120 (79%)	2 (1.32%)

* Total women tested positive for HBsAg which includes those tested positive for HBsAg alone and those tested positive for HBsAg and HBeAg.

** Women tested positive for HBeAg and HBsAg.

B型肝炎病毒子宮內感染之調查研究

劉桂霞

為進一步瞭解，孕婦B型肝炎病毒子宮內感染的情形，以作為B型肝炎帶原母親將病毒傳染給胎兒或新生兒之預防決策依據。

抽取273位孕婦之靜脈血，以酵素免疫分析法(ELISA)，篩檢HBsAg, HBeAg, Anti-HBs, Anti-HBe and Anti-HBc 標誌作為初篩。對HBsAg單陽性或HBsAg, HBeAg雙陽性的母親, 所生的所有嬰兒, 在出生後二十四小時之內，出生後一個月，六個月，各抽取靜脈血，分離血清，以放射免疫檢定法(Radio-immunoassay)，連續三次HBsAg篩檢。

273位健康孕婦，抽血檢驗結果，發現HBsAg 陽性者有27位、佔9.89% ，其中HBsAg 單陽性者有9位、佔3.3%，另18位為HBsAg ，HBeAg雙陽性佔6.59%，Anti-HBs 陽性者有2位、佔 0.73%，Anti-HBe 陽性者有13位、佔4.76%，Anti-HBc陽性者有14位、佔 5.13%。9位HBsAg單陽性母親，所生的嬰兒從出生到六個月，連續三次HBsAg篩檢，結果到六個月時都沒發現有HBsAg陽性反應。但另18位為HBsAg ，HBeAg雙陽性母親，所生的嬰兒從出生到六個月，也連續三次HBsAg篩檢，結果到六個月時發現有3位、佔16.67% 嬰兒HBsAg 陽性反應，此3位嬰兒在所有273位被篩檢HBsAg 帶原者佔 1.1%。

建議結婚夫婦在婚前、孕前或妊娠早期做B型肝炎病毒檢查。同時也建議對據有B型肝炎表面抗原(HBsAg)陽性及B型肝炎病毒e抗原(HBeAg)陽性帶原母親所生的嬰兒，在出生二十四小時內給予B型肝炎免疫球蛋白(hepatitis B immunization)，然後再給予B型肝炎疫苗注射。

關鍵詞：子宮內感染， B型肝炎，懷孕婦女

中山醫學院護理學系