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ORIGINAL ARTICLE

The Association of Maternal HBsAg Carrier Status and Perinatal Outcome

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Background and Aims: **Hepatitis B virus infection is still a major public health concern all over the world, and much research must be carried out on the various aspects of this issue. Since infection with hepatitis B virus in pregnant mothers is a threat for both mother and her fetus, this study was performed to determine the relationship between maternal HBsAg carrier status and perinatal outcome.**

Methods: **A retrospective case-control study was performed on 450 carriers of hepatitis B surface antigen (HBsAg) pregnant women and compared to 450 controls. Both groups were matched for age, parity, and body mass index (BMI).**

Results: **When compared to the control group, patients with HBsAg displayed significantly higher incidence of gestational diabetes mellitus (GDM) (7.7% *vs.* 2% P=0.001), increased hospitalization period after delivery (22.9% *vs.* 3.33%, P<0.0001), preterm labor at less than 37 weeks (10.9% *vs.* 2.67%, P<0.0001), pregnancy induced hypertension (13% *vs.* 2.89%, P<0.0001), and preterm premature rupture of membranes (3.55% *vs.* 1.1%, P=0.03). Also, the incidence of macrosomy (6.67% *vs.* 2.22%, P=0.02), intrauterine fetal death (5.56% *vs.* 0.44%, P=0.001), still birth (2.89% *vs.* 0.44%, P=0.005), and NICU admission (25.78% *vs.* 2.22%, P<0.0001) in the carrier mothers were higher.**

Conclusions: **HBsAg carriers have increased risk of hospitalization period after delivery, preterm labor, gestational hypertension, preterm premature rupture of membranes. In addition higher incidence of macrosomy, intrauterine fetal death, still birth, and NICU admission were observed. Therefore our results showed HBsAg carrier mothers have increased maternal and neonatal complications.**

Keywords: **Pregnancy Outcomes, Hepatitis B Virus, Carrier State, HBsAg**

Introduction

Hepatitis B virus (HBV) is a common cause of liver disease in the world. Over 2 billion people today have been infected with HBV and 400 million of them are chronically infected carriers without significant liver disease [1, 2]. Over 70% of the chronic hepatitis B patients in the world are Asians [3, 4]. Fortunately, as Alavian *et al.* have reported, since Iran's national vaccination program implementation in 1993, the number of HBV patients in the age group 2-14 has declined from 1.3% to 0.8% [5].

HBV is present in blood, saliva, semen, vaginal secretions, and menstrual blood of infected individuals [6]. Perinatal vertical transmission is the most common mode of transmission worldwide [7]. The age at acquisition of hepatitis B infection influences the risk of chronicity, with rates of persistent infection being substantially higher in individuals infected perinatally or during infancy than in those infected as adults [8]. Furthermore, the age at infection has an impact on the natural history of the disease. Spontaneous hepatitis B e antigen (HBeAg) sero-conversion rates are low in children and those infected early in life [9, 10].

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Presence of chronic carrier state of hepatitis B surface antigen (HBsAg) in pregnant women is a major health concern. In some parts of the world endemic for hepatitis infection, such as Hong Kong, the incidence of the chronic carrier states in the obstetric population has been estimated to be up to 10 % [10-12].

According to the latest protocols for screening during pre and antenatal cares, all pregnant women are screened for hepatitis B surface antigen at the first perinatal visit [13].

Furthermore, routine antenatal maternal screening for HBsAg has been shown to be cost effective and beneficial as neonatal immunization and vaccination is effective in the prevention of vertical transmission. Most transmission occur intra-partum and intrauterine infection is rare [7].

Despite its prevalence, there is little data on the effects of maternal chronic HBV infection on pregnancy outcomes.

Review of few published articles on this issue demonstrated controversial findings. Gambarin-Gelwan *et al.* and Tse *et al.* have reported increased maternal and neonatal complication in HBsAg carrier mothers [14, 15]. While according to the study made by Wong *et al.*, hepatitis B surface antigenemia in pregnant women does not pose additional risk for the pregnancy [16].

Therefore, in order to evaluate the situation in our country, we have conducted a retrospective case-control study to assess the impact of maternal hepatitis B antigenemia on maternal and neonatal outcomes.

Materials and Methods

A retrospective case control study was carried out over a 7 year period from March 2001 to December 2008 on HBsAg positive women attending the labor ward in Mahdieh and Vali Asr Tertiary Care Hospital affiliated to Shahid Beheshti University of Medical Sciences and Tehran University of Medical Sciences in Tehran, Iran. The study included HBsAg positive women with singleton pregnancy (case group) and 450 HBsAg negative women with singleton pregnancy (control group). The result of the routine antenatal HBsAg screening was retrieved from patient records. Unfortunately, neither of the patients had HBeAg status record in their medical history. Two groups were matched for age, parity, and BMI. Only singleton pregnancies were selected and those patients who were diagnosed to have had active hepatitis from any cause at any time during their pregnancy were excluded from the subsequent analysis. All women participating in the study gave their informed consent. The study was approved by the local ethics committees.

The clinical information of the cases and controls were extracted from medical records. The demographic characteristics including age, parity, past medical history, body mass index (BMI), and antenatal complication such as pregnancy induced hypertension (PIH), gestational diabetes (GDM), preterm labor (PTL), preterm premature rupture of membrane (PPROM), premature rupture of membrane (PROM), Superimposed PIH, ante partum hemorrhage, post partum hemorrhage and increased hospitalization period after delivery were retrieved from the obstetric records. Perinatal data including neonatal birth weight, intrauterine fetal death (IUFD), still birth, and NICU admission were extracted from the neonatal records.

Statistical analysis

Statistical analyses were performed using SPSS -15 (Statistical Package for the Social Sciences, for Windows, Chicago). In the primary stage, continuous variables were analyzed and reported as means and tested by t-test for comparison between the HBsAg negative and positive groups. Categorical variables were analyzed using Chi-square test or Fisher's exact test and odds ratios with 95% confidence interval were calculated. In the second stage, Multinomial logistic regression was performed to determine the role of HBsAg status in the subsequent perinatal outcome complications, by considering confounding factor effects.

Results

There was no difference in the mean age, parity, and BMI between the HBsAg positive and negative groups (Table 1). There were no significant

Table 1. Maternal demographic parameters with respect to HBsAg status.

	HBsAg positive (n=450)	HBsAg negative (n=450)
Parity		
Primiparous	180 (40%)	185 (41.11%)
Multiparous	270 (60%)	265 (58.88%)
Age (years)	25/2249	26/9818
BMI (kg/m^2)*	20.70±2.91	20.61±3.02
Hb at admission (g/dL)*	11.25±1.09	11.28±1.16

*Hb: hemoglobin; **BMI: body mass index. Results are expressed in number (%) or mean± standard deviation (SD) as indicated.

differences in the past health history between the two selected groups. All selected cases had no clinical manifestations of liver disorders or hepatitis during the index pregnancy based on their medical records. In the case group, there was a significantly higher incidence of gestational diabetes, pre-eclampsia, preterm labor at less than 37 weeks, preterm premature rupture of membranes and hospitalization period of mothers after delivery compared to control group. Although the incidence of maternal death and premature rupture of membranes, were higher in the case group, but this difference was not statistically significant. There were no significant differences in the incidences of superimposed pre-eclampsia, ante partum and post partum hemorrhage between two groups (Table 2).

The effects of HBsAg status on the neonatal outcomes was also analyzed (Table 3). The increased risk of macrosomia, intrauterine fetal death, and also still birth of infants in the case group was statistically significant when compared with the control group. There was also significant increase in NICU admission of new born neonates in the case group compared to the control. There was no significant difference between case group and control group regarding in the Apgar score at 1st and 5th minutes, meconium stained liquor in labor, and fetal distress.

Discussion

The prevalence of HBV carriers varies from 0.1 percent to 2 percent in low prevalence areas (United States and Canada, Western Europe, Australia and New Zealand) to 10 to 20 percent in high prevalence areas (Southeast Asia, China, sub-Saharan Africa) [17]. In Iran, due to the implementation of national-wide vaccination program for all neonates and high risk group since 1993 and increased public awareness about HBV risk, the prevalence of HBV has dramatically declined (1.3% to 0.8% in the age group of 2-14 year) [5]. The wide range in HBV carrier rate in different parts of the world is largely related to the

Table 2. Maternal complications with respect to HBsAg status.

	HBsAg positive n=450	HBsAg negative n=450	P-value	OR (95% CI)
GDM	35 (7.78%)	9 (2%)	0.001	3.62 (1.6-7.9)
PIH	59 (13%)	13 (2.89%)	<0.0001	4.2 (2.2-8.1)
PTL	49 (10.9%)	12 (2.67%)	<0.0001	3.9(1.9- 7.8)
PROM	31(6.89%)	11(2.44%)	0.07	2 (0.9-4.4)
PPROM	16 (3.55%)	5(1.1%)	0.03	3.2(1.1-9.3)
Prolong maternal hospitalization	103 (22.9%)	15 (3.33%)	<0.0001	7.4(4.2-13.2)
Maternal death	1 (0.22%)	0	0.31	
Superimposed PIH	5 (1.1%)	3(0.67%)	0.6	0.63 (0.17-3.4)
Ante partum hemorrhage	7(1.55%)	6 (1.33%)	0.7	0.67 (0.18-2.4)
Post partum hemorrhage	6 (1.33%)	5 (1.11%)	0.5	1.5 (0.4-5.2)

GDM: gestational diabetes mellitus; PIH: pregnancy induced hypertension; PT: preterm labor; PROM: prelabor rupture of membranes; PPROM: premature prelabor rupture of membranes

Table 3. Neonatal complications with respect to HBsAg status.

	HBsAg positive n=450	HBsAg negative n=450	P-value	OR (95% CI)
Meconium stained liquor in labor	23 (5.11%)	21(4.67%)	0.95	0.96 (0.48-1.9)
5 min Apgar score<7	16 (3.55%)	11 (2.44%)	0.22	1. 7 (0.72-3.9)
1 min Apgar score <4	6 (1.33%)	4 (0.89%)	0.51	0.58 (0.11-2.9)
IUFD	25 (5.56%)	2 (0.44%)	0.001	12.1 (2.7-52.6)
Stillbirth	13 (2.89%)	2 (0.44%)	0.005	8.8 (1. 9-29.7)
Fetal distress	15 (3.33%)	9 (2%)	0.29	1.6 (0.65-3.9)
NICU admission	116 (25.78%)	10 (2.22%)	<0.0001	14.9 (7.6-29.1)
Macrosomia	30 (6.67%)	10 (2.22%)	0.02	2.5(1.2-5.6)

IUFD: intra uterine fetal death

mode of transmission of HBV. For example, in high prevalence areas such as china, perinatal infection is the predominant mode of transmission [18]. While in low prevalence areas like the united state HBV transmission occurs primarily among unvaccinated persons with behavioral risks for HBV transmission (e.g., heterosexuals with multiple sex partners, injection-drug users) [19].

The rate of progression from acute to chronic HBV infection is approximately 90 percent for perinatally acquired infection [8]. Since risk factor based perinatal screening protocols have been shown to detect almost 60% of the women who are HBV carrier, testing for HBsAg should be performed on all women at the first perinatal visit and repeated late in pregnancy in those at high risk for HBV infection [7].

An increased incidence of maternal and neonatal morbidity such as gestational diabetes, pre-eclampsia, ante-partum hemorrhage, preterm labor, premature rupture of membranes, fetal distress, and meconium peritonitis in the HBsAg positive mothers was reported [14]. While, Wong *et al.* study on 824 HBsAg positive mothers and 6281 controls revealed that there are no differences in the incidence of preterm birth, there is a small risk involved with gestational age, birth weight, rupture of membranes, prenatal asphyxia and perinatal mortality in HBsAg carrier mothers compared to control [16].

Based on our results, carrier mothers had a higher prevalence of GDM (P=0.001, OR 3.62, 95% CI 1.6-7.9), increased hospitalization period after delivery (P<0.0001, OR 7.4, 95% CI 4.2-13.2), preterm labor at less than 37 weeks (P<0.0001, OR 3.9, 95% CI 1.9- 7.8), pregnancy induced hypertension (P<0.0001, OR 4.2, 95% CI 2.2-8.1), and preterm premature rupture of membranes (P=0.03, OR 3.2, 95% CI 1.1-9.3). The maternal mortality and premature rupture of membranes were not significantly higher in the case group. The incidence of macrosomy (P=0.02, OR 2.5, 95% CI 1.2-5.6), intrauterine fetal death (P=0.001, OR 12.1, 95% CI 2.7-52.6), still birth (P=0.005, OR 8.8, 95% CI 1. 9-29.7), and NICU admission (P<0.0001, OR 14.9, 95% CI 7.6-29.1) of the carrier mothers were significantly higher compared to control.

Numerous extrahepatic manifestations of acute and chronic forms of viral hepatitis such as polyarteritis nodosa and glomerulonephritis have been reported. Immune complexes and increased systemic inflammatory state are thought to be responsible for these extra-hepatic manifestations [20]. On the other hand, an elevated level of pro-inflammatory mediators has been shown in the amniotic fluid of women with PTL, PPROM, PIH and GDM [21-25]. As Tse *et al.* work mentioned, it is likely that the increase of systemic inflammatory state in HBsAg carrier mothers is responsible for the increased of prevalence of these complications [15].

But to confirm this hypothesis we need to carry out more investigations regarding obtaining the level of pro-inflammatory cytokines in patient's serum and amniotic fluid. Hepatic damage due to the HCV infection has been reported. This hepatic damage with combination of super-imposed effect of pregnancy on insulin resistance may lead to the more than 3 times increase of GDM in the HBsAg carrier mothers [26]. Our finding, in support of this report, showed 3.6 times increase in prevalence of GDM in HBsAg carrier mothers.

In addition, our study showed the incidence of macrosomia, NICU admission, still birth and IUFD were higher in the newborn of the HBsAg carriers in comparison with HBsAg negative mothers.

But in order to come to a definite conclusion for explaining the potential role of chronic HBV infection in pregnancy complications, more investigation with more data must be carried out in a prospective manner.

Conclusions

HBsAg carriers have increased risk of hospitalization period after delivery, GDM, preterm labor, pre-eclampsia, preterm premature rupture of membranes and their infants have increased incidence of macrosomy, intrauterine fetal death, still birth, and NICU admission.

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