Hepatitis B Carriers in Hong Kong: Prevalence and Pregnancy Outcomes

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Objectives: To determine whether the point prevalence of hepatitis B surface antigen (HBsAg) carriers varies with maternal age, and to assess the impact of hepatitis B virus carrier status on pregnancy and perinatal outcomes.
Methods: A total of 9526 patients who had delivered in Queen Elizabeth Hospital in Hong Kong between 1 October 2010 and 31 December 2011 were included in this retrospective study.
Results: The HBsAg carrier rate was lower in younger maternal age-groups, being 11.3% in women aged ≥43 years and 8.0% in women aged ≥22 to <43 years, and 4.4% in women aged <22 years (p=0.016). Parity was higher among HBsAg carriers (0.70 vs. 0.58, p<0.001). The prevalence of positive HBsAg status was significantly lower in Hong Kong residents compared with non–Hong Kong residents (6.8% vs. 13.3%, p<0.001). There was no significant difference in the point prevalence of major antenatal complications in HBsAg carriers and non-carriers. Among the hepatitis B carriers, the elective Caesarean section rate was higher (13.8% vs. 12.9%, p=0.018), as was the rate of postpartum haemorrhage (4.0% vs. 2.7%, p=0.033). By contrast, the rate of epidural analgesia use was lower (4.4% vs. 6.2%, p=0.045), as was the rate of emergency lower segment Caesarean section (11.6% vs. 15.5%, p=0.018). Moreover, the mean birth weights of babies delivered by hepatitis B carriers were significantly greater (3184.3 g vs. 3144.3 g, p=0.042), but there were no other major differences in perinatal outcomes.
Conclusion: Declining maternal carrier rate of HBsAg in women aged <22 years was observed, probably due to the effects of the universal neonatal vaccination programme implemented since 1998. Carrier status was associated with a higher elective Caesarean section rate and a mildly larger birth weight. Further studies are warranted to elaborate these associations.
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Introduction

Hepatitis B infection is a global health problem involving 350 million people who are chronically infected worldwide[1]. It gives rise to acute hepatitis episodes, liver cirrhosis, liver failure and liver cancer, whilst also resulting in significant morbidity and mortality. Hong Kong is an endemic area where about 10.4% of male adults and 7.7% of female adults are reported to carry the hepatitis B surface antigen (HBsAg)[2]. According to the Department of Health, in 1993, 50 to 80% of the population aged >50 years had evidence of previous hepatitis B infection[3]. In an attempt to contain this widespread problem, since 1984 the Hong Kong Government introduced the neonatal hepatitis B virus (HBV) vaccination programme. For at-risk first-parity babies delivered by carrier mothers in public hospitals, hepatitis B immunoglobulin and hepatitis B vaccine were administered. By 1986, any parity at-risk babies born in public hospitals were also covered. Since November 1988, all newborns have been offered the vaccine and more than 80% of the children born in 1991 received full courses of the vaccine[3]. A supplementary Primary 6 vaccination programme was introduced in 1998[2]. According to statistics collected and maintained by Family Health Services of the Department of Health, coverage with the first-dose HBV vaccine has been consistently above 99% over several years[2]. However, statistical data indicated a reduction in the rate for second or the third doses of the vaccine. Two explanation for this phenomenon were proposed by the Department of Health as follows: (1) some locally born babies had returned to mainland China after delivery and did not attend Maternal and Child Health Centres (MCHCs) thereafter, and (2) some babies received the combined vaccine in private facilities not known to MCHCs[2]. Since the universal neonatal hepatitis B vaccination programme started in 1988, the first batch of privileged targeted babies would have been around 22 years old by the year 2010, when this study was designed. If the vaccination programme was effective, a reduction in the point prevalence of HBsAg carriers was to be expected

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in 22-year-old local subjects. However, one local study in 2009 reported that the point prevalence of maternal HBV infection had remained unchanged during the past 10 years, despite implementation of neonatal vaccination for more than 20 years, and a vaccination uptake rate in adults of up to 33%[4].

Studies on the impact of hepatitis B carrier status in pregnancy showed contradictory results. Wong et al[5] suggested an absence of a significant impact in their study, which evaluated 824 HBsAg-positive women in comparison to 6281 controls, all seen from 1996 to 1998. Whereas Tse et al[6] found an increased risk of gestational diabetes mellitus (GDM) and antepartum haemorrhage (APH) in 253 HBsAg carriers having singleton pregnancies compared with 253 controls matched for age, parity, and year of delivery, all from 2000 to 2002.

Thus, the objective of this study were first, to determine whether the prevalence of HBsAg carrier status varies with maternal age, and second, to assess the impact of HBV carrier status on pregnancy and perinatal outcomes.

Methods

All pregnant women who had delivered in the Department of Obstetrics and Gynaecology in Queen Elizabeth Hospital, Hong Kong during the period 1 October 2010 to 31 December 2011 were included in the study. Since Hong Kong has universal antenatal blood screening for chronic HBsAg carrier using status, all women in the sample were checked for hepatitis B status at the time of their booking visit. For non-booked patients including those who did not have the right of abode in Hong Kong (e.g. tourists from mainland China classified as non-entitled persons [NEPs]), hepatitis B status was checked during hospital admission. Blood samples were sent to Department of Health and tested using enzyme immunoassay (Abbott Murex HBsAg test, Version 3), which has a sensitivity of 100% and specificity of >99.5%. Samples yielding borderline or positive results were retested with other enzyme immunoassay kits. Liver function tests were carried out only in indicated cases when there was a suspicion of acute liver diseases. Viral load and hepatitis B virus early antigen (HBeAg) status were not assessed in this study, as they were not checked as part of the hospital's routine procedures. Intrapartum management was the same for both HBsAg carriers and non-carriers. In addition to universal hepatitis B vaccination at birth, babies born from HBsAg-positive mothers received passive immunisation with immunoglobulin.

All necessary data were retrieved and logged by designated midwifery and nursing staff in the antenatal and labour wards. Every labour ward nurse had to have performed at least 30 supervised data entries before being sanctioned to undertake independent data entry. The patient's hepatitis B status logged in the antenatal ward was cross-checked again in the labour ward. All patients with deliveries 24 weeks or more after gestation were included in the present study. Demographic information of the subjects, past medical health, antenatal complications, mode of delivery, labour outcomes, postpartum complications and perinatal information were analysed (Table). We did not undertake universal screening for GDM with oral glucose tolerance test (OGTT), which was only performed for patients considered at higher risk for GDM, by virtue of obesity, age ≥35 years, a family history of diabetes mellitus in a first-degree relative, and macrosomia.

Statistical analysis was performed using Statistical Package for the Social Sciences (Windows version 16.0; SPSS Inc, Chicago [IL], US). Differences in categorical variables were analysed with the Pearson Chi-square test. Differences in continuous variables were analysed with the t-test. A p value of <0.05 was considered significant.

Results

Of a total of 9526 pregnant women delivered, 748 were hepatitis B carriers and 82.1% were Hong Kong residents. The HBsAg carrier rate was significantly lower among the Hong Kong residents than in those who were NEP (6.8% vs. 13.3%, p<0.001). The HBsAg carrier rate yielded a downward trend of 11.3% in women aged ≥43 years, 8.0% in those aged ≥22 to <43 years, and 4.4% in those aged <22 years (p=0.016; Figure). Parity was higher among HBsAg carriers (0.70 vs. 0.58, p<0.001).

Maternal Condition and Past Medical Health

There was no significant difference in the point prevalence of liver and other maternal medical diseases in HBsAg carriers and non-carriers (Table).

Antenatal Complications

No significant difference was detected with respect to the frequency of major antenatal complications between HBsAg carriers and non-carriers, including GDM (7.9% vs. 8.1%, p=0.847), APH (5.5% vs. 5.4%, p=0.935), pre-eclamptic toxaemia (PET) [1.2% vs. 1.6%, p=0.384], and eclampsia (0% vs. 0.0%, p=0.613) [Table].

Maternal Outcomes

On comparing carriers with non-carriers, the former demonstrated higher rates of elective Caesarean sections

Table. Comparison of medical disorders, obstetric complications and outcomes in carriers and non-carriers of hepatitis B surface antigen (HBsAg)

Medical disorders, obstetric complications and outcomes	No. (%) or as otherwise stated		p Value
	Non-HBsAg carriers (n=8778)	HBsAg carriers (n=748)	
Maternal condition and past medical health			
Anaemia	496 (5.7)	41 (5.5)	0.847
Maternal renal disease	32 (0.4)	0 (0)	0.098
Maternal liver disease	7 (0.1)	0 (0)	0.44
Maternal respiratory disease	132 (1.5)	9 (1.2)	0.513
Maternal gastrointestinal disease	12 (0.1)	0 (0)	0.312
Pre-existing epilepsy	24 (0.3)	0 (0)	0.152
Maternal psychiatric disease	107 (1.2)	8 (1.1)	0.719
Maternal immunological disease	9 (0.1)	0 (0)	0.381
Maternal thyroid disease	215 (2.4)	16 (2.1)	0.596
Maternal surgical disease	289 (3.3)	32 (4.3)	0.152
Maternal cardiac disease	99 (1.1)	5 (0.7)	0.246
Pre-existing diabetes mellitus	22 (0.3)	0 (0)	0.170
Chronic hypertension	14 (0.2)	2 (0.3)	0.489
Antenatal complications			
Gestational diabetes mellitus	710 (8.1)	59 (7.9)	0.847
Eclampsia	3 (0.0)	0 (0)	0.613
Gestational hypertension	114 (1.3)	7 (0.9)	0.395
Pre-eclampsia	142 (1.6)	9 (1.2)	0.384
Antepartum haemorrhage	475 (5.4)	41 (5.5)	0.935
Maternal outcomes and fetal condition			
Augmentation of labour	395 (4.5)	27 (3.6)	0.256
Epidural analgesia	548 (6.2)	33 (4.4)	0.045
Induction of labour	3335 (38.0)	283 (37.8)	0.932
Previous uterine scar	1089 (12.4)	96 (12.8)	0.733
Manual removal of placenta	64 (0.7)	7 (0.9)	0.528
Postpartum haemorrhage	235 (2.7)	30 (4.0)	0.033
Emergency Caesarean section	1361 (15.5)	87 (11.6)	0.018
Elective Caesarean section	1129 (12.9)	103 (13.8)	0.018
Normal vaginal delivery	5685 (64.8)	507 (67.8)	0.495
Vaginal breech delivery	15 (0.2)	1 (0.1)	0.495
Vacuum extraction	517 (5.9)	43 (5.7)	0.495
Forceps delivery	65 (0.7)	6 (0.8)	0.495
Cephalic presentation	8277 (94.3)	707 (94.5)	0.431
Breech presentation	474 (5.4)	37 (4.9)	0.431
Transverse or oblique presentation	25 (0.3)	4 (0.5)	0.431
Perinatal complications			
Preterm delivery	205 (2.3)	19 (2.5)	0.723
Neonatal intensive care unit admission	760 (8.7)	56 (7.5)	0.272
Live birth rate	8749 (99.7)	745 (99.6)	0.849
Apgar score <7 at 1 minute	359 (4.1)	28 (3.7)	0.645
Apgar score <7 at 5 minutes	67 (0.8)	4 (0.5)	0.485
Apgar score <4 at 1 minute	66 (0.8)	5 (0.7)	0.799
Apgar score <4 at 5 minutes	37 (0.4)	3 (0.4)	0.934
Birth weight <2500 g	710 (8.1)	50 (6.7)	0.357
Birth weight 2500 g – 3999 g	7763 (88.4)	674 (90.1)	0.357
Birth weight >3999 g	305 (3.5)	24 (3.2)	0.357
Mean birth weight (g)	3144.3	3184.3	0.042

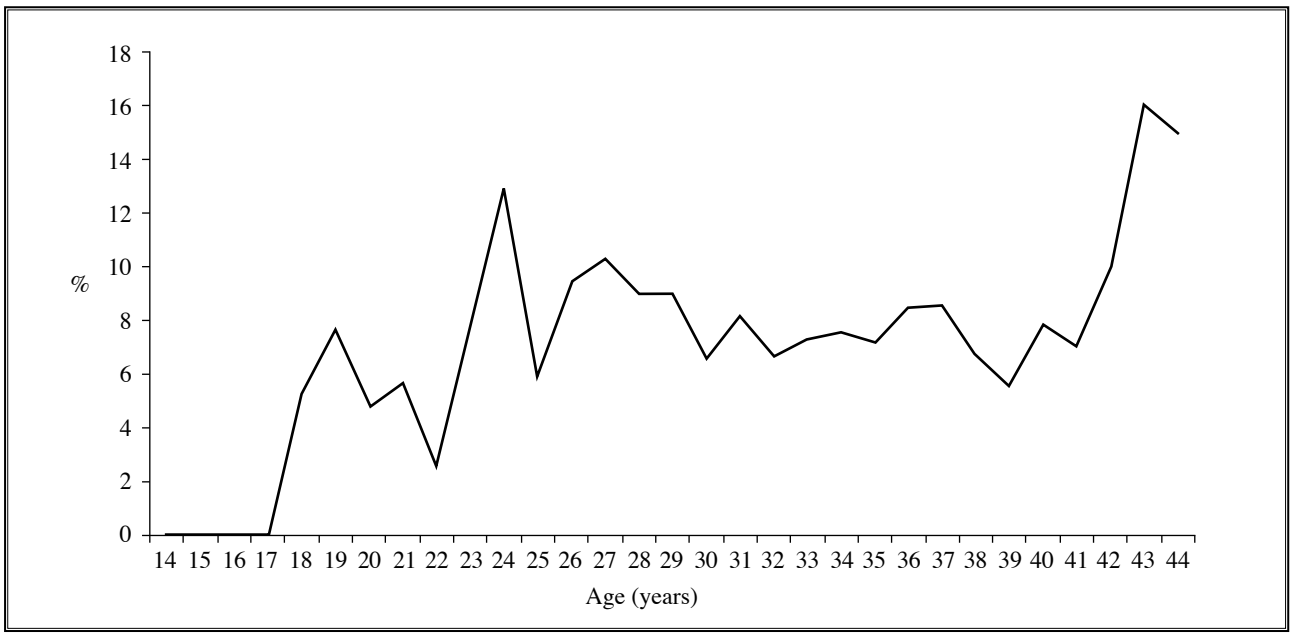

Figure. Percentage of hepatitis B surface antigen (HBsAg) carriers versus maternal age during the study period (1 October 2010 to 31 December 2011)

(13.8% vs. 12.9%, p=0.018), and postpartum haemorrhage (4.0% vs. 2.7%. p=0.033). However, carriers had lower rates of epidural analgesia (4.4% vs. 6.2%, p=0.045) and emergency lower segment Caesarean sections (11.6% vs. 15.5%, p=0.018) [Table].

Perinatal Outcomes

There were no differences in other maternal outcomes and preterm birth rates between the carriers and non-carriers. Mean birth weights of babies delivered by carriers were significantly higher (3184.3 g vs. 3144.3 g, p=0.042). However, there were no differences between the two groups for the frequencies of macrosomia (3.2% vs. 3.5%, p=0.357), livebirths (99.6% vs. 99.7%, p=0.849), neonatal intensive care unit (NICU) admissions (7.5% vs. 8.7%, p=0.272), and the proportion of babies with low Apgar scores (Table).

Discussion

The HBsAg carrier rate trend was downwards, from 11.3% in women aged ≥43 years to 8.0% in women aged ≥22 to <43 years, to 4.4% in those aged <22 years. The youngest age-group (those <22 years old) coincided with the population that benefited from the universal neonatal hepatitis B vaccination programme introduced around 22 years ago. As such, the corresponding lower carrier rate was consistent with the effectiveness of the programme. Current medical literature also provides evidence for the success of universal neonatal hepatitis B vaccination programme. Immunising infants of HBsAg- and HBeAg-positive mothers, with a combination of hepatitis B immunoglobulin and hepatitis B vaccine after birth reduced the risk of transmission from 90% to less than 10%[7,8]; the transmission rate was even lower if the mother was HBeAg-negative. In 1990, the World Health Organization (WHO) recommended universal vaccination against hepatitis B in all nations. By the end of 2007, a total of 171 (88%) of the 193 WHO member states reported having integrated HBV vaccines into their routine infant vaccination schedules. The coverage rate with three doses of HBV vaccines has increased from 32% in 2000 to 65% in 2007[9]. In Taiwan, which is similar to Hong Kong in many ways, the universal vaccination programme was established in 1984, after which its HBV infection rate in high-risk groups decreased from 90% to 14%, and the carrier rate decreased from 9.8% to 1.3%[9-11].

If the vaccination programme was completely successful, we would expect a much lower carrier rate in those younger than 22 years. Failure of vaccination or incomplete vaccination are not entirely plausible explanations for the current discrepancy between the actual and expected carrier rate. Non-coverage could be one of the reasons, whereby a proportion of the younger subjects might not have had hepatitis B vaccination. These groups may include NEPs who were tourists from China where universal neonatal vaccination programme has not yet started. Besides, some young Hong Kong residents were new immigrants from mainland China, and may not yet have received hepatitis B vaccination. Kwan et al[12] studied

the prevalence of hepatitis B carriers in 2480 women in 1996, and derived an overall HBsAg prevalence of 10.0%. For those born in Hong Kong, the figure was 8.4% whereas for those born in mainland China it was 13.1%[12]. Thus, the steady influx of immigrants from mainland China could have contributed to the higher-than-expected rates of HBsAg carriers. A third reason could be related to horizontal transmission of hepatitis B, within a family in early childhood[13], through close contact with parents who were hepatitis B carriers, or in adulthood through sexual intercourse. Suen et al[4] discovered that multiparous women had a higher HBsAg carrier rate than nullips, with it being suggested that the former tended to have sexual exposure over longer periods and possibly with more sexual partners. In our study too, parity was higher in HBsAg carriers than non-carriers (0.70 vs. 0.58, p<0.001). Moreover, invasive procedures associated with prenatal diagnosis, and fetal-maternal haemorrhage can also increase the risk of intrauterine infection.

The 8.0% carrier rate in women aged 22 to 42 years was consistent with the results of a previous study[12]. Indeed, even before the era of universal neonatal vaccination, a reduction in the HBsAg carrier rate appeared to have occurred due to several factors[12]. First, the economic boom in 1980s was associated with higher individual and public expenditure on healthcare. Thus, infection control measures, such as the elimination of reusable needles and syringes since the early 1980s, and the screening of blood donors for HBsAg (since 1978) were also important. Besides, promotion of universal neonatal hepatitis B vaccination had an educational impact on the general population, such that in the 1990s about 13% of local pregnant women had received self-financed HBV vaccination. Moreover, AIDS prevention programme in 1985 possibly resulted in behavioural changes among high-risk groups, resulting in a decline in HBsAg carrier rate at the same time. It is therefore likely that hepatitis B carrier rate trends have been influenced by an interplay of multiple factors.

A study by Kwan et al[12] showed that the hepatitis B carrier rate in the local population had declined from 11.2% in 1983 to 9.7% in 1995, and derived a carrier rate for pregnant women of about 8.4%. Compared to our findings of 6.8% as the hepatitis B carrier rate in local pregnant population, it appeared that a further containment of the infection rate had ensued. In the study by Suen et al[4], although Hong Kong has the same prevalence as reported 20 years ago, it was observed that the rate was lower in the younger age-group. The HBsAg carrier rate was 11.3% in the 1980-1984 cohort and 7.3% in the 1985 and later cohort, when subjects were categorised into 5-year cohorts by year of birth[4].

On comparing NEPs who were tourists from China with Hong Kong residents, the former had a higher hepatitis B carrier point prevalence, irrespective of age (6.8% vs. 13.3%, p<0.001), mostly because of the lower hepatitis B vaccination rate among NEPs. This too illustrates the benefit of the vaccination programme. As some Hong Kong residents are new immigrants from mainland China, the observed difference in prevalence rates could be less than expected. Routine vaccination for infants against hepatitis B infection was first recommended by the Chinese Government in 1992[14], primarily in the wealthier eastern provinces until 2002, when hepatitis B vaccination for newborns was included in China's National Immunization Programme. National vaccination coverage surveys conducted by the China Ministry of Health estimated that recourse to three-dose hepatitis B vaccination increased from 70.7% for children born in 1997 to 89.8% for those born in 2003[14].

Our study did not suggest a higher rate of antenatal complications, such as GDM, PET, APH and eclampsia, in subjects with hepatitis B antigenemia. Similarly, a German study performed by Lobstein et al[1] revealed no significant differences in point prevalence of GDM and PET in carriers and non-carriers. Besides, To et al[15] evaluated 1340 HBsAg-positive women, and estimated that there was a lower risk for gestational hypertension and pre-eclampsia than in non-carriers. On the other hand, our previous studies had confirmed an independent association between hepatitis B infection and GDM[6,16]. It was postulated that the association between chronic HBV infection and the development of GDM involved increased insulin resistance[17] induced by chronic subclinical inflammation with raised immune markers[18,19], which could be remedied by treatment with interferon-α[20]. One of the factors involved in the insulin resistance state of pregnancy is tumour necrosis factor alpha (TNF-α); excessive production of which ensues in patients with chronic hepatitis B infection (in response to secondary stimuli)[21], levels of TNF and the number of its receptors being increased in such infections[21,22]. TNF-α and its soluble receptors are also found to be increased in patients with GDM[23]. The severity of any associated liver disease in chronic hepatitis B carriers may also be influential in the development of GDM, but such causality can only be well-assessed in the postpartum period. Unlike others, this study showed insignificant difference in the prevalence of GDM in hepatitis B carriers and non-carriers, possibly because some hepatitis B carriers with

GDM were missed as there was no universal screening for GDM in our institution. A recent local study by Lao et al[24] showed that being HBsAg positive was significantly associated with macrosomic infants, even when the effects of high body mass index, advanced age, GDM, and infant gender were controlled. Our study also showed that HBsAg carriers delivered slightly larger babies. Whether this was related to missed cases of GDM requires further studies. According to the Hong Kong College of Obstetricians and Gynaecologists, HBsAg carriage is regarded as a risk factor for GDM in Asian (including Chinese) women[25]. Universal OGTT might provide more comprehensive information on this issue.

In our series, a higher rate of elective Caesarean sections was noted in carriers than in non-carriers. According to a survey by Guo et al[26] in China, HBsAg-positive pregnant women generally demonstrated a growing awareness of mother-to-infant transmission of HBV and more than 80% opted for Caesarean sections. Caesarean sections as well as hepatitis B immunisation have been shown to reduce hepatitis B infection rates in infants of mothers testing positive for HBsAg and HBeAg[27]. Maternal anxiety concerning mother-to-child transmission of hepatitis B infection may play a role in increased elective section rate wherever options for the mode of delivery are discussed with at-risk women. A higher elective Caesarean section rate could be the reason for a higher rate of postpartum haemorrhage, and lower rates of epidural analgesia and emergency lower segment Caesarean sections. Other studies suggested there were no significant effects of Caesarean section on the risk of immunoprophylaxis failure against hepatitis B carriage[28]. Moreover, disagreements still exist on the issue of whether the mode of delivery affects the risk of mother-to-infant transmission[29]. The National Institute for Health and Clinical Excellence advises against elective Caesarean section for the prevention of mother-to-child transmission of hepatitis B, as evidence on this issue is insufficient[30].

Our study did not suggest worse perinatal outcomes in subjects with hepatitis B antigenemia, in terms of preterm labour, rates of macrosomia, mean birth weight, stillbirth rates, and NICU admissions. In the study performed by Wong et al[5], perinatal outcomes were comparable in HBsAg carriers and non-carriers. The point prevalence of preterm births, being small for gestational age, perinatal asphyxia, congenital abnormalities, and perinatal mortality were similar in the two groups. The German study performed by Lobstein et al[1] showed that the point prevalence of preterm births was higher among HBsAg carriers, but the difference was not statistically significant. In contrast, a study from Israel showed significantly higher rates of preterm deliveries, perinatal mortality, congenital malformations and low birth weight in newborns among HBsAg and/or anti–hepatitis C virus–seropositive women who delivered during the period 1988-2007[31]. Variations in prenatal and neonatal care among different centres and over time may have contributed to some of the differences in outcomes in these studies.

One limitation of our study was its reliance on retrospective data. Differences in social background might have played a role in the course of these pregnancies. Regrettably, other risk factors such as alcohol intake, drug consumption, obesity, and smoking had not been consistently recorded and could not be analysed. We suggest a matching for age and parity in future studies, as these factors also have an influence on the pregnancy course. Impact on pregnancies might also differ according to the stage of the infection, which imposes another limitation and detailed information like HBsAg viral load and HBeAg status were lacking. Such data were not available because they were not routinely checked in our institution.

Conclusion

The point prevalence of HBsAg carriers was lower in women below aged <22 years, which was consistent with benefits of the universal neonatal hepatitis B vaccination programme. The mean birth weight of babies delivered by hepatitis B carriers was significantly higher than that of non-carriers. The elective Caesarean section rate was also higher in carriers. Further studies should explore these associations in detail.

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