

Screening of pregnant Saudi women for hepatitis B surface antigen

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Background: The high prevalence of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) in pregnant women is considered the most important factor contributing to the higher carrier rate of HBsAg in some populations, including Saudi Arabia. Universal hepatitis B vaccination in infancy was implemented in Saudi Arabia in 1990 to avoid early acquisition of infection. At the same time, another program was launched to vaccinate all school children at school entry as a second target group. The aim of this study was to evaluate the HBsAg prevalence rate in Saudi pregnant women 12 years after launching the program and to assess regional variation, if any.

Methods: In a cross-sectional study, 2664 pregnant Saudi women were recruited from the five main regions in Saudi Arabia. Blood samples were tested for HBsAg. Positive samples were tested also for HBeAg.

Results: Of 2664 pregnant Saudi women, 65 were positive for HBsAg (2.46%, 95% CI=2.11%- 2.69%). Four were positive for HBeAg (0.15%). The HBsAg prevalence rate was higher in Gizan (4.2%) and lower in Tabuk (1.4%) ($P=0.035$). Only one case was positive for HBsAg in women under the age of 20 years (1/186), a 0.5% positivity rate in this age group compared with 2.6% in the older age group ($P=0.049$ for the one-sided test). A history of surgical procedures was associated with a higher (3%), but not significantly higher rate of HBsAg positivity. No significant association was found between HBsAg positivity and a history of dental procedures or blood transfusion.

Conclusion: Although the HBsAg prevalence rate among Saudi pregnant women was lower than previously published data, the full impact of the hepatitis B vaccination program in infancy and childhood will take more years to decrease the prevalence rate in pregnant women. The MOH should continue to give the first dose of hepatitis B vaccine at birth to prevent early acquisition, but in the meantime a regional policy can be adopted to deal with the high prevalence rate of HBsAg among pregnant Saudi women.

Key words: Hepatitis B virus infection, hepatitis B surface antigen, hepatitis B e antigen, Saudi Arabia

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Hepatitis B is of major public health importance. It is estimated that there are 350 million chronic hepatitis B virus (HBV) carriers in the world, and that over one million deaths per year are due to progression of the chronic disease to cirrhosis and/or hepatocellular carcinoma.¹ Chronic HBV infection with persistence of hepatitis B surface antigen (HBsAg) occurs in as many as 90% of infants infected by perinatal transmission, in 30% of children 1 to 5 years old infected after birth, and in 5% to 10% of older children, adolescents, and adults with HBV infection. Chronically infected persons are at high risk for developing chronic liver disease (cirrhosis, chronic active hepatitis, or chronic persistent hepatitis) or primary hepatocellular carcinoma later in life.² The high prevalence of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) in pregnant

women is considered the most important factor contributing to the high carrier rate of HBsAg. Several factors, including the age at which infection occurs, predispose to the acquisition and frequency of the carrier state.³ Vaccination of the newborn of infected mothers can interrupt 85% to 90% of such mother-infant transmission. However, the transmission of HBV through placenta within the uterus cannot be interrupted by hepatitis B vaccination. Intrauterine transmission is an important mode of spreading HBV infection. Reported proportions of intrauterine transmission vary from 4.4% to 23.5%, but are mostly in the range of 5% to 15%.^{4,5}

Before the vaccination era in Saudi Arabia, the HBsAg carrier rate was 16.7% in adults⁶ and 6.7% in children in a baseline survey before the introduction of mass immunization.⁷ The rate was higher in some regions, 11.1% for

children in Gizan in the southwest,⁸ and as high as 19.9% in adult Saudi males.⁹ Materno-foetal transmission of hepatitis B virus in utero or during the perinatal period does not seem to be important in maintaining the carrier state in Saudi Arabia. The prevalence of HBeAg in asymptomatic Saudi mothers is low compared to asymptomatic carrier mothers from the Orient. This may explain the minor role of vertical transmission in Saudi Arabia.^{10,11} A high incidence of primary hepatocellular carcinoma has been reported,¹² especially in Gizan, where the prevalence of the HBsAg carrier state is high.¹³

Universal hepatitis B vaccination in infancy was implemented in Saudi Arabia in 1990 to avoid early acquisition of infection. At the same time, another program was launched to vaccinate all school children at school entry as a second target group. It was expected that by the year 2002, 12 years after the beginning of the program, this vaccination strategy would have led to the protection of all Saudis aged 0-18 years, who are at higher risk for acquiring hepatitis B virus and for developing the chronic carrier state. Based on the fact that the group less than 15 years of age represents 46.2% of population,¹⁴ and the 15-19 year old group represents 10.9% of population, more than 55% of the population was covered by vaccination in the year 2002.

After the mass vaccination era, the overall HBsAg carrier rate in children dropped from 6.7% in 1989 to 0.3% in 1997,¹⁵ indicating that the program had a tremendous impact. The full impact of the vaccine on pregnant Saudi women will not be realized until the vaccinated cohorts reach the age of marriage. Evaluation of the carrier state in this important group should be done not only as an indicator to increase the hepatitis B vaccine dose given at birth, but also to monitor any regional variation and to develop regional policies if needed.

Methods

Our study was part of a national study to evaluate the serological status of different age groups of the population with respect to the pattern of diseases targeted by the Extended Program of Immunization in Saudi Arabia. The aim was to evaluate the prevalence of hepatitis B surface antigen (HBsAg) positivity among pregnant Saudi women attending primary health care centers. In a cross-sectional study, samples of 2910 pregnant Saudi women were recruited from the five main regions of Saudi Arabia (northern, southern, eastern, western and central regions). Blood samples were collected and sent for assay in the central lab in Riyadh to be tested for HBsAg. Positive samples were tested also for HBeAg.

Multistage sampling was used to draw the samples. In the first stage, the Kingdom was divided into five main regions (northern, southern, eastern, western and central).

Within each region, one health province was selected randomly. The following provinces were selected: Tabuk (northern), Gizan (southern), Al-Qatif (eastern), Medina (western) and Al-Qassim (central). In the second stage, 12 primary health care centers were selected from each province, 8 centers from urban areas, and 4 from rural areas. The number of pregnant Saudi women included in each province depended on the population size of the province in relation to the total population of the Kingdom. Sample size was determined to calculate a national prevalence figure for the HBsAg positivity rate and to detect with 80% power and 95% confidence interval the difference between regions in the prevalence rate. Table 1 shows the sample distribution in each region.

Five milliliters of blood was collected in plain tubes from each woman. All serum samples were stored (in duplicates) at -20°C and transported frozen in cold boxes by DHL to the virology department in the central laboratory and blood bank, Riyadh. The request form signed by the doctor in charge was included with the samples.

Enzyme linked immunosorbent assay (ELISA) tests for HBsAg and HBeAg screening and an HBsAg confirmatory test (neutralization) were applied using the following Abbott diagnostic products (Murex):

| Diagnostic product | List No. | Lot No. | Exp Date |
|------------------------------|----------|----------|-----------|
| HBsAg screening version 3 | 9F 80-01 | H 413010 | 2002 - 07 |
| HBsAg confirmation version 3 | 8E 21-01 | H 390910 | 2002 - 09 |
| HBeAg/Anti-HBe | 9E 20-01 | H 446810 | 2002 - 09 |

Data entry and analysis was done using SPSS PC v. 10. Analysis of variance (ANOVA) was used to compare means while the Chi-square test was used to compare categorical data.

Results

The mean age of the sample population was 28.44±6.76 years with regional values ranging from 29.42 years in Qassim to 27.39 years in Qatif ($P=0.0001$) (Table 2). There were significant regional differences in the number of pregnancies and the proportion of pregnant Saudi women under the age of 20 years. The proportion of pregnant women under the age of 20 years for all regions was 7.1%. The oldest girl vaccinated in 1990 during her first year of primary school is now 18 to 19 years of age. The mean age at first pregnancy was 22.7±4.1 years with a significant regional variation from 23.5 years in Qassim to 21.2 years in Tabuk ($P=0.0001$). This may reflect a higher age at marriage in Qassim.

Of the 2664 samples screened, 84 were initially positive. After HBsAg confirmation, 65 were positive (Table 3).

Table 1. Number of pregnant Saudi women in the study by region.

| Region | Planned | Enrolled* | Dropped | Laboratory** |
|--------|---------|-----------|---------|--------------|
| Qatif | 400 | 400 | 0 | 398 |
| Madina | 840 | 599 | 241 | 596 |
| Qassim | 840 | 840 | 0 | 840 |
| Gizan | 550 | 550 | 0 | 550 |
| Tabuk | 280 | 280 | 0 | 280 |
| Gizan | 550 | 550 | 0 | 550 |
| Total | 2910 | 2669 | 241 | 2664 |

* Enrolled=planned minus dropped

** Laboratory: samples processed in the lab; the difference between number processed and number enrolled was due to inadequate samples or other technical reasons.

Table 2. Mean age of pregnant Saudi women, number of pregnancies and proportion of pregnancies in women under the age of 20 years.

| | Qatif | Medina | Qassim | Gizan | Tabuk | Total* | P value |
|--------------------|-----------|-----------|-----------|------------|-----------|------------|---------|
| Age (years) | | | | | | | |
| Mean | 27.39 | 28.71 | 29.42 | 27.79 | 27.72 | 28.44 | 0.0001 |
| N | 396 | 581 | 836 | 544 | 279 | 2636 | |
| SD | 6.02 | 6.95 | 6.67 | 7.14 | 6.48 | 6.76 | |
| No. of pregnancies | | | | | | | |
| Mean | 3.56 | 4.48 | 3.97 | 4.84 | 4.82 | 4.29 | 0.0001 |
| N | 380 | 528 | 824 | 531 | 279 | 2542 | |
| SD | 2.75 | 3.19 | 3.1 | 3.79 | 3.31 | 3.28 | |
| Percent <20 years | 5.8% (23) | 5.7% (33) | 5.6% (47) | 10.8% (59) | 8.6% (24) | 7.1% (186) | 0.001 |
| N | 396 | 581 | 836 | 544 | 279 | 2636 | |

* Missing data for 28 women (2664 minus 2636)

Table 3. Hepatitis B surface antigen and e positivity rate by region.

| | Qatif | Medina | Qassim | Gizan | Tabuk | Total | P value |
|-----------------------------|-----------|-----------|-------------|-----------|-----------|--------------|---------|
| HBsAg positivity | | | | | | | |
| % (n) | 2.5% (10) | 2.3% (14) | 1.7% (14) | 4.2% (23) | 1.4% (4) | 2.4%* (65) | 0.035 |
| N | 398 | 596 | 840 | 550 | 280 | 2664 | |
| HBeAg | | | | | | | |
| % | 0.5% (2) | 0.2% (1) | 0 | 0.2% (1) | 0 | 0.15% (4) | 0.28 |
| N | 398 | 596 | 840 | 550 | 280 | 2664 | |
| Positivity <20 years of age | 0% (0/23) | 0% (0/33) | 2.1% (1/47) | 0% (0/59) | 0% (0/24) | 0.5% (1/186) | 0.65 |

* 95% confidence interval, 2.11% to 2.69%

Table 4. Hepatitis B surface and e antigen by age group, history of surgery, dental procedures or blood transfusion.

| Variable | HBsAg positivity rate | | Total | P value |
|--------------------|-----------------------|-----------------|-----------------|------------------------------------|
| | Yes | No | | |
| < 20 years of age | 0.5% (1/186) | 2.6% (64/2450) | 2.46% (65/2636) | 0.085 two sided 0.049 one sided |
| History of surgery | 3% (15/499) | 2.3% (50/2163) | 2.4% (65/2662) | 0.224 |
| Blood transfusion | 1.7% (3/174) | 2.5% (62/2490) | 2.4% (65/2662) | 0.7 |
| Dental procedures | 2.27% (32/ 1408) | 2.62% (33/1256) | 2.4% (65/2662) | 0.64 |

Of the 2664 samples screened, 84 were initially positive. After HBsAg confirmation, 65 were positive (Table 3). Accordingly, 2.4% of the total sample was HBsAg positive (95% confidence interval, 2.11%- 2.69%). There was a regional variation as high as 4.2% in Gizan and as low as 1.4 in Tabuk ($P=0.035$). Only 4 among the 65 HBsAg carriers were positive for HBeAg, making a proportion of 0.15% (4/2664) of the total sample or 6.15% of the HBsAg carriers.

Only one case was positive for HBsAg among women under the age of 20 years (1/186), a 0.5% positivity rate in this age group compared with 2.6% in the older age group ($P=0.085$ for the two-sided and $P=0.049$ for the one-sided test). The age of this woman was 19 years while the age of the first cohort vaccinated at school entry in 1990 was about 18 years.

Surgical procedures were associated with a higher (3%, 15/449), but not significantly higher rate of HBsAg positivity. No significant association was found between HBsAg positivity and dental procedures or blood transfusion (Table 4).

Discussion

The year 2002 marks the twelve anniversary of the implementation of the mass hepatitis B vaccination in Saudi Arabia. Since 1990, substantial progress has been made towards eliminating HBV transmission in children. Accordingly, a substantial decline in the incidence of HBV infection has occurred among groups with high coverage by the vaccine, such as young children, but the relative burden of HBV-related diseases acquired from infections in childhood still exist. Adult carriers still represent a risk of infection to their unvaccinated contacts.

In early 80's, the prevalence of hepatitis B surface antigen in pregnant Saudi mothers ranged from 3.9%¹¹ to 16%,¹⁰ which is higher than the prevalence in this study. This decline in prevalence cannot be explained by the introduction of mass immunization, which most of the sample population were not exposed to, but by the adoption of universal procedures to decrease exposure to the virus. This was evident in this study where no increased association was found between the carrier rate and known risk factors like dental procedures, surgical operations and blood transfusions (Table 4).

Our results show that the full impact of the hepatitis B vaccination program has not yet reached women during the maternity period. This was evident by comparing mothers less than 20 years with the rest of the group. The positivity

rate in the less than 20 years age group was 0.5% compared with 2.6% in the older age group ($P=0.085$ for the two-sided and $P=0.049$ for the one-sided test). One of 186 women was positive, a 19-year-old, while the age of the first cohort vaccinated at school entry in 1990 was about 18 years during the study. Regional variation was prominent. Gizan showed the highest prevalence rate of 4.2% (Table 3). Regional variation may present a challenge to policy makers.

Screening of pregnant mothers for the purpose of giving immunoglobulin at birth and giving the vaccine to infants of positive mothers proved to be not cost effective,¹⁶ even in a community with a high prevalence like Saudi Arabia where vertical transmission plays a minor role.^{10,11}

Infection with HBV in adulthood is associated with a lower risk of chronic complications (5-10%).² Hence, targeting older age groups with hepatitis B vaccine should take into consideration a cost-benefit assessment. Vaccination of Saudi mothers in the maternity period can be done at least on a regional basis as in Gizan where the infection rate is higher than other regions.

The national strategy to eliminate HBV infection in Saudi Arabia is based mainly on vaccinating all infants as part of a childhood vaccination schedule. Screening of all pregnant women is not part of this strategy as vertical transmission is not an important route of infection, as reported in local studies. To accelerate elimination, additional interventions are needed.

In a few more years, the vaccinated cohort will reach the age of marriage in Saudi Arabia. By that time the prevalence of HBsAg in pregnant Saudi mothers will reach a minimal level sufficient to shift the first dose hepatitis B vaccine to a higher age instead of giving it at birth. At that time combined vaccines containing hepatitis B can be given with DPT and *Haemophilus influenzae* type b.

Regional policies should be considered to deal with the situation in Gizan, where the prevalence rate is still significantly higher than other regions. Pregnant Saudi mothers should be screened and the appropriate preventive measures adopted. Vaccination of negative mothers should be considered, taking into consideration the added value to the hepatitis B control program as a whole.

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