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Effectiveness of different strategies in the prevention of mother to child transmission of hepatitis B virus; A Tunisian cohort study

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SUMMARY:

Background: the international strategy to eliminate hepatitis B (HB) is based on preventing perinatal Hepatitis B Virus (HBV) transmission, by a universal screening of pregnant women for HB surface antigen (HBsAg) during pregnancy and on the provision of immunoprophylaxis for infants born to infected mothers. We aimed at determining the efficiency of the HB immune-prophylaxis among infants born to mothers positive for HBsAg. **Methods:** an

analytical cross-sectional study was conducted in the gastroenterology ward in the University Hospital of Monastir, (Tunisia) between 2012 and 2014. A hepatitis B serology was requested for children who have been properly vaccinated. **Results:** We included 155 children, 81 boys, and 74 girls with an average age of 9.86 ± 4.64 years .The prevalence of HBV infection despite HB vaccination was 4.5 %. All mothers of positive HBsAg infants ignored their hepatitis B status and had not received HB immunoglobulin. Administration of HBIG has been associated with a significant reduction in the risk of the mother to child transmission of HBV ($p<0.05$). Overall seroprotection rate was 50.3%. **CONCLUSION:** Our results illustrate that the efficiency of HB vaccination is low in our country. We recommended a serological control of the HB vaccination efficiency at the age of one year after the application of systematic screening of pregnant women for HBsAg.

INTRODUCTION

Hepatitis B virus (HBV) infection remains a public health problem. Approximately 240 million people are chronic HBV surface antigen carriers[1], most as a result of mother to child transmission, especially in highly endemic areas. Even in areas with low endemicity, perinatal or early childhood transmission may account for more than one-third of chronic infections[2]. The probability of developing chronic HBV infection is inversely proportional to age at time of HBV exposure. Five to ten percent of HBV exposed adults will develop chronic infection, compared to 90% of HBV exposed neonates[3]. Thus, the prevention of vertical transmission of HBV plays an important role in the limiting of the disease prevalence. This prevention is based on three measures, namely screening of pregnant women for HBV infection, administration of antiviral drugs (tenofovir disoproxil fumarate) for HBe antigen (HBe Ag) positive women with high viral loads (>10^6 copies /ml), sero-vaccination at the birth of neonates born to HBsAg-positive mothers and routine practice of post-vaccination serology (from the first month and at latest 12 months after the last dose) for all infants of mothers carrying HBsAg. Since 1996, screening for HBsAg has been mandatory during the sixth month of pregnancy in Tunisia [4]. In case of positivity, prophylactic HBV vaccination and HBV immunoglobulin(HBIG) administration are recommended for the neonate.

In our country, to our knowledge, the application and effectiveness of these measures haven't been evaluated properly.

The purpose of this study was to evaluate the efficiency of these strategies implemented for the prevention of mother to child transmission of hepatitis B virus in Tunisia.

PATIENTS AND METHODS

Study population

This analytical cross-sectional study was conducted from January 2012 to December 2014. We enrolled fully vaccinated children born to hepatitis B surface antigen (HBsAg) positive mothers followed-up in the gastroenterology department of Fattouma Bourguiba Hospital. The immunization status of all included children has been verified from their health records. Children who didn't receive or who had an incomplete hepatitis B vaccination were excluded from this study. All included children have been tested for HBs-Ag, the antibody to hepatitis B core antigen (anti-HBc) with a quantitative determination of hepatitis B surface antibody (anti-HBs).

Study Protocol

Data collection required two follow-up visits. At the first consultation, hepatitis B serology including HBsAg, anti-HBc, and quantitative anti-HBs was requested from children vaccinated against HBV and born to mothers with chronic HBsAg carriers. In the second visit, according to the viral status and the level of anti-HBs, children were categorized into 4 subgroups: infected children group [HBsAg (+), antiHBc (+), antiHBs(-)]; children who have previous contact with HBV [HBsAg (-) , antiHBc (+)]; HBV-protected children group [HBsAg (-),anti-HBc (-), anti-HBs ≥ 10 IU / L], and non-sero-protected children group [HBsAg (-), anti-HBc (-), anti-HBs<10 IU / L]

DATA entry and analysis

Statistical analysis was performed using SPSS version 21.0. Qualitative variables were described by numbers and proportions, and quantitative variables by means and standard deviation. Differences in frequency were tested by the chi-square test or Fisher exact test. A p-value inferior to 0.05 was considered to be statistically significant.

RESULTS

A total of 59 mothers and 155 children were included in this study. Maternal and infants characteristics are summarized in Table 1. The mean mother_age was 39.8 (SD=6.65 years). The male to female ratio was 1. Children's mean age was 9.86 years (SD= 4.6 years) within a range from 1 to 19. Among mothers, chronic active hepatitis B was noted in 10 (16.2%) cases. A total of 109 (70.3%) children were breastfed. All children were born at term. None of the newborns had immunodeficiency disease. Seventy-eight (50.3 %) children received combined passive and active immuno-prophylaxis after birth, and 77 (49.6%) were vaccinated without serotherapy.

Table 1: Description of the study population

Mothers	N	%
Diagnosis		
Inactive carriage of HBsAg	48	81.3
chronic active hepatitis B	10	16.2
Unspecified	1	1.7
Infants		
Gender		
Boys	81	52.3
Girls	74	47.7

Breastfeeding		
Yes	109	70.6
No	46	29.4
Born at term		
Yes	155	100
No	0	0
Immunization schedule		
Serovaccination	78	50.3
Vacination without serotherapy	77	49.6

The prevalence of HBV infection despite HB vaccination was 4.5 %. All infected infants had not received HB immunoglobulin since HBsAg testing was not performed for their mothers during pregnancy. Administration of HBIG has been associated with a significant reduction in the risk of the mother to child transmission of HBV ($p<0.05$).; OR =0.455 ($p = 0.05$) (Table 2).

Table 2: Sero-prevalence of hepatitis B markers in the study population

Hepatitis B markers	**n (%)**
HBsAg positive	7(4.5)
HBs Ag(-); AntiHBc (+) and antiHBs(+)	5(3.2)
HBs Ag(-); AntiHBc (-) and antiHBs ≥10UI/ml	78(50.3)
HBs Ag(-); AntiHBc (-) and antiHBs≤10UI/ml	65(41.9)

As shown in table 3, An old contact with hepatitis B virus (positive hepatitis B surface and core antibodies) was noted in 5 children (3.2 %). The study of the prevalence of seroprotection years after vaccination against HBV revealed that

among the 155 explored children, 78 (50.3 %) are sero-protected and 65 (41.9%) are not sero-protected.

Table 3 : Impact of the administration of hepatitis B immunoglobulin's on the viral status of children

		Infected N(%)	Not infected N(%)	p	OR	CI95%
HBIg	Yes	0(0)	78 (100)	0.005	0.455	0.380-0.544
	No	7(4.5)	65 (95.5)			

HBIg: Hepatitis B immunoglobulin's; OR : Odds ratio ; CI: Confidence interval

DISCUSSION

In this study, we have demonstrated that 4.5% of infants are chronic HBsAg carriers despite vaccination against this virus.

The prevalence of chronic HBV carriers despite vaccination of infants varies between 0 and 4.8% [5-8]. In Tunisia, a rate of 4.8% was revealed by a national survey conducted after the integration of HBV vaccination into the national calendar. The percentage (4.5%) revealed by our study is higher than the other countries, but it is close to that of the national survey.

Differences between our findings and others might be due to several factors including (1) The lack of adherence to routine screening for HBsAg during pregnancy and to the administration of hepatitis B immunoglobulins (HBIg) combined to hepatitis B vaccine at the birth of neonates born to HBsAg-positive mother or unknown HBs status. A study conducted in China found that the blocking effect of HBIG combined with hepatitis B vaccination was better than

the blocking effect of hepatitis B vaccination alone for infants born to mothers who were HBsAg-positive, which is consistent with our findings and these of other studies[9,10]; (2) The variabilities of immunization Schedules and prevalence of HBV infection; (3)The differences of genetic factors, as the main cause that increases the risk of maternal-fetal transmission of the virus is the expression of hepatitis B vaccine escape variants. Indeed, it is well established that HBsAg has significant variability, in particular at its pre-S region, and a modification, following a mutation, of the amino acid sequence of this region may be at the origin from an escape to immune control and subsequently to the effect of vaccination[11-12].

It is well established that the protection against HBV infection conferred by the universal vaccination of infants is due to the production of HBs antibodies at a rate greater than or equal to 10 IU / L (this is the seroprotection threshold) [13-14].

Years after the integration of infant immunization into national programs in Malaysia, China, Taiwan, and Iran, studies have shown that the seroprotection rate ranged between 30.2 and 88%. In our series, Seroprotection rate was estimated at 50.3% is close to that of Taiwan and Malaysia [15-16], however, it is lower than in Iran [17] and higher than in China [18]. This variability between the seroprotection rate of our children compared to others can be explained by the difference in age, the type of vaccine administered, the immunization Schedule applied (the age at which the first and last doses are taken and the number of doses) and the differences in genetic and immune factors in our population compared to other study populations. Indeed, the production of anti-HBs antibodies can be altered by certain types of HLA, in particular DR14-DR52 association, probably dominantly expressed, may be involved in the low immune responsiveness to hepatitis B vaccine [19-22].

CONCLUSION

Our study concludes that the preventive efficacy of infant vaccination seems to be lower in our country. Intending to eradicate hepatitis B in Tunisia, we invite health authorities to oversee the application of the HBsAg screening during pregnancy by strengthening the information of obstetricians and, secondly, of routine practice of post-vaccination serology for all infants of mothers carrying HBsAg.

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