Vaccination of Newborns from Chronically Infected Mothers is Effective in Preventing Hepatitis B in Infants

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Abstract

Objective: Infants born to hepatitis B surface antigen (HB_sAg)-positive mothers are exposed to hepatitis B virus (HBV) at birth and do not receive proper post-exposure prophylaxis. Approximately 90% of infants who acquire HBV infection at birth go on to become chronic carriers. An estimated 15-25% of these carriers ultimately will die of liver failure secondary to chronic active hepatitis, cirrhosis, or primary hepatocellular carcinoma. On the other hand, 90% of perinatal HBV infections can be prevented by post-exposure prophylaxis given within 12 hours of birth. This study aimed to evaluate the prevalence of chronic hepatitis B infection among pregnant women in Şanlıurfa; to screen their newborns for vertical transmission; and to prevent neonatal infection by vaccination.

Materials and Methods: Blood samples from 1162 pregnant women paying their first antenatal visit to Harran University Research Hospital Obstetrics and Gynecology Clinic between June 1998 and June 2002 were screened for HB_sAg, hepatitis B infectivity antigen (HB_eAg) and anti-HBs by ELISA.

Results: Fifty-nine (5.1%) were HB_sAg-positive, while 415 (35.7%) women had anti-HB_s. None were positive for HB_eAg. Vertical transmission was not identified. Babies of the 48 carriers who delivered in the clinic were immunized with Hepatitis B hyperimmunoglobulin (HBIG) and a recombinant hepatitis B vaccine and were examined at approximately 28 months of age. In 44 (91.6%) of the infants, the vaccine was found safe and effective.

Conclusion: Hepatitis B vaccine is recommended for all newborns, and the series may be started during the delivery admission. For infants who are born either to women who are positive for HB_sAg or to women whose HB_sAg status is unknown, vaccination should be started within 12 hours of birth to prevent perinatal and early childhood hepatitis B virus infection. This study supports that vaccination of babies born to HB_sAg carriers is effective in preventing their developing hepatitis B infection. Increases in hepatitis B vaccine coverage at birth are necessary to reduce the risk of perinatal infection. All health professionals and hospitals should protect all infants from HBV infection by administering the first dose of hepatitis B vaccine to every infant at birth and no later than hospital discharge. All infants born to HB_sAg-positive mothers receive timely and appropriate immunoprophylaxis with HBIG and hepatitis B vaccine.

Key words: hepatitis B, pregnancy, vaccination

Özet

Kronik Enfeksiyonlu Annelerin Yenidoğanlarının Aşılanması İnfantların Hepatit B'den Korunmasında Etkilidir

Amaç: Hepatit B yüzey antijeni (HB_sAg) pozitif olan annelerden doğan bebekler doğumda hepatit B virüsüne (HBV) maruz kalmakta ve bunlara doğum sonrası uygun profilaksi yapılmamaktadır. Doğumda HBV ile enfekte olan infantların %90'ı kronik taşıyıcı olmaktadır. Bu taşıyıcıların %15-25'i ileride kronik aktif hepatit, siroz veya primer hepatoselüler kansere sekonder gelişen karaciğer yetmezliğine bağlı olarak ölmektedirler. Diğer taraftan, perinatal HBV enfeksiyonlarının %90'ı, doğumu takiben 12 saat içinde yapılacak uygun profilaksi ile önlenebilir. Bu çalışmada Şanlıurfa ilindeki gebe kadınlarda kronik hepatit B enfeksiyonu prevalansının belirlenmesi, vertikal geçiş yönünden yenidoğanların taranarak, aşılamanın enfeksiyondan koruyuculuğunun değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: Haziran 1998-Haziran 2002 tarihlerinde Harran Üniversitesi Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'ne başvuran 1162 gebede ELISA ile HB_sAg, hepatit B enfektivite antijeni (HB_eAg) ve anti HB_s taraması yapıldı.

Sonuçlar: Gebelerin 59'unda (%5.1) HB_sAg pozitif bulunurken, anti HB_s 415 gebede (%35.7) pozitif olarak belirlendi. HB_eAg hiçbir olguda pozitif değildi. Olguların hiçbirinde vertikal geçiş saptanmadı. Kliniğimizde doğum yapan 48 taşıyıcı annenin bebeğine doğumu takiben hepatit B hiperimmünoglobülin (HBIG) ve rekombinant hepatit B aşısı yapıldı. Ortalama 28 ay takip edilen infantların 44'ünde (%91.6) aşının güvenilir ve etkin olduğu bulundu.

Tartışma: Tüm yenidoğanlara, ilk dozu doğumda başlamak üzere hepatit B aşısı yapılması önerilmektedir. Perinatal ve erken çocukluk dönemi HBV enfeksiyonundan korunmak için HB_sAg durumu bilinmeyen veya HB_sAg pozitif olduğu bilinen kadınlardan doğan infantlar, doğumu takiben 12 saat içinde aşılanmalıdırlar. Bu çalışma, HB_sAg taşıyıcı annelerden doğan bebeklerin aşılanmasının hepatit B enfeksiyonunun engellenmesinde etkin bir koruyucu olduğunu destekle-

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mektedir. Perinatal enfeksiyon riskini azaltmak için doğumda hepatit B aşısı yapılması gereklidir. İlgili sağlık görevlileri ve hastaneler, taburcu olmadan önce ilk doz hepatit aşısını uygulayarak tüm yenidoğanları HBV enfeksiyonundan korumalıdırlar. HB_sAg pozitif annelerden doğan infantlara, HBIG ve hepatit B aşısı ile zamanında ve uygun immün profilaksi yapılmalıdır.

Anahtar sözcükler: hepatit B, gebelik, aşılama

Introduction

Transmission of hepatitis B virus (HBV) occurs horizontally through parenteral inoculation of infected blood or other body fluids or through having a close relationship e.g. amongst family members or at day care centers. Parenteral route can also lead to spread via blood products, contaminated needles, surgical instruments, IV drug abuse, tattooing, acupuncture needles, ear piercing etc., and 50–70% of the carrier pool is contributed by horizontal transmission. The sexual route of transmission, which occurs when one partner is infected is a common route in developed countries.

Vertical transmission occurs from hepatitis B surface antigen (HB_sAg)-positive pregnant women to their babies during the perinatal period. It mainly occurs due to maternal blood infecting the baby. The rate of vertical transmission is 10-20% during the prenatal period (1). However, this rate can be as high as 90% in cases where the mother carries hepatitis B infectivity antigen (HB_eAg) (2, 3).

Distribution of HBV infection varies throughout the world (4). The carriage rate in regions of high endemicity is about 5-20%. Occurrence of the disease in the early period of life is common in these regions (4).

Seroprevalence rates for anti-HB_s and HB_sAg reported in Turkey vary between 25-60% and 3.9-12.5% respectively, which means that more than half of the population in some regions have already suffered from HBV infection (5).

Şanlıurfa, where the study was conducted, is the largest city in the South-Eastern Region of Turkey. Results of previous studies indicate that HBV is hyperendemic (6, 7).

The aims of this study were to evaluate the prevalence of chronic hepatitis B infection among pregnant women, to screen newborns of carriers for vertical transmission and to prevent infection in children of carriers by vaccination.

Materials and Methods

Patients

Blood samples were obtained from 1162 pregnant women from the Şanlıurfa inner-city area who paid their first prenatal visit to the Obstetrics and Gynecology Department of Harran University Hospital between June 1998 and July 2002. None had received hepatitis B vaccination. The newborns of HB_sAg carriers were screened for vertical transmission and mothers of these infants were later contacted by telephone for follow-up evaluation of the effectiveness of vaccination.

Medical questionnaire

The demographics, including age, number of house members, marital status, literacy, gravidity and parity numbers, smoking, alcohol consumption and drug abuse, of the subjects were recorded (Table 1).

Serological tests

Blood samples of pregnant women and their infants were tested by ELISA for HB_sAg, HB_eAg and anti-HB_s, using the commercial kits Abbott AxSYM HB_sAg (V2), Abbott AxSYM HB_eAg and Abbott AxSYM AUSAB (Abbott Laboratories, Diagnostic Division, Abbott Park, Illinois, USA) in an auto-analyzer. Effectiveness of the vaccine was determined by anti-HB_s titer and ≥10 mU/ml accepted as effective.

Statistical analysis

Student's *t* test was used for comparison of HB_sAg values across demographic variables (age, gravidity, parity, abortions, live children and gestational age). Correlations between antibody titration values and time to follow-up were determined using Pearson correlation analysis. $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS for Windows Version 11.0.

Results

The subjects involved in the study had never received detailed information on hepatitis B or on its transmission and prevention. None had received vaccination. The demographic characteristics of patients are indicated in Table 1.

The rate of Hb_sAg carriage in the group was found to be 5.1% (59 subjects), while the positivity rate for anti-HB_s was 35.7% (415 subjects). 48 carrier mothers gave birth in the clinic but their newborns were negative for HB_sAg and Anti-HB_s.

No subject was positive for HB_eAg or for HB_sAg together with Anti-HB_s.

Forty-four newborn infants of carrier mothers were followed up to determine the effectiveness of the vaccine. After an average 28.6±10.4 (range 6-46) months, anti-HB_s antibody levels averaged 258.8±291.6 mIU/ml (range: 0-1000) and

Table 1. Demographic characteristics of subjects

Variables		Results
Mean age, years ± SD		27.4±4.9
Mean gestational age, weeks ± SD		20.0±8.9
Mean gravidity, number ± SD		2.9±1.9
Mean parity, number ± SD		1.5±1.6
Marriage status, number (%)		
	Married	1162 (100)
	Unmarried	None (0)
Education status, number (%)		
	Illiterate	872 (75)
	Literate	290 (25)
Alcohol Consumption		None
Drug Abuse		None
Smoking		59 (5.1)

were at a preventative level in 44 (91.6%). No correlation was found between the length of follow-up period and antibody levels ($p = 0.242$).

Discussion

HBV infection can be serious because it can lead to chronic (long-term) infection, liver cancer, cirrhosis, and death. In United States, other than influenza and pneumococcal infections, hepatitis B causes more deaths each year than any other vaccine-preventable disease (8). HBV can pass on to newborn baby during delivery whether a woman give birth naturally or through surgery. Therefore, cesarean section can not prevent infecting newborn. Infants who are exposed to HBV have more than a 90% chance of becoming chronically infected; children aged 1 to 5 years have a 45% chance of becoming chronically infected; and children older than 5 years have less than 10% chance of becoming chronically infected.

The study indicates that HBV infection is an essential public health problem in the region and that vaccination of newborns provides an effective prevention for the disease. This study is the widest study that has been conducted on pregnant women in the region so far.

Hepatitis B vaccine is encouraged for all newborn infants and the series may be started during the delivery admission. To protect infants who are born either to women who are positive for HB_sAg or to women whose HB_sAg status is unknown, vaccination should be started within 12 hours of birth to prevent perinatal and early childhood HBV infection which requires 3 or 4 shots (9). The hepatitis B vaccination series is unlike other pediatric vaccinations because it can be routinely initiated in an inpatient setting— the hospital nursery. The newborn nursery represents the first opportunity to immunize children and establish immunization practices and attitudes at the family and individual levels. The newborn period may be a time when parents are especially receptive to information about immunizations, because HBV at birth is associated with timely receipt of other vaccines (10). The vaccination schedule consists of giving 3 doses at 0, 1 and 6th months. The first dose of vaccine should ideally be given within 2–3 days, preferably within 12 hours of birth. If it is missed at birth, it should be given as early as possible and no age is late for starting vaccination. Dose depends on the age of the child. For a child <10 years, 10 mcg/dose is advocated and for a child >10 years, 20 mcg. It is given IM in the anterolateral aspect of thigh, or in the deltoid muscle in older children while avoiding using gluteal region, as the fat mass is large in that area which can lead to poor sero response.

Hepatitis B Immune Globulin or Hepatitis B hyperimmunoglobulin (HBIG) prepared from human blood from selected donors who already have a high level of antibodies to hepatitis B. HBIG is recommended following exposure to HBV because it provides immediate, short-term protection against the virus. A dose of hepatitis B vaccine is given at the same time. Two additional doses of hepatitis B vaccine are given to complete the series and ensure long-term protection (11). If available, HBIG 0.5 ml should be given IM on the other thigh within 6 hours of birth (do not give HBIG and vaccine on the same thigh). It is then followed by 2 more doses of the vaccine at 1 and 6 months. One can also use accelerated schedule of 0, 1, 2 and 12 months especially if HBIG is not given. Vaccination alone will bring down the chances of becoming a carrier by 65–90% and if HBIG is also given, it will bring it down further by another 5–20% to give almost 95% efficacy. Medically stable preterm and low birth weight infants should receive full doses routine vaccines at a chronologic age consistent with the schedule recommended for full-term infants. Newborns with birth weight less than 2000 g may require modification of the timing of hepatitis B immunoprophylaxis depending on maternal HB_sAg status. Newborn, <2.0 kg will have lesser chances of seroconversion than full term child so, if the mother is known to be HB_sAg-

negative one can postpone the vaccination. But if the mother is HB_sAg-positive or if the status is not known, one should give first dose hepatitis B vaccine (0.5 mL, IM) at birth. If mother is carrier, giving HBIG (0.5 mL, IM) on other thigh will be mandatory. However, this dose should not counted as the first dose. Then the hepatitis B vaccine series initiated at 1–2 months of age. This can be followed by completion of course using 0, 1, 6 or 0, 1, 2 and 12 schedule (12, 13). Importantly, the mother has to provided with educational and written materials regarding: the importance of having her baby complete the hepatitis B vaccination schedule on time; the importance of postvaccination testing for the infant following the hepatitis B series to assure immunity; the mother's need for ongoing medical follow-up for her chronic HBV infection; and the importance of testing household members for hepatitis B and then vaccinating if susceptible (14).

In the 2000 report issued by the Association Fighting Viral Hepatitis, it is reported that positivity for anti-HB_s in Turkey ranges between 20.6% and 52.3% (15). In studies conducted in the South-Eastern region, which has a low socio-economic level and therefore low hygiene and education level, it was reported that the rate of asymptomatic HBV carriage was 12.5-13.9% (7, 16). In another study conducted on pregnant women in Şanlıurfa, the same author found the carriage rate was 7.3%, while 41.1% were positive for anti-HB_s. In developed western regions, the rate of carriage is 4.2-6.5% (17, 18).

Less than 10% of chronic carriers have anti-HBs antibodies (19). In this study none of the HB_sAg-positive pregnant women had anti-HB_s antibodies.

The high incidence of transmission of HBV from carrier mothers to infants reported from Taiwan (40%) and Japan (73%) suggests that the virus easily passes the placental barrier (20, 21). However, a study in Denmark (22) did not find any vertical transmission, while in the United States it also appears to be low (23). No vertical transmission was found in the present study.

Today, a highly reliable and effective recombinant vaccine is available for hepatitis B immunization. Hepatitis B vaccine is one of the most effective vaccines available (24). Studies have shown that infants of the most highly infectious mothers (women who are both HB_sAg and HB_eAg-positive) who receive post-exposure prophylaxis with hepatitis B vaccine alone (without HBIG) at birth are protected in 90–95% of cases, Given the large number of infants involved in a large, prospective study, parents should be reassured that the HBV vaccine, which may prevent the infant from becoming HBV infected, is safe and does not increase the risk of adverse outcomes (25).

The vaccine programme recommended by the World Health Organization (WHO) in 1997 is still applied for routine vaccination of infants and adolescents in 129 countries in their national schedule giving the vaccine free of cost (26). The target set was inclusion by 1997 of hepatitis B vaccine in national schedule by all the countries with >2% carrier rate and by 2000 by all the countries. This covers more than 50% of target population of the world which includes predominantly the western world. Turkey has accepted this concept and was included in the program in 1998 (27).

Prophylaxis is particularly important for infants of mothers infected with HBV, since it has been found that perinatal infections become chronic in as many as 90% of those infected (2, 3). Tragically, hundreds of newborns do not receive appropriate prophylaxis (0.5 mL hepatitis B vaccine and 0.5 mL HBIG) within 12 hours of birth. The annual "Recommended Childhood Immunization Schedule" encourages the routine use of hepatitis B vaccine for all infants before hospital discharge to protect neonates discharged to households in which hepatitis B chronic carriers other than the mother may reside and to enhance the completion of the childhood immunization series (9). If HBIG and recombinant hepatitis B vaccination are given concurrently to infants immediately after birth, 94% protection is provided (28). In a study by Szmuness et al., coadministration of HBIG and hepatitis B vaccine did not interfere with response to the vaccine (29). The 12-month anti-HB_s titer has been found to be the strongest predictor of efficacy (1).

In this study, HBIG and recombinant hepatitis B vaccine were given concurrently to newborns of mother carrying HB_sAg. Blood antibody levels were then measured at an average 28.6±10.4 months after birth (range 6-46), and it was found that immunization was effective in 91.6% (44).

In conclusion, the prevention of perinatal HBV infection with a dose of hepatitis B vaccine has been shown to prevent 90% of perinatal infections if given within 12 hours of birth. However, in certain circumstances i.e. infants and children who are exposed to HBV even though their mothers are HB_sAg negative, are consistent with a particular situation because two-thirds of HBV-infected children do not have HBV-infected mothers. These infections result from close contact with HB_sAg-positive persons living in the child's household or other households and 30-50% of children who become infected with HBV between 1-5 years of age become chronic carriers. Therefore, given the lack of vertical transmission found in this study and the high risk of later horizontal transmission, it would seem wise to vaccinate all newborns of carrier mothers. Furthermore, there is a greater likelihood of complete vaccination; multiple studies indicate children who received the first dose of hepatitis B vaccine during their first month of life (usually the birth dose) were more likely to complete the hepatitis B vaccine series and other important immunizations which the younger an infant is, the more likely she or he is to complete the entire three dose hepatitis B vaccine series (30, 31, 32).

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