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Erzurum'da Hepatit B'li Annelerin Bebeklerine Verilen Pasif-Aktif İmmunoprofilaksinin Sonuçları, Türkiye

Outcomes of Passive-Active Immunoprophylaxis Administered to Infants of Mothers Infected with Hepatitis B Virus in Erzurum, Turkey

Handan Alay[1], Melek Şahiner[2], Berrin Göktuğ Kadıoğlu[3], Ragıp Afşin Alay[4]

1Atatürk Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

2Nenehatun Kadın Doğum Hastanesi, Enfeksiyon Kontrol Birimi

3Nenehatun Kadın Doğum Hastanesi, Kadın Hastalıkları ve Doğum

4Atatürk Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları

ÖZ

GİRİŞ ve AMAÇ: Hepatit B virüsü (HBV) ile infekte annelerden doğan bebekler pasif-aktif immünoprofilaksiye rağmen infekte olabilirler. Bu çalışmada HBV'nin bulaşmasında maternal vireminin rolünü ve HBV ile infekte annelerden doğan bebeklerin pasif-aktif immunoprofilaksi sonuçlarını değerlendirmeyi amaçladık.

YÖNTEM ve GEREÇLER: Bu çalışmaya bir Kadın Hastalıkları ve Doğum hastanesinde 2014 ve 2016 yılları arasında HBV ile infekte anneler ve pasif-aktif immünoprofilaksi uygulanan bebekleri dahil edildi. Hastaların sosyodemografik verileri, hepatit belirteçleri, viral yükleri ve çocukların hepatit belirteçleri değerlendirildi.

BULGULAR: 2014-2016 yılları arasında 26925 gebe kadın HBsAg için tarandı. 328 HBsAg pozitif gebe kadının 271'i hastanemizde doğum yaptı. Sadece 53 anne ve bebeğine ulaşabildik. HBsAg pozitif 53 anneden 2(% 3,72)'si HBeAg pozitif, 51(% 96,23) anne ise AntiHBe pozitifti. Beş annede(% 9,43) viral yük ≥2000 IU / ml idi. 28(% 52,83) annenin viral yüklerine ulaşılamadı. Maternal HBeAg durumu ve viral yük ile infant antikor yanıtı arasında istatistiksel olarak anlamlı ilişki vardı (p <0,05). Doğum ağırlığı, gestasyonel yaş ve HBIG yapılma zamanı ile infant antikor yanıtı arasında istatistiksel olarak anlamlı bir ilişki yoktu (p> 0,05).

Sorumlu yazar yazışma adresi: Handan ALAY. Nenehatun Obstetrics and Gynecology Hospital, Infectious Diseases and Clinical Microbiology, Erzurum, Türkiye

E-posta: alayhandan@gmail.com

TARTIŞMA ve SONUÇ: HBV ile infekte annelerin bebeklerinde pasif-aktif immunoprofilaksi, perinatal bulaşmanın önlenmesinde oldukça etkilidir. HBsAg taraması tüm gebelere hamilelikleri sırasında yapılmalıdır. Hamileliklerinde HBsAg pozitif olarak saptanan annelerin bebeklerine doğumdan 6-12 saat içinde pasif-aktif immunoprofilaksi verilmelidir. Sonrasında mutlaka immünizasyon sonuçları değerlendirilmelidir. Ebeveynlere taburculuk sırasında bilgi verilmesi, toplumun farkındalığını artıracak ve hepatit B'nin ortadan kaldırılmasına katkıda bulunacaktır.

Anahtar Kelimeler: HBsAg pozitif anneler, çocuklar, pasif-aktif immünoprofilaksi

SUMMARY

*OBJECTIVES***:** Infants born to mothers with hepatitis B virus (HBV) may be infected despite receiving passive-active immunoprophylaxis. The purpose of this study was to assess the role of maternal viremia in the transmission of HBV and the passive-active immunoprophylaxis outcomes of infants born to women infected by HBV.

METHODS: HBV-infected mothers and infants up to 12 months of age receiving passive-active immunoprophylaxis at the Erzurum Nenehatun Obstetrics and Gynecology Hospital, Turkey, between 2014 and 2016 were included in the study. Socio-demographic data for the patients, and hepatitis markers, viral loads and hepatitis markers of children were evaluated.

RESULTS: A total of 26,925 pregnant women were screened for HBsAg between 2014 and 2016. Three hundred twenty-eight HBsAg-positive pregnant women, of whom 271 delivered at our hospital, and 53 mother-infant pairs were included in the study. Of the 53 HBsAg-positive mothers, HBeAg status was positive in 2 (3.72%) and antiHBe status was positive in 51 (96.23%). Viral load was ≥2000IU/ml in 5 mothers (9.43%). The viral loads of 28 mothers (52.83%) were unavailable. Statistically significant associations were determined between maternal HBeAg status, maternal viral load and antibody response ($p<0.05$). No statistically significant associations were observed between birth weight, gestational age, timing of HBIG and antibody response ($p>0.05$).

CONCLUSIONS: Passive-active immunoprophylaxis in babies of HBV-infected mothers was highly efficacious in preventing perinatal transmission. Antepartum HBsAg markers must be examined in all pregnancies, and passive-active immunoprophylaxis should be given in the first 6-12 h of life to infants of mothers who are HBsAg-positive during pregnancy. Immunization results should be evaluated subsequently. Healthy generations can be produced by treating HBsAg-positivity with high maternal viremia by means of passive-active immunoprophylaxis, thus reducing the economic impact of diseases and care, and improving quality of life. Giving information to parents during discharge training will increase community awareness and contribute to the eradication of hepatitis B.

Key words: HBsAg-positive mothers, children, passive-active immunoprophylaxis

Introduction:

Hepatitis B virus (HBV) infection is one of the most common infectious diseases in the world [1]. One of the main routes of HBV transmission is from asymptomatic carrier mothers to their infants. Mother-to-child transmission often occurs in the uterus or through exposure to blood or blood-contaminated fluids at or around birth. Such perinatal transmission is believed to account for 35% to 50% of HBV carriers [2].

It has been reported that 5%-20% of infants born to HBsAg-seropositive and HBeAg-seronegative mothers and 70–90% of infants born to HBeAg-seropositive mothers will become infected if not given immunoprophylaxis [3]. When such infants become chronically infected, an estimated 25% will progress to chronic liver disease or develop hepatocellular carcinoma [4]. Therefore, in order to protect infants and young children from HBV transmission, the National Advisory Committee on Immunization in the United States, the Center for Disease Prevention and Control (CDC) and World Health Organization (WHO) have recommended since 1984 that all pregnant women be screened for hepatitis B surface antigen (HBsAg) and that babies of carrier mothers be vaccinated and given hyperimmunoglobulin (HBIG) at birth [5-9]. Numerous studies have shown that 10-20% of infants born to HBeAg-seropositive mothers may be carriers even if they receive active and passive immunization [10-15].

The CDC and American College of Obstetrics and Gynecology recommend that all pregnant women be tested for HBsAg during every pregnancy [16, 17]. Screening of all pregnant women for HBsAg has been shown to be a cost-effective measure [18]. It has been reported that 10-20% of infants born to women infected by HBV may be non-responders despite receiving active and passive immunization, followed by completion of vaccine series [10, 11, 19].

Intrauterine infection in infants is reported to be associated with many factors such as virus structure, HBV mutations, maternal HBV DNA level, HBeAg positivity, placental barrier, maternal immunity and fetal susceptibility, despite appropriate immunization [20, 21]. HBsAg-positivity in pregnancies ranges from 1.2% to 12.3% in Turkey [22].

Infants born to HBV-infected mothers may be infected despite receiving passive-active immunoprophylaxis and vaccination series. The purpose of this study was to assess the role of maternal viremia in the transmission of HBV and the passive-active immunoprophylaxis outcomes of infants born to women infected by HBV. We also aimed to detect cases of vertical transmission in the early period despite vaccination and HBIG, to initiate diagnostic and therapeutic procedures, and to provide primary immunization for individuals without immune response.

Methods:

HBV-infected mothers and infants receiving passive-active immunoprophylaxis over a two-year period between 2014 and 2016 at the Erzurum Nenehatun Obstetrics and Gynecology Hospital in Turkey were assessed retrospectively. All children born to HBsAg-positive mothers receiving immunoprophylaxis were followed-up for markers of HBV infection (HBsAg, AntiHbs, and AntiHBc) up to 9 months of age. HBeAg, anti-HBe, HBVDNA and sociodemographic data were evaluated for all these mothers. Preterm birth, birth weight, timing of HBIG and mode of delivery of all children born to HBsAg-positive mothers were also evaluated.

The infants of these mothers received HBIG from a single-use 1 ml vial containing 220 international units, together with the first dose of HBV vaccine (Euvax-B) at birth and the second and third doses of HBV vaccine at 1 and 6 months of age, respectively, in line with the Turkish Ministry of Health Expanded Program on Immunization. Infants with birth weight <2000 g received four doses of HBV vaccine. All mothers were recalled with their babies up to 12 months of age in order to assess the vaccine response. Infants with anti-HBs less than 10 mIU/ml and who were HBsAg negative were considered non-responders and received the second series of HBV vaccine using the 0-, 1-, and 6-month schedule without HBIG. Anti-HBs in these children were re-evaluated 1 month after the final dose.

Statistical analysis: Categorical data were expressed as number and percentage, and numerical data as mean and standard deviation (SD). Normal distribution of numerical data was evaluated using histograms and skewness tests. The Chi-square was used for hypothesis testing.

Results

A total of 26,925 pregnant women were screened for HBsAg between 2014 and 2016. Three hundred twenty-eight HBsAg-positive pregnant women, of whom 271 delivered at our hospital and 53 mother-infant pairs, were contacted and included in the study (Table 1).

Table 1: HBsAg screenings and positivity rates by years

Year	HBsAg Screening (n)	HBsAg Positivity (n)	%
2014	9362	133	1.42%
2015	8793	105	1.19%
2016	8770	90	1.02%

HBsAg- Hepatitis B surface antigen.

Among the mother-infant pairs, mean maternal age was 31.8±5.9 years. In terms of educational status, 10 (18.87%) mothers were illiterate. Eighteen (33.96%) women were diagnosed during pregnancy. There were no multiple pregnancies among these mothers. Fifty-two (98.11%) infants had a gestational age ≥37 weeks. One infant (1.89%) weighed <2000 g and 52 (98.11%) weighed ≥2000 g. Timing of HBIG was ≤6 h in 48 (90.57%) infants and >6 h in 5 (9.43%) (Table 2).

Table 2. Demographic characteristics of HBsAg[¥]-positive mothers and children

		n	%
Maternal Age	<25 years	7	13.2
	25-34 years	27	50.9
	35-45 years	19	35.9
Maternal Education Status	Illiterate	10	18.9
	Elementary school	33	62.2
	High School	6	11.3
	University	4	7.6
Diagnosis Type	During Pregnancy	18	33.9
	Blood donation	1	1.9
	Marriage formality	13	24.5
	Family history	8	15.1
	Other	13	24.6
Infant Gender	Female	14	26.4
	Male	39	73.6
Infant Gestational Age	<37 weeks	1	1.9
	≥37 weeks	52	98.1
Infant Weight	< 2000 g	1	1.9
	≥ 2000 g	52	98.1
Timing of HBIG*	≤6h	48	90.6
	6-12h	5	9.4

**HBIG- Hepatitis B immunoglobulin ¥-HBsAg- Hepatitis B surface antigen*

Of the 53 mothers who were HBsAg-positive, HBeAg status was positive in 2 (3.72%) and antiHBe status was positive in 51 (96.23%). Viral load was ≥2000 IU/ml in 5 mothers (9.43%), while the viral loads of 28 mothers (52.83%) were unavailable. Statistically significant associations were determined between status of maternal HBeAg, maternal viral load and antibody response ($p<0.05$) (Table 3).

Table 3. Predictors of infant antibody response

	Anti-HBs[£]<10 mIU/ml (n=4)		Anti-HBs[£]≥10 mIU/ml (n=49)		p
	n	%	n	%	
Maternal HBeAG[#] status					
HBeAg[#] positive	1	25	1	2	0.021
HBeAg[#] negative	3	75	48	98	
Maternal Anti-HBeAg[€] status					
Anti-HBeAg[€] positive	3	75	48	98	0.021
Anti-HBeAg[€] negative	1	25	1	2	
Maternal Viral Load					
< 2000 IU/ml	1	5	19	95	0.031
≥ 2000 IU/ml	2	40	3	60	
Infant gestational age					
< 37 weeks	-	-	1	2	0.773
≥ 37 weeks	4	100	48	98	
Infant weight					
< 2000 g	-	-	1	2	0.773
≥ 2000 g	4	100	48	98	
Timing of HBIG[*]					
≤6 h afterbirth	3	75	45	91.8	0.268
6-12 h afterbirth	1	25	4	8.2	

[€]Anti-HBeAg- antibody to hepatitis B e antigen
[£]Anti-HBs- antibody to hepatitis B surface antigen
[#]HBeAg- Hepatitis B e antigen
[*]HBIG- Hepatitis B immunoglobulin

Vaccine response was 1% for infants weighing <2000 g at birth and 48% for infants weighing ≥2000 g. No statistically significant associations were determined between birth weight, gestational age, timing of HBIG and antibody response (Table 3). The geometric mean anti-HBs titer value in infants was 442.6 IU/ml (±377.1 SD).

Three (75%) infants of anti-HBe seropositive mothers and one (25%) infant of an HBeAg-positive mother had anti-HBs levels lower than 10 IU/ml and were considered as non-responders. Three non-responder infants of antiHBe seropositive mothers responded to the second series of HBV vaccination. One non-responder infant of an HBeAg seropositive mother was HbsAg positive, with a viral load of 19,874,497 IU/ml.

Discussion

The prevention and eradication of hepatitis B is an objective shared by Turkey and the rest of the world. Perinatal transmission is usually caused by the baby being exposed to infected body fluids at time of birth, through abrasions on the infant's body, the swallowing of maternal fluids, and transplacental transmission. Some studies have shown that type of delivery plays no role in the transmission of infection, but rather that the infection is acquired at the time of birth and in the postpartum period. The rate of transplacental transmission is low, at 5%, but HBV is transmitted by the transplacental pathway in infants born to HBsAg-positive mothers or in the presence of Anti-HBc IgG in cord blood. Neonatal death and hepatocellular carcinoma can develop in infants with chronic HBV infection, including factors such as newborn immaturity. This emphasizes the importance of immunoprophylaxis [23-25].

The screening of all pregnant women for HBsAg, and vaccine and hepatitis B immunoglobulin (HBIG) administration to the babies of carrier mothers at birth has been recommended since 1984. However, in most regions where HBV is endemic today, and even in developed countries, it is still not possible to perform HBsAg screening at the desired level. In Turkey, HBV infection can be determined by means of screening tests at initial examinations, preoperative procedures, during pregnancy, in blood donors and during formalities required before marriage. Prevalence studies are therefore particularly valuable. Most of the patients in our study were diagnosed during pregnancy. The numbers of HBsAg screenings performed in 2014, 2015, and 2016, were 9362, 8793, and 8770, respectively. HBsAg was detected in 133, 105, and 90 of these, respectively. HBsAg positivity in pregnancies in Turkey has mostly been determined at similar levels to the general population in recent studies, and varies between 1.2% and 12.3%. Positivity is reported to be higher in subjects who were born in or migrated from the East and Southeast Anatolia regions of Turkey. HbsAg positivity levels in pregnancy in our study were 1.42% (2014), 1.19% (2015), and 1.02% (2016).

Studies have shown that HBeAg status, infection by escape mutant HBV and in utero infection may constitute risk factors for chronic infection in infants. The high viral load in HBeAg-seropositive mothers predisposes to intrauterine HBV transmission and failure of immunoprophylaxis given to the infected infant [20, 21]. There is also a known relationship between viral load and rate of transmission to the baby. One recent review of 63 studies emphasized that transition is high if the mother has HBV DNA> 10^6 IU / ml and is HBeAg positive [26]. A consensus report on hepatitis B management in pregnancy in Turkey emphasized that the maternal serum HBV DNA level is the most important independent risk factor for vertical transition, and antiviral prophylaxis is therefore recommended in the last trimester of pregnancies with HBeAg positivity and HBV DNA levels ≥6 log10 copies / ml (≥ 200 000 IU / ml). In our study, one infant born to a woman actively infected by HBV became chronically infected. The mother was HBeAg seropositive, with a viral load of 327,922,274 IU/ml.

One notable finding from our study was that HBsAg-positive pregnancies were not referred to the infectious diseases clinic by obstetricians, although our hospital has one of the highest birth rates in the eastern part of Turkey. Although passive-active immunoprophylaxis is an effective method of preventing HBV transmission, it is still important to monitor HBsAg-positive pregnancies and to establish standardization and cooperation with physicians from other branches.

The achievement of sufficient anti-HBs in infants born to HBV-infected mothers is critical. In this study, following passive-active immunization, we observed protective levels of anti-HBs in 49 (92.45%) neonates of HBV-infected mothers, while 4 (7.55%) infants did not respond to vaccination. Numerous studies have reported non-responder infants despite receipt of active and passive immunization. Sloan et al. and Prakash et al. reported non-responder rates of 3.7% and 22%, respectively [27, 28]. Non-responder infants are at risk of HBV infection if not followed-up. It is important to identify children needing additional doses of vaccine because of the potential for horizontal transmission from the mother or other hepatitis B-infected household members. In order to increase public awareness and to ensure that HBV is eradicated, systems should be established to ensure that babies born to HbsAg-positive mothers are evaluated for hepatitis B after the age of 9 months, and parents should be informed accordingly during discharge. We attribute the lack of access to all infants who received vaccination and HBIG to their families not being given sufficient information during discharge. In order to eradicate hepatitis B, babies born from HBsAg-positive pregnancies should be standardized, and special follow-up policies should be developed by family medicine practices for these cases. For babies born from HBsAg-positive pregnancies, it may be beneficial to add hepatitis B tests after the age of 9 months to the national vaccine schedule and for vaccine recommendations to be applied in case of need. Cases of non-responder vaccination or HBsAg-positive children can thus be identified in the early period, healthy generations can be raised, and health can be protected and improved.

Hepatitis B is a preventable disease. The prevention of horizontal and vertical transmission is only possible through careful follow-up of the source patient. Warning alerts for physicians following diagnosis of chronic hepatitis B should therefore be set up on the systems used in health institutions. This can help maintain the health of both the carrier individual and the wider community. In our study, only one baby developed vertical transmission despite passive-active immunization. The mother was HBsAg-positive, she was diagnosed with hepatitis B during the formalities required for a marriage license, but did not attend follow-ups. Examination of the mother's family history also revealed that her mother was a hepatitis B carrier and that she had not been monitored either. This demonstrates the importance of follow-up, in addition to diagnosis.

In conclusion, some infants may not respond to passive-active immunization and are therefore at risk of HBV infection and chronic hepatitis B in later life. It is important that these infants born to mothers with hepatitis B be followed-up after completion of their immunoprophylaxis and vaccination

programs. HBV vaccine + HBIG should be given to the babies of HBsAg positive mothers within the first 6-12 hours after birth. In situations where vertical transmission cannot be avoided, it is crucially important to improve child health and increase quality of life. All women should receive HBsAg screening during pregnancy.

Limitations: Despite the high number of infants born to HBsAg-positive mothers who received immunoprophylaxis in our hospital, we were unable to access all patients due to gaps in the hospital data system. Despite the low numbers, the point we wish to emphasize in this study is that while HBsAg screening of pregnant women is performed at adequate levels, subsequent follow-up is inadequate. In addition, the reactions to vaccination of babies receiving passive-active immunoprophylaxis are not monitored.

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