



Consideration Whether Hepatitis B Exists in Children Whose Mothers Suffer from Chronic Hepatitis B and These Mothers in Gestational Age

Kronik Hepatit B Enfeksiyonu Olan Annelerin Gebeliklerinde ve Çocuklarında Hepatit B Enfeksiyonunun Değerlendirilmesi

İlknur Esen Yıldız¹, Selma Tosun², Semra Şen³, Lütfiye Nilsun Altunal⁴, Kenan Uğurlu⁵, Ayşenur Bahşi⁶

¹Recep Tayyip Erdoğan University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Rize, Turkey

²University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İzmir, Turkey

³Celal Bayar University Faculty of Medicine, Department of Paediatric Infectious Diseases, Manisa, Turkey

⁴University of Health Sciences Turkey, İstanbul Ümraniye Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

⁵Gaziantep 25 Aralık State Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Gaziantep, Turkey

⁶Manisa Merkez Efendi State Hospital, Clinic of Gynaecology, Manisa, Turkey

ABSTRACT

Objectives: Perinatal and intrauterine transmission of the hepatitis B virus (HBV) represents a major factor, leading to the development of chronic infection. This study aimed to explore the status of mothers and their children for hepatitis B (HB) infection during pregnancy and childhood, and whether active and passive immunoprophylaxis was administered to infants shortly after birth.

Materials and Methods: We performed multicenter, retrospective research on voluntary hepatitis B surface antigen (HBsAg)-positive mothers admitted to infectious diseases polyclinics was performed. Mothers and their children were queried by a questionnaire about their HB infection status. Data from the electronic data recording system was scanned retrospectively.

Results: Three hundred-one mothers and 616 children were included in the study. HBsAg was examined in 354 (57.4%) of pregnancies. Of 91 children with HBsAg positivity, 83 were not applied active and passive immunoprophylaxis after birth. Eight 276 babies received both immune prophylaxes after birth were then detected as HBsAg positive. On HBV examination, 148 children

ÖZ

Amaç: Hepatit B virüsünün (HBV) perinatal ve intrauterin bulaşı, kronik enfeksiyonun gelişmesine yol açan önemli bir faktörü temsil etmektedir. Bu çalışmada, annelerin ve çocuklarının hamilelik ve çocukluk döneminde hepatit B (HB) enfeksiyonu için değerlendirilme durumlarını ve doğumdan hemen sonra bebeklere aktif ve pasif immünoprofilaksi uygulanıp uygulanmadığının araştırılması amaçlandı.

Gereç ve Yöntemler: Enfeksiyon hastalıkları polikliniğine başvuran gönüllü hepatit B yüzey antijeni (HBsAg)-pozitif annelere yönelik çok merkezli, retrospektif araştırma yaptık. Annelere ve çocuklarına HB enfeksiyonu durumları hakkında bir anket uygulandı. Elektronik veri kayıt sistemindeki verileri geriye dönük olarak tarandı.

Bulgular: Üç yüz bir anne ve 616 çocuk çalışmaya dahil edildi. HBsAg gebeliklerin 354'ünde (%57,4) tetkik edildi. HBsAg pozitifliği olan 91 çocuğun 83'üne doğumdan sonra aktif ve pasif immünoprofilaksi uygulanmadığı saptandı. Doğumdan sonra her iki immün profilaksiyi de alan 276 bebekten 8'i HBsAg pozitif olarak tespit edildi. HBV incelemesinde, 148 çocuğun HBV ile karşılaştığı bulundu. HBsAg

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ABSTRACT

were found to encounter the HBV. HBsAg positivity rate was significantly higher in children born before 1997.

Conclusion: The remarkable decrease in HBsAg positivity of children reveals the efficacy of national vaccination. By informing both healthcare workers and society, awareness about examining pregnant for HBsAg during pregnancy should be increased.

Keywords: Pregnant, HBsAg, immune prophylaxis

Öz

pozitiflik oranı 1997'den önce doğan çocuklarda anlamlı olarak daha yüksek olarak belirlendi.

Sonuç: Çocukların HBsAg pozitifliğindeki dikkat çekici azalma, ulusal aşılamanın etkinliğini ortaya koymaktadır. Hem sağlık çalışanlarını hem de toplumu bilgilendirerek, hamilelik sırasında HBsAg için gebelerin tetkik edilmesi konusunda farkındalık artırılmalıdır.

Anahtar Kelimeler: Gebe, HBsAg, immün profilaksisi

Introduction

Hepatitis B virus (HBV) infection remains to be a significant global public health issue affecting more than 257 million people in the whole world (1,2,3). By the World Health Organization (WHO), it was reported that one million people for reasons related to viral hepatitis have been dying every year, and there has been a 22% increase in deaths since 2000. WHO, for 2030, aims to reduce the number of hepatitis infections by 90% and mortality by 65%, also suggests essential strategies (2,3). One of these strategies is the prevention of transmission from mothers with hepatitis infection to the baby, which is one of the main ways to reduce the incidence of HBV in the community (2,4,5). The perinatal or vertical transmission of the virus in pregnancy, birth, early infancy to babies of hepatitis B surface antigen (HBsAg) positive mothers plays a vital role in endemic infection and to develop chronic infection (3,6). The administration of active and passive immunoprophylaxis [hepatitis B hyperimmune globulin (HBIG) with HBV vaccine] within the first 12-24 hours immediately after birth to infants of mothers with HBsAg positivity prevents 90-95% transmission of the HBV to the baby (1,2). This application is, therefore, crucial to prevent both becoming chronic of the infection and complications of the infection by not being taken the virus at an early age (2,4,6). Screening mothers for hepatitis B (HB) infection in pregnancy and administering active and passive immune prophylaxis to their babies in the presence of HB is one of the most critical viral hepatitis prevention strategies of WHO to reduce the incidence of HB infection in the community (3,5,7,8,9). Also, after examining and following up the pregnant for HB, the initiation of antiviral therapy or prophylaxis, if necessary, and monitoring of exacerbations that may develop due to HB infection during and after pregnancy, are essential for the prevention of transmission. Perinatal transmission all over the world and in our country is one of the most common transmission ways of HBV infection (3,8). The perinatal transition rate of 5-15% could be seen in babies of hepatitis B e antigen (HBeAg) positive or high viral loaded pregnant women, in whom HBsAg positivity was detected despite appropriate active and passive immune prophylaxis (10,11,12). The risk of transition from mother to baby is tried to be reduced further even in high viral loaded (200000 IU/mL) pregnant women in recent years by using antiviral medication in addition to active and passive immune prophylaxis (13,14,15,16,17).

We aimed in our study to determine the status of evaluating the pregnant for HB infection during pregnancy, whether active and passive immunoprophylaxis was administered to infants

immediately after delivery and then, whether HBV examination was made and immunity was developed in children of mothers against current HB infection, and to reveal the related deficiencies.

Materials And Methods

Our study was planned as a multicenter, retrospective, descriptive cross-sectional research, and it was held in five different provinces (Rize, İzmir, Gaziantep, Manisa, İstanbul) from five different regions of Turkey. The mothers with HBsAg positivity who were followed by infectious diseases and clinical microbiology clinics of tertiary universities or educational research hospitals or referred by obstetrics and gynaecology clinics were included in the study. Ethical permission: A multicenter study permit from the Ethics Committee University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital (approval number: 27.10.2015/2) and permission from the Republic of Turkey Public Health Agency (approval number: 45202601) were obtained for the study.

Collection of Data

The study was conducted on HBsAg positive mothers admitted to infectious diseases polyclinics between 2015 and 2017 after obtaining their consent, by performing a questionnaire through the face-to-face interviews. Mothers whose children were born after 1991, and their children were included in the study. We also scanned files and evaluated the electronic registration data system of the study participants retrospectively.

Data Collection Tools

Besides the demographic data of mothers and their children, examinations performed and treatments administered during and after their pregnancy, and the follow-up status of their children was questioned. For this purpose, we asked the mothers whether they were examined for HBsAg during their pregnancy and whether vaccine and HB immunoglobulin was administered to their babies within the first 12-24 hours immediately after delivery. The questions regarding the screening of mothers for HBV were asked; besides, children too, were questioned about the immune status of them after the completion of three doses of HB vaccines. The current situation of their children for HBV acquisition was also re-examined. Relevant information that could not be obtained from subjects were tried to be reached from the patient files.

Statistical Analysis

SPSS for Windows 21.0 program was used for statistical analyses. Descriptive statistics and frequency distributions were

calculated in line with the characteristics of the variables in the study. According to whether the data obtained were categorical or not and were independent or not, and the number of groups of the obtained data, the Pearson chi-square test, Student's t-test, and Mann-Whitney U test was performed. For the comparison of more than two groups, we used ANOVA for parametric data and the Kruskal-Wallis test for non-parametric data. The statistical significance level was accepted as $p < 0.05$.

Results

In our study, 301 mothers and 616 children were evaluated. The mean age of mothers was 38.6 ± 7.5 (19-64), and the mean age at diagnosis was detected to be 24.3 ± 10.6 (6-54). In 262 of 616 pregnancies, mothers were found to be not examined for hepatitis infection. The sociodemographic characteristics of mothers (data) were summarized in Table 1. The mean age of children was 12.8 ± 6.6 (2-28) years, and the female to male ratio was identified to be 295/321 (47.8%, 52.2%). The socio-demographic characteristics (data) of children were given in Table 2.

When we questioned mothers, we learned that HBsAg had been examined in 57.4% of pregnancies. Furthermore, the HBV examination was done to only 294 (47.7%) children at any time, while 96 (15.6%) had no HBV examination until now. Of those children undergoing HBV examinations, 91 (20%) were with HBsAg positivity, and 57 (14.5%) had natural immunity. The status of being examined for HBV, the HBV examination results, and the status of vaccine and HBIG administration after birth in children were summarized in Table 3.

Despite the administration of active and passive immunoprophylaxis within the first 12-24 hours immediately after delivery, 8 (2.9%) of 276 infants had HBsAg positivity. Based on the electronic registration data, we found the mothers of these children to be with HBeAg positivity and high HBV-DNA levels in their pregnancies. It was also determined that they had used medication, too, in their follow-up after their pregnancies. In the current study, HBsAg positivity was found to be significantly higher in children born before 1997 ($n=34$ and $\%37.2$) ($p < 0.001$). We observed the mothers of the majority of children who have HBsAg

Table 1. Socio-demographic data of mothers (n=301)

	Characteristic	n	%		Characteristic	n	%
Age	19-25 years	7	2.3	How was HBV infection diagnosed?	During pregnancy	86	27.7
	25-29 years	17	5.6		Due to another HBV in the family	47	15.2
	30-39 years	154	51.2		In the preoperative period	17	5.5
	40-49 years	104	34.6		While getting married	60	19.4
	50-59 years	14	4.7		At the time of blood donation	4	1.3
	60 years and older	5	1.7		While starting a job	4	1.3
Educationstatus	Not literate	24	8.0	HBV status in pregnancy*	Coincidentally, in the examination	41	13.2
	Literate	14	4.7		Others	42	13.5
	Primary school graduate	157	52.2		Inactive carrier	304	49.4
	Secondary school graduate	41	13.6		Previously treated	19	3.1
	High school graduate	46	15.3		Currently under treatment	28	4.5
	Graduated from a university	19	6.3		Cirrhosis	3	0.5
				Unknown	262	42.5	

*A total of 616 pregnancies were taken as the number of birth, HBV: Hepatitis B virus

Table 2. Socio-demographic data of the children (n=616)

	Feature	n	%		Feature	n	%
Age	1-6 years	156	25.9	State of having received vaccination or HBIG at birth	Vaccination	154	25.0
	6-12 years	197	32.8		Vaccination + HBIG	276	44.8
	13-18 years	149	24.8		Unknown	84	13.6
	19-23 years	41	6.8		None	102	16.6
	24-28 years	73	12.1	State of having been given vaccination card	Given	420	68.2
Mode of delivery	Spontaneous vaginal delivery	420	68.2		Not given	68	11.1
	C/S	196	31.8		Not remembered	128	20.1
Place of delivery	Hospital	467	75.8	State of having received HBVexamination	At age one	294	47.7
	Home	18	2.9		After age one	197	31.8
	Community clinic	131	21.3		Never	96	15.6
-	-	-	-		Not remembered	29	4.7

HBIG: Hepatitis B hyperimmune globulin, HBV: Hepatitis B virus, C/S:

positivity, not to be examined for HBsAg during pregnancy (46.2% not examined, 16.4% examined, 39.4% unknown). Again, the vast majority of these children have not received vaccines and immunoglobulin (n=83 and 91.2%). The comparison of the clinical status of children, whose mother was positive for HBsAg during pregnancy by age in terms of hepatitis infection was summarized in Table 4.

Discussion

It is reported in various studies that the administration of active and passive immune prophylaxis to babies of mothers with HBsAg

positivity in the first 12-24 hours of life immediately after birth prevents 90-95% transmission of the HBV to the infant (1,2,18,19).

In our country, despite all efforts, in general, routine screening of HBsAg in pregnant women, administration of active or passive immune prophylaxis to the babies of mothers with HB infections, and then monitoring the immune status of those is not at the desired level (20). It is seen that the awareness and application of the "Prenatal Care Guide" created by the Ministry of Health and updated in 2014 in the field are quite low and that the HBsAg test is not requested enough for pregnant women in many institutions (20,21). With this aim, by the Ministry of Health in 2018, Viral

Table 3. Children's states of having received HBV examination, examination results and states of having received vaccination + hyper immunoglobulin

	State of having received HBV examination					State of having received vaccination and HBIG after delivery				
	At age one	After age one	Does not know	Never	Total	Vaccinated	Vaccine + HBIG	Does not know	None	Total
Anti-Hbs positive	167	105	1	0	273	39	165	23	46	273
Immune	48	9	0	0	57	21	26	5	5	57
HBsAg positive	57	34	0	0	91	28	8	19	36	91
Anti-HBc IgG positive	2	1	0	0	3	1	1	0	1	3
Kr HBV on treatment	1	2	0	0	3	1	0	0	2	3
Ex	0	1	0	0	1	0	0	0	1	1
Not remembered	8	29	28	96	161	64	62	31	4	161
HBV negative	11	16	0	0	27	0	14	6	7	27
Total	294	197	29	96	616	154	276	84	102	616

HBV: Hepatitis B virus, HBIG: Hepatitis B hyperimmune globulin

Table 4. Comparison of the clinical states of children born from HBsAg positive mothers in terms of birth year

		1991-1997	1998-1999	2000-2005	2006-2011	2012-2017	Total	p
HBV state	Anti-HBs positive	10	16	70	98	79	273	<0.001
	Immune	13	2	8	20	14	57	
	HBsAg positive	34	12	29	14	2	91	
	Isolated anti-HBc IgG	0	0	1	1	1	3	
	Chronic HBV treatment	3	0	0	0	0	3	
	Ex	0	0	0	1	0	1	
	Not examined	9	11	31	54	56	161	
	HBV negative	4	0	10	9	4	27	
Total	73	41	149	197	156	616		
State of having received vaccination-HBIG at delivery	Not vaccinated	17	7	34	62	34	154	<0.001
	Vaccine + HBIG	5	9	47	102	113	276	
	None	35	15	36	16	0	102	
	Unknown	16	10	32	17	9	84	
	Total	73	41	149	197	156	616	
State of having received HBV examination	At age one	41	15	61	102	75	294	0.01
	After age one	25	17	61	49	44	196	
	Unknown	1	2	5	8	13	29	
	Never	6	7	22	38	24	97	
	Total	73	41	149	197	156	616	

HB: Hepatitis B, HPV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen, HBIG: hepatitis B hyperimmune globulin

Hepatitis Prevention and Control Program was put into effect, and performing the HBsAg test for pregnant women has been made compulsory by no longer being a recommendation (5,8).

No studies are examining whether the HB vaccine and HBIG prophylaxis could be administered together or separately. In our study, the rates of administering alone HB vaccine to babies after birth were 25% (n=154). In contrast, the rate of administering vaccine and immune globulin was found at 44% (n=276). In 55.6% (n= 340) of pregnancies, no immunoglobulin was applied, or whether applied or not of those were identified to be unknown. Some of the mothers even stated that they heard this expression for the first time. This situation suggests the insufficiencies in efforts leading pregnant women to be followed up and informed. In this context, a multidisciplinary joint action by all healthcare professionals, primarily including the clinicians working at Family Medicine, Obstetrics and Gynecology, and Infectious Diseases Clinics, is thought to be going to increase awareness. First, informative training for HBV examination during pregnancy should be given to pregnant women. Second, the control of the mother and child monitoring and the support of hospital administrations in eliminating the related deficiencies need to be increased. Third, intervention commissions should be established, and audits and feedback should be conducted. In this way, we think that both the rates of making the diagnosis of HB infection and the rates of administration of active and passive immunoprophylaxis to newborns could be increased. In Koruk et al.'s (22) intervention research from our country to prevent HB infection, the informative education, the identification of the deficiencies and taking the relevant measures, and acting together of all healthcare professionals, of hospital management, and public cooperation have been seen to yield successful results. The rate of immunoglobulin administration, which was 28.2% before that study, increased 5.8 times after the intervention, whereas that of vaccine administration increased two times (22,23). Such practices need to be increased nationwide.

Vaccines protecting the health of the entire society, especially children, is the most effective method of preventing diseases in terms of cost and reliability (2,3,12,20,22,24,25,26). Thanks to widespread vaccination campaigns, with vaccination studies carried out in one of the poorest countries in the world, 6.4 billion people survived between 2011-2020, and treatment costs seemed to decrease (9). HB infection is one of the primary vaccine-preventable diseases. Co-administration of active and passive immunoprophylaxis enhance immune protection. In our study, the determination of HBsAg positivity in only %2,9 (n=8) of infants who received the vaccine and hyper immunoglobulin prophylaxis proved such co-administration to be quite effective in preventing HBV transmission. The relationship between anti-HBs positivity in infants and increased postpartum immunoprophylaxis over the years was found to be statistically significant. Other studies, too, described the efficacy of the application of HB immunoglobulin with the vaccine to increase protection (18,23,27,28,29). In Lee et al.'s (18) research, HB infection has been shown to develop much less frequently in vaccine or vaccine plus hyper immunoglobulin prophylaxis administered group compared to the placebo or untreated group. Again, Yi et al. (28) reported in their study that HBIG and vaccine combination reduced the rate of viral

transmission from mother with HBeAg positivity to baby from 90% to 3-7%. HBsAg incidence with universal vaccination of infants was, moreover, noted to fall from 9-12% to less than 1%; besides, the protective efficacy of the HB vaccine with HBIG administration was shown to increase to 90-95% (30). In the research of Pande et al. (25), six babies from 259 babies born from HBeAg positive mothers had hepatitis infection, and they observed those babies be in the group without active and passive immunoprophylaxis (24). In our country, after the HB vaccine has been available and entered the calendar, although the incidence of HBV has been declared to decrease, no studies have been encountered in literature, documenting the rate of passive immune prophylaxis (24). At the same time, proper and effective administration of active and passive immunoprophylaxis remarkably prevents to get the HBV in infancy or early childhood and reduces becoming infection chronic and the deaths associated with HB that may develop in advanced ages (12,25,31).

The vaccine and HBIG immunoprophylaxis in the prevention of transmission of HBV are 90-95% effective; however, especially in pregnant women with high viral load and HBeAg positivity, there is a 5-10% viral transmission (4,11,12). In the study of Farmer et al. (10), despite vaccination and HBIG immune prophylaxis, protection was accounted for 81%. Whereas occult HB infection in Pande et al.'s (25) study developed at 64%, the majority of these patients were in the group receiving active and passive immunoprophylaxis. Those results of several studies mentioned above support the requirement for giving antiviral medication to pregnant women, particularly with HBeAg positive and viral load >10⁷-8. Many other guides and studies today recommend, too, the use of oral antivirals, especially in subjects with HBeAg positivity and high viral load (HBV-DNA >10⁷-8) and in subjects, whom liver damage begins (13,14,15,16,17).

Follow-up of babies after birth is important in terms of HB infection and immunization. In our country, few studies are examining immune prophylaxis and then the immune status of the baby against HB infection, and our research is one of them (24). In our trial, both the follow-up of the babies who were given immune prophylaxis could not be done enough, and their immune controls could not be screened adequately in the first year. HB infection has been detected in 34 of 197 children who were examined in later ages, but not being examined in the first year of infancy. Moreover, it has been stated that 17 of the children examined have not developed immunity, and booster doses have been made. This situation on the field suggests that there are deficiencies in the monitoring of mothers and children with HB infection. In our study, under the influence of National Viral Hepatitis Vaccination Programs, although the number of babies with HBsAg positivity has decreased over the years, the status of being examined mothers for the presence of HB infection during pregnancy and the follow-up of their babies' immune status one year after birth was determined to be not enough. Also, awareness of whether hyperimmune globulin prophylaxis was applied to infants or not was insufficient, and we saw troubles in the storage of documents or cards indicated immune prophylaxis had been done. The consciousness levels of mothers about the presence, follow-up, treatment, and prevention of HB infection are required to be

increased to be monitored themselves and their babies. Providing controllability and increasing the sensitivity may help increase awareness in terms of informing mothers for the importance of conducting HB tests and monitoring their results, of automatizing the hepatitis-related examinations as being visible in all centers, of arranging documents showing that immune prophylaxis has been done, and of following the cards about the vaccination. The application of the following recommendations could, therefore, reduce the frequency of HB infection among mothers and babies: 1- acting all together of family physicians, pediatricians, gynecology and infection clinics, and all healthcare professionals, especially hospital management, 2- the identification of deficiencies and the establishment of intervention commissions, 3- organizing training and ensuring continuity of that to increase the level of knowledge of the entire society.

Strength of the Study

Our study is the first multicenter study conducted in our country, examining the follow up of mothers with HB infection, whether babies are given both hepatitis vaccine and HBIG at birth, and the current status of children in terms of HB infection. The identification of deficiencies and making new arrangements even partially in the monitoring of HB infection in mothers and their babies could shed light on and contribute to future studies.

Study Limitations

Based on information from file scans and electronic data records, mothers evaluated for HB in their pregnancies were observed to be examined only in terms of HBsAg. Although the results were positive for HBsAg in most of them, deficiencies were found in requesting and examining for HBeAg and HBV-DNA. This was one of the limitations of our study and caused babies born from HBeAg positive mothers not to be compared with babies born from HBeAg negative mothers. Also, since HBV-DNA data are not available in most pregnancies, no comparison could be made in terms of viral load in children. Moreover, the study is limited to five centers and does not reflect the country. The number of data needs to be supported by reflecting the whole country and with patient information, where all HB examinations are regularly monitored.

Conclusion

The follow-up of mothers and babies is not at the desired level in terms of preventing HB infection. Awareness should, therefore, be raised by eliminating related deficiencies.

Ethics

Ethics Committee Approval: A multicenter study permit from the Ethics Committee University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital (approval number: 27.10.2015/2) and permission from the Republic of Turkey Public Health Agency (approval number: 45202601) were obtained for the study.

Informed Consent: The study was conducted on HBsAg positive mothers admitted to infectious diseases polyclinics between 2015 and 2017 after obtaining their consent, by performing a questionnaire through the face-to-face interviews.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Design: S.T., Data Collection or Processing: İ.E.Y., S.T., S.Ş., L.N.A., K.U., A.B., Analysis or Interpretation: İ.E.Y., Literature Search: S.T., Writing: İ.E.Y.

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