Original Investigation / *Özgün Araştırma*

DOI: 10.5578/ced.20240402 • *J Pediatr Inf 2024;18(4):e215-e220*

How Important are the Maternal Hepatitis B Viral Load and HbeAg Status in Neonatal Immunoprophylaxis Failure?

Yenidoğan İmmünoprofilaksi Başarısızlığında Maternal Hepatit B Viral Yükü ve HbeAg Durumunun Önemi

Şekibe Işık Dişci[1*](İD), Halil Haldun Emiroğlu[2*](İD), Melike Emiroğlu[3](İD), Meltem Gümüş[2](İD), Muslu Kazım Körez[4](İD)

[1] *Clinic of Child Health and Diseases, Konya Seydişehir State Hospital, Konya, Türkiye*
[2] *Division of Pediatric Gastroenterology and Hepatology, Department of Child Health and Diseases, Selçuk University Faculty of Medicine Hospital, Konya, Türkiye*
[3] *Division of Pediatric Infectious Diseases, Department of Child Health and Diseases, Selçuk University Faculty of Medicine Hospital, Konya, Türkiye*
[4] *Department of Biostatistics, Selçuk University Faculty of Medicine Hospital, Konya, Türkiye*

**Şekibe Işık Dişci and Halil Haldun Emiroğlu contributed equally to the article.*

Cite this article as: Dişci ŞI, Emiroğlu HH, Emiroğlu M, Gümüş M, Körez MK. How important are the maternal hepatitis B viral load and HbeAg status in neonatal immunoprophylaxis failure?. J Pediatr Inf 2024;18(4):e215-e220.

Abstract

Objective: The present study aimed to determine the significance of maternal hepatitis B viral load and HBeAg status in neonatal immunoprophylaxis failure.

Material and Methods: The present study was designed as a retrospective case study (n= 52). Children who were followed up due to immunoprophylaxis failure and the development of chronic hepatitis B infection were included in the case group (n= 16). The control group (n= 36) included children with successful immunoprophylaxis. The viral load (high/low) and HBeAg status (positive/negative) of the mothers of both groups of the children were compared. Furthermore, possible factors that could lead to immunoprophylaxis failure (gestational age, birth weight, delivery method, premature membrane rupture, breastfeeding length) were also analyzed in both groups.

Results: A moderate positive correlation (φ= 0.549, p< 0.001) was determined between the viral loads and a strong positive correlation (φ= 0.758, p< 0.001) was determined between HBeAg statuses. However, gestational age, birth weight, delivery methods, history of premature rupture of membranes, and breastfeeding duration were similar in both groups.

Conclusion: Neonatal immunoprophylaxis failure risk was statistically higher if the mother is HBeAg positive and/or has a high viral load (≥2000 IU/mL).

Keywords: Hepatitis B, neonatal immunoprophylaxis, HbeAg, viral load

Öz

Giriş: Bu çalışmanın amacı yenidoğan immünoprofilaksi başarısızlığında maternal hepatit B viral yükü ve HbeAg durumunun önemini belirlemektir.

Gereç ve Yöntemler: Bu çalışma retrospektif bir vaka çalışması olarak tasarlanmıştır (n= 52). İmmünoprofilaksi başarısızlığı nedeniyle takip edilen ve kronik hepatit B enfeksiyonu gelişen çocuklar olgu grubuna dahil edildi (n= 16). Kontrol grubunda (n= 36) başarılı immünoprofilaksi uygulanan çocuklar yer almıştır. Her iki gruptaki çocukların annelerinin viral yükü (yüksek/düşük) ve HBeAg durumu (pozitif/negatif) karşılaştırılmıştır. Ayrıca, immünoprofilaksi başarısızlığına yol açabilecek olası faktörler (gebelik yaşı, doğum ağırlığı, doğum yöntemi, erken membran rüptürü, emzirme süresi) de her iki grupta analiz edilmiştir.

Bulgular: Viral yükler arasında orta düzeyde pozitif korelasyon (φ= 0.549, p< 0.001) ve HBeAg durumları arasında güçlü pozitif korelasyon (φ= 0.758, p< 0.001) tespit edilmiştir. Bununla birlikte gebelik yaşı, doğum ağırlığı, doğum yöntemleri, erken membran rüptürü öyküsü ve emzirme süresi her iki grupta benzerdi.

Sonuç: Anne HBeAg pozitif ve/veya yüksek viral yüke (≥2000 IU/mL) sahip ise yenidoğan immünoprofilaksi başarısızlık riski istatistiksel olarak daha yüksektir.

Anahtar Kelimeler: Hepatit B, yenidoğan immünoprofilaksi, HbeAg, viral yük

Correspondence Address/Yazışma Adresi

Şekibe Işık Dişci

Clinic of Child Health and Diseases,
Konya Seydişehir State Hospital,
Konya, Türkiye

E-mail: drisikdisci@gmail.com

Received: 16.05.2024 **Accepted:** 25.08.2024 **Available Online Date:** 13.12.2024

Introduction

Hepatitis B virus (HBV) infection is a known significant cause of chronic liver disease worldwide (1). It is known that chronic HBV infection exhibits a benign course during childhood and adolescence. However, 3-5% of the children with chronic HBV infection develop cirrhosis and 0.01-0.03% of these children develop hepatocellular carcinoma (HCC) before adulthood (2).

About two million new HBV cases have been reported among children younger than five in various countries every year. Chronic HBV infection is usually induced by mother-to-child transmission (MTCT) during the perinatal period (3,4).

The World Health Organization (WHO) aims to eliminate HBV infection by 2030. For this purpose, they aimed to administer three or more doses of HBV vaccine to at least 90% of infants, where the first dose would be administered within the first 24 hours after birth (5). However, both the HBV vaccine and hepatitis B immunoglobulin (HBIG) administered to newborns in the first 12-24 hours were never 100% protected.

The present study aimed to investigate the significance of maternal hepatitis B virus load and HBeAg status in neonatal immunoprophylaxis failure despite active immunoprophylaxis with HBV vaccine and passive immunoprophylaxis with HBIG.

Materials and Methods

Study Design and Ethical Concerns

The current retrospective case study was conducted between January 2013 and 2019. It was approved by the local ethics committee (approval no: 2019/21, date: 06.03.2019). The study was conducted in accordance with the Declaration of Helsinki principles.

Clinical Data

File records of the children followed up by the pediatric gastroenterology department were reviewed (n= 19). Among the patients with chronic HBV infection, children without birth, maternal clinical, or laboratory data were excluded from the study (n= 3). Since one of the 65 children born in the obstetrics department was previously diagnosed with chronic HBV infection, she was already under follow-up of the pediatric gastroenterology department.

The hospital electronic database was scanned to determine the infants who were born between January 2013 and January 2019 in the obstetrics department of the university hospital from HBsAg positive mothers (n= 64). The children whose parents did not volunteer to participate in the study were excluded (n= 21). Children whose contact data were not available or current in hospital records were also excluded from the study (n= 7). Children without birth data or incomplete maternal clinical and laboratory data were also excluded from the study (n= 3) (Figure 1).

The population of the study is shown in Figure 1.

The present retrospective case-control study was conducted with 52 children whose mothers had chronic HBV infection, were born between January 2013 and January 2019, and received HBV vaccine and HBIG within 12-24 hours after birth:

1. The case group included 16 pediatric patients who were followed up by the pediatric gastroenterology outpatient clinic due to HBV infection MTCT.
2. The control group included 36 children without HBV infection MTCT.

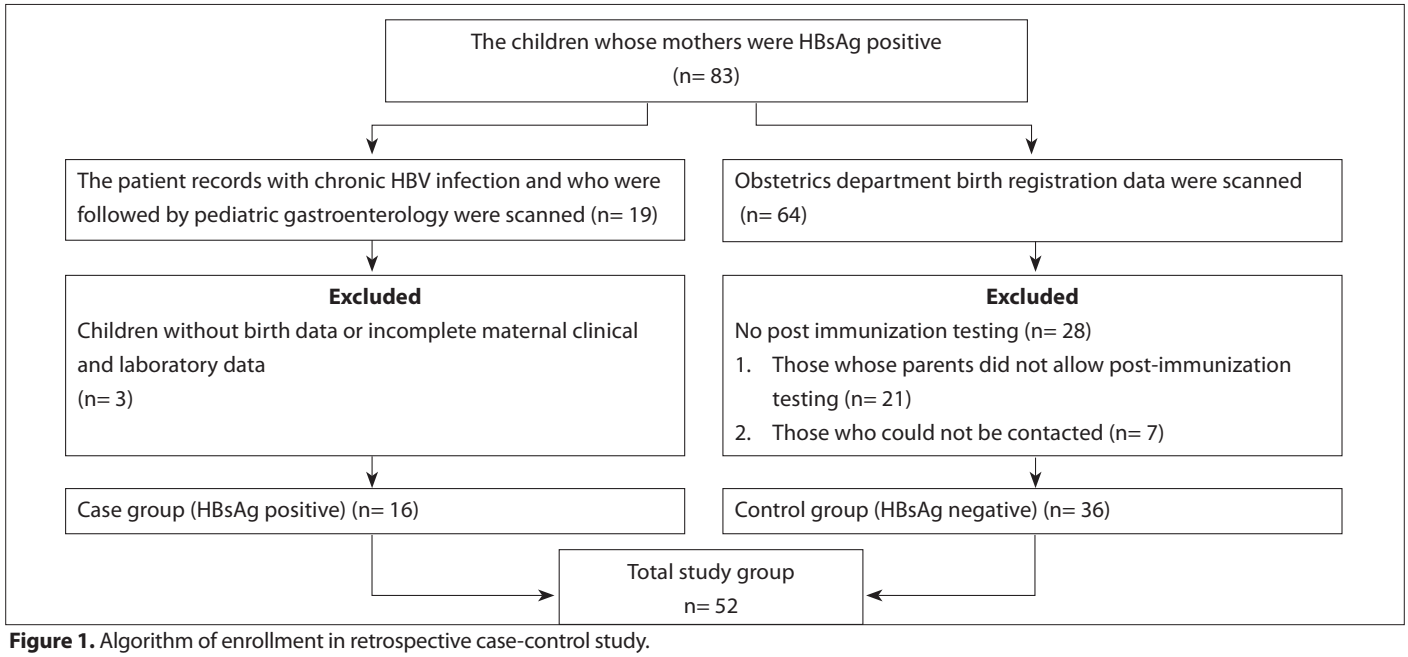

Figure 1. Algorithm of enrollment in retrospective case-control study.

An a priori power analysis was conducted with the "pwr" software in R 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org) to test the difference between the two independent groups with the two-tailed test. We determined that when there were 52 participants, 16 in the case group and 36 in the control group, the power was 0.95 based on the effect size (d= 0.50), and the alpha coefficient was 0.05.

Data Sources, Measurement, and Variables

1. The gestational age (GA), weight of the children at birth, and breastfeeding duration were recorded based on the data provided by their mothers.

2. The delivery method, premature rupture of membranes (PROM) history, HBeAg, and HBV DNA level data were also provided by the mothers.

Participant Grouping Method and Definitions

The gestational age, birth weight, and breastfeeding duration of the children were determined. A history of rupture of the gestational membrane before the onset of labor was accepted as PROM (6).

Those who were born before 37 complete weeks of gestation (i.e., GA <37 weeks) were accepted as premature (7).

The children were analyzed based on prematurity, presence of PROM, and duration of breastfeeding history. They were also categorized into two groups based on the birth method: Vaginal birth (VB) and cesarean section (CS).

All mothers were categorized into two groups based on HbeAg positivity at birth.

The mothers were also categorized into two groups based on viral load: Low viral load and high viral load. The HBV DNA level of the mothers at birth was categorized as low viral load when it was undetectable or <2000 IU/mL, and high viral load when it was ≥2000 IU/mL (8).

Statistical Analysis

Statistical analyses were conducted with the R Statistical Language (version 4.1.2; www.r-project.org). The normal distribution of the data was determined with the Shapiro-Wilk's test and Q-Q plots were employed. The homogeneity of the variances was determined with the Levane test. Welch's t-test and Mann-Whitney U test were conducted to determine the statistically significant differences between the ages, gestational ages, birth weight, and breastfeeding duration of the children across the study groups. Furthermore, the chi-square test with Yates continuity correction and Fisher's exact test were conducted to determine the statistically significant correlations between gender, delivery method, EMR history, HBeAg, and HBV DNA across the study groups. The phi (φ) coefficient was also calculated to determine the correlations between the two qualitative variables. A two-tailed p-value lower than 0.05 was accepted as statistically significant.

Results

In our study, 52 children with 35 HBsAg-positive mothers were analyzed. Sixteen children (30.8%) were in the case group, and 36 children (69.2%) were in the control group. Among these children, 20 were males (38%), 32 were females (62%), and 4 males (25%) and 12 females (75%) children were in the case group, and 16 males (44.4%) and 20 females (55.6%) children were in the control group.

Participant demographics and clinical data are presented in Table 1. Mean age of the children was significantly higher in the case group when compared to the control group (11.56 ± 4.91 vs. 4.97 ± 2.47, p< 0.001). There were no significant differences between the groups based on sex (4/12 vs. 16/20, p= 0.307), gestational age [38 weeks (range= 31-39) vs. 38.5 (range= 32-43), p= 0.206], birth weight [3000 g (range= 1000-3500) vs. 3100 g (range= 2200-4200), p= 0.190], and breastfeeding duration [16 months, (range= 6-24) vs. 14 months (range= 1-25), p= 0.216].

Table 1. Participant demographics and clinical data

	Case Group (n= 16, 30.7%)	Control Group (n= 36, 69.3%)	p
Age (years), mean ± SD	11.56 ± 4.91	4.97 ± 2.47	<0.001[1]
Sex (male/female), n (%)	4 (25)/12 (75)	16 (44.4)/20 (55.6)	0.307[2]
Gestational age (weeks), median (range)	38 (31-39)	38.5 (32-43)	0.206[3]
Prematurity history (presence), n (%)	1 (6.2)	6 (16.7)	0.415[4]
Birth weight (g), median (range)	3000 (1000-3500)	3100 (2200-4200)	0.190[3]
Delivery method (VB/CS), n (%)	13 (81.3)/3 (18.8)	28 (77.8)/8 (22.2)	>0.999[4]
PROM history (presence), n (%)	0 (0)	3 (8.3)	0.544[4]
Breastfeeding duration (months), median (range)	16 (6-24)	14 (1-25)	0.216[3]
Anti-Hbs status (mIU/mL)	1 (0-3)	76 (24.25-185.25)	<0.01[3]
HBeAg status (positive/negative)	15 (75)/1 (3.1)	5 (25)/31 (96.9)	<0.001[2,5]
Viral load (high/low)	11 (68.8)/5 (13.9)	5 (31.3)/31 (86.1)	<0.001[4,5]

[1]Welch's t-test, [2]Chi-square test with Yates continuity correction, [3]Mann-Whitney U test, [4]Fisher's exact test, [5]Phi (φ) coefficient.

Furthermore, there were no significant differences between the groups based on PROM history (0% vs. 8.3%, p= 0.544) and delivery method (13/3 vs. 28/8, p> 0.999). Comparison of the post-immunoprophylaxis serology results revealed that the anti-Hbs level was significantly higher in the control group [76 mIU/mL (range= 24.25-184.25) vs. 1 mIU/mL (range= 0-3), p< 0.01] (Table 1).

When the mothers were HBeAg-positive (75% vs. 25%, OR= 93, 95% CI: 9.96–868.16, p< 0.001), and/or with high viral load (≥2000 IU/mL) (68.8% vs. 31.3%, OR= 13.64, 95% CI: 3.31-56.29, p< 0.001), the MTCT risk was statistically higher in their children. Phi (φ) coefficient was calculated to determine these correlations, and a moderate positive correlation (φ= 0.549, p< 0.001) was determined based on viral load, and a strong positive correlation (φ= 0.758, p< 0.001) was determined in the HBeAg status.

Discussion

WHO aims to eliminate HBV infection public health threats by 2030 (9). In Türkiye, HBV vaccine was added to the routine childhood vaccination schedule in 1998 (10).

Both the vaccine and HBIG are administered to newborns of HBsAg-positive mothers within 12-24 hours of birth. However, it is known that the immunogenicity of the HBV vaccine is affected in preterm or low birth weight infants (11-15).

Infants with a birth weight above 2000 grams receive three doses of the HBV vaccine: One at birth, the second in the first month, and the third in the sixth month. Infants with a birth weight below 2000 grams receive four doses: The first at birth, the second in the first month, the third in the second month, and the fourth in the sixth month (16). In our study, the gestational age (weeks) and birth weight (grams) of the case group and control group children were statistically similar. Prematurity history data were also similar across both groups. In both groups, the infants were vaccinated based on the recommended vaccination schedule.

Since HBV infection is transmitted via bodily fluids, it could be suggested that the delivery method could affect the transmission risk. However, the reports of the studies that investigated the superiority of delivery methods in the reduction of MTCT risk were not consistent. Certain studies reported that CS was not superior to VB, while others reported that CS was superior (17-23). The present study findings demonstrated that similar CS and VB rates in the case and control groups suggested that CS could not reduce the HBV MTCT risk when compared to VB. However, due to the limitations of the current study such as the small sample group, these findings could not elucidate the claim that the delivery method could reduce MTCT risk due to low statistical power.

Duration of membrane rupture and labor were not reported to affect the vertical HBV transmission risk in infants after standard HBV vaccination and HBIG administration (24). In the present study, the PROM history frequency was similar in both groups, similar to the reports in the literature.

It was also reported that breastfeeding did not significantly contribute to HBV transmission from infected mothers to infants with active or passive immunoprophylaxis (25,26). Thus, breastfeeding is encouraged for properly vaccinated infants if their mothers' nipples are not cracked or bleeding (2). In our study, breastfeeding duration was similar in the case and control groups.

It was reported that infants born to HBeAg-positive and negative mothers were 90% and 98% protected (2). Breakthrough HBV infection rates were previously reported to be directly associated with maternal viral load in the literature (27-29). The present study findings were consistent with previous reports, where the MTCT risk was significantly higher in infants whose mothers were HBeAg positive and/or with high HBV DNA (≥2000 IU/mL).

Post-vaccination serological tests should be conducted to determine the success of HBV vaccination in infants with HBsAg-positive mothers (30). However, it was advised that the infants should not be tested before they are nine months old to prevent anti-HB detection due to HBIG administered at birth (31). It was reported that detection of late HBV infection should also be maximized if post-vaccination testing was conducted in the first nine months or later (32). It was recommended that post-immunization tests should be conducted on infants with HBsAg-positive mothers when they are 9-15 months old (33). In our study, the case group included HBsAg-positive children who were referred to us by health professionals they consulted for some reason. Similarly, when the parents of the infants born in the obstetrics department of the hospital were called for post-vaccination tests, the parents of 21 out of 65 infants (32.3%) refused the offer. The main reason was the disbelief of the parents in the possibility of the failure of HBV vaccination. Our study demonstrated the importance of informing HBsAg-positive mothers about the possibility of the failure of HBV vaccination and postvaccination testing. Naturally, primary healthcare professionals should routinely follow up the infants for postvaccination testing when they are 9-15 months old to prevent the failure of HBV immunization.

Study Limitations

The limitations of our study include the small sample size and its retrospective nature.

Conclusion

WHO targeted the elimination of viral hepatitis by 2030 as a public health threat. However, despite active and passive

immunization within the initial 12-24 hours of birth, MTCT risk is still prevalent in infants. This risk is especially higher in the infants of HBeAg-positive mothers or with an HBV DNA level of ≥2000 IU/mL. The parents of all infants who receive active or passive immunization should be informed about the possibility of failure of the HBV vaccination, and postvaccination serological tests should be administered when the infants are 9-15 months old.

Ethics Committe Approval: This study was obtained from Selçuk University Local Ethics Committee (Decision no: 2019/01, Date: 06.03.2019).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - ŞID, HHE; Design - HHE; Supervision - HHE, ME; Resource - ŞID, HHE, ME; Data Collection and/or Processing - ŞID, HHE; Analysis and/or Interpretation - ŞID, MKK; Literature Search - ŞID, MD; Writing - ŞID, HHE; Critical Review - HHE, ME.

Conflict of Interest: All authors declare that they have no conflicts

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. *Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: A systematic review of data published between 1965 and 2013. Lancet 2015;386(10003):1546-55. https://doi.org/10.1016/S0140-6736(15)61412-X*
2. *Sokal EM, Paganelli M, Wirth S, Socha P, Vajro P, Lacaille F, et al. European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. J Hepatol 2013;59(4):814-29. https://doi.org/10.1016/j.jhep.2013.05.016*
3. *World Health Organization (WHO). Global hepatitis report, 2017. Geneva: World Health Organization, 2017.*
4. *Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: A modelling study. Lancet Gastroenterol Hepatol 2018;3(6):383-403. https://doi.org/10.1016/S2468-1253(18)30056-6*
5. *United Nations. Transforming our world: The 2030 agenda for sustainable development. New York: United Nations, 2015.*
6. *Dayal S, Hong PL. Premature Rupture of Membranes. [Updated 2023 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532888/*
7. *Quinn JA, Munoz FM, Gonik B, Frau L, Cutland C, Mallett-Moore T, et al. Brighton Collaboration Preterm Birth Working Group. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine 2016;34(49):6047-56. https://doi.org/10.1016/j.vaccine.2016.03.045*
8. *European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370-98.*
9. *Global health sector strategy on viral hepatitis 2016-2021. Toward sending viral hepatitis. Geneva: World Health Organization, 2016.*
10. *Gökler ME, Özcan M. Epidemiology of hepatitis B virus infection in children and current situation in Türkiye. In: Emiroğlu HH, editor. Hepatitis B virus infection in all aspects in childhood. 1st Edition. Ankara: Türkiye Klinikleri; 2023, p. 1-3.*
11. *Fan W, Zhang M, Zhu YM, Zheng YJ. Immunogenicity of hepatitis B Vaccine in preterm or low birth weight infants: A meta-analysis. Am J Prev Med 2020;59(2):278-87. https://doi.org/10.1016/j.amepre.2020.03.009*
12. *Lei D, Miller T, Carr J, Buttery J, Nold-Petry CA, Nold MF, et al. Timing of the first dose of the hepatitis B vaccine in preterm infants. Vaccines (Basel) 2022;10(10):1656. https://doi.org/10.3390/vaccines10101656*
13. *Ost K, Oster NV, Jacobson EN, deHart MP, Englund JA, Hofstetter AM. Hepatitis B vaccination of low birth weight infants in Washington State. Am J Perinatol 2022;39(9):980-6. https://doi.org/10.1055/s-0040-1721372*
14. *Tüfekci S, Aygün E, Halis H. Evaluation of immunogenicity after first dose of hepatitis B vaccine in newborns with very low birth weight. Hum Vaccin Immunother 2021;17(12):5590-4. https://doi.org/10.1080/21645515.2021.1942715*
15. *Chen CY, Chen HL, Chou HC, Tsao PN, Hsieh WS, Chang MH. Weight-based policy of hepatitis B vaccination in very low birth weight infants in Taiwan: A retrospective cross-sectional study. PLoS One 2014;9(3):e92271. https://doi.org/10.1371/journal.pone.0092271*
16. *American Academy of Pediatrics. Summaries of infectious diseases. In: Kimberlin DW, Barnett ED, Lyn eld R, Sawyer MH, eds. Red Book: 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics. 2021, p. 381-99.*
17. *Wang J, Zhu Q, Zhang X. Effect of delivery mode on maternal-infant transmission of hepatitis B virus by immunoprophylaxis. Chin Med J (Engl) 2002;115(10):1510-2*
18. *Hu Y, Chen J, Wen J, Xu C, Zhang S, Xu B, et al. Effect of elective cesarean section on the risk of mother-to-child transmission of hepatitis B virus. BMC Pregnancy Childbirth 2013;13:119. https://doi.org/10.1186/1471-2393-13-119*
19. *Yang J, Zeng XM, Men YL, Zhao LS. Elective caesarean section versus vaginal delivery for preventing mother to child transmission of hepatitis B virus-a systematic review. Virol J 2008;5:100. https://doi.org/10.1186/1743-422X-5-100*
20. *Chang MS, Gavini S, Andrade PC, McNabb-Baltar J. Caesarean section to prevent transmission of hepatitis B: A meta-analysis. Can J Gastroenterol Hepatol 2014;28(8):439-44. https://doi.org/10.1155/2014/350179*
21. *Yang M, Qin Q, Fang Q, Jiang L, Nie S. Cesarean section to prevent mother-to-child transmission of hepatitis B virus in China: A meta-analysis. BMC Pregnancy Childbirth 2017;17(1):303. https://doi.org/10.1186/s12884-017-1487-1*
22. *Peng S, Wan Z, Liu T, Li X, Du Y. Cesarean section reduces the risk of early mother-to-child transmission of hepatitis B virus. Dig Liver Dis 2018;50(10):1076-80. https://doi.org/10.1016/j.dld.2018.05.004*
23. *He R, Wen P, Xiong M, Fan Z, Li F, Luo D, et al. Cesarean section in reducing mother-to-child HBV transmission: A meta-analysis. J Matern Fetal Neonatal Med 2022;35(18):3424-32. https://doi.org/10.1080/14767058.2020.1819229*
24. *Cheung KW, Seto MTY, So PL, Wong D, Mak ASL, Lau WL, et al. The effect of rupture of membranes and labour on the risk of hepatitis B vertical transmission: Prospective multicentre observational study. Eur J Obstet Gynecol Reprod Biol 2019;232:97-100. https://doi.org/10.1016/j.ejogrb.2018.11.017*

25. *Shi Z, Yang Y, Wang H, Ma L, Schreiber A, Li X, et al. Breastfeeding of newborns by mothers carrying hepatitis B virus: A meta-analysis and systematic review. Arch Pediatr Adolesc Med 2011;165(9):837-46. https://doi.org/10.1001/archpediatrics.2011.72*

26. *World Health Organization. Hepatitis B and breastfeeding. J Int Assoc Physicians AIDS Care 1998;4(7):20-1.*

27. *Wang Z, Zhang J, Yang H, Li X, Wen S, Guo Y, et al. Quantitative analysis of HBV DNA level and HBeAg titer in hepatitis B surface antigen positive mothers and their babies: HBeAg passage through the placenta and the rate of decay in babies. J Med Virol 2003;71(3):360-6. https://doi.org/10.1002/jmv.10493*

28. *Chen HL, Lin LH, Hu FC, Lee JT, Lin WT, Yang YJ, et al. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterol 2012;142(4):773-81.e2. https://doi.org/10.1053/j.gastro.2011.12.035*

29. *Chen Y, Wang L, Xu Y, Liu X, Li S, Qian Q, et al. Role of maternal viremia and placental infection in hepatitis B virus intrauterine transmission. Microbes Infect 2013;15(5):409-15. https://doi.org/10.1016/j.micinf.2013.02.008*

30. *Huang H, Zhang X, Luo Y, Chen J, Feng J, Dai Y, et al. The optimal interval for post-vaccination serological test in infants born to mothers with positive hepatitis B surface antigen. Hum Vaccin Immunother 2021;17(12):5585-9. https://doi.org/10.1080/21645515.2021.1992213*

31. *Centers for Disease Control and Prevention (CDC). Hepatitis. Available from: https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm*

32. *Centers for Disease Control and Prevention (CDC). Hepatitis. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6439a6.htm*

33. *Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatol 2018;67(4):1560-99. https://doi.org/10.1002/hep.29800*