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HEPATITIS B VERTICAL TRANSFER AND ITS RISK FACTORS IN PREGNANT WOMEN IN THE EASTERN PART OF IRAN

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Ключевые слова: *инфекция гепатита В, HBV, вертикальная передача*

Abstract. Hepatitis B vertical transfer and its risk factors in pregnant women in the eastern part of Iran. Moghadam M.N., Amirian S., Afshari M., Parooie F., Keikhaie K.R., Shahramian I., Bazi A., Ostadrahimi P., Sheikh M., Mirzaie H., Aminisefat A. *One of the main causes of chronic hepatitis is mother to child transfer which is also known as vertical transfer (VT). Although there are several studies regarding the VT mechanism and its risk factors, none of these studies succeeded in explaining this process, completely. We conducted this study aiming at investigating VT mechanism and risk factors in this region. The present study was a descriptive-analytic cross-sectional study on HBS Ag positive pregnant women, which was conducted from March 2018 to March 2020 in Amir-Al-Momenin Hospital in Zabol, Sistan-and-Baluchestan province, Iran. In this study all samples were tested for HBV markers (HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, and HBV-DNA) and anti-HCV by enzyme-linked immunosorbent assay (ELISA). All statistical analyzes were performed using SPSS version 22 software. Totally 43 infants of HBS antigen positive mothers were investigated. HBe antibody and HBe antigen were found in 25 (62.5%) and 2 (5%) of mothers, respectively. There was no significant difference between the newborns with and without hepatitis B infection regarding maternal age (p=0.216), duration of the infection in mother (p=0.892), AST (0.779), AL (0.449) and ALP (0.065). Mothers with positive viral load during pregnancy delivered newborns with positive HBS antigen much more than mothers with negative HBS antigen. However, this difference was not statistically significant (p=0.642). Although positive viral load was more common in neonates delivered from positive viral load mothers, the observed difference was also remained non-significant (p=0.978). Our study provided evidences regarding that demographic, immunologic and clinical characteristics of mothers with hepatitis B infection did not play considerable role in the vertical transmission of the infection to the newborns as well as the severity of the following infection. We also suggested the possibility of placenta acting as a source of infection in VT. Further longitudinal studies with larger sample sizes are needed to show the exact predictors of transmission of the infection from infected mothers to their children.*

Реферат. Вертикальна передача гепатиту В та його фактори ризику у вагітних жінок у східній частині Ірану. Могадам М.Н., Аміріан С., Афшарі М., Паруі Ф., Кейхаі Х.Р., Шахраміан І., Базі А., Остадрахімі П., Шейх М., Мірзаї Х., Амінісефат А. *Однією з основних причин хронічного гепатиту є передача його від матері до дитини, яка також відома як вертикальна передача (ВП). Хоча є кілька досліджень, що стосуються механізму ВП та її факторів ризику, жодному з цих досліджень не вдалося повністю пояснити цей процес. Це дослідження проведено з метою вивчення механізму ВП та факторів ризику у вагітних жінок у східній частині Ірану. Це дослідження було описово-аналітичним міжсекторальним дослідженням вагітних жінок з позитивним результатом HBS Ag, яке проводилося з березня 2018 року до березеня 2020 року в лікарні Амір-Аль-Моменін у Заболі, провінція Сістан-і-Белуджистан, Іран. У цьому дослідженні всі зразки були перевірені на наявність маркерів вірусу гепатиту В (HBV) (HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, і HBV-DNA) та anti-HCV за допомогою імуноферментного аналізу (ІФА). Усі статистичні аналізи проводили за допомогою програмного забезпечення SPSS версії 22. Усього було досліджено 43 немовляти матерів з позитивним антигеном HBS. Антитіло до HBe та антиген HBe виявлено у 25 (62,5%) та 2 (5%) матерів відповідно. Не було достовірної різниці між новонародженими з інфекцією гепатиту В та без нього відносно віку матері (p=0,216), тривалості інфекції в матері (p=0,892), AST (0,779), AL (0,449) та ALP (0,065). Матері з позитивним вірусним навантаженням під час вагітності народжували новонароджених з позитивним антигеном HBS набагато частіше, ніж матері з негативним антигеном HBS. Однак ця різниця не була статистично значущою (p=0,642). Хоча позитивне вірусне навантаження було більш поширеним у новонароджених, народжених від матерів з позитивним вірусним навантаженням, спостережувана різниця також залишалася незначущою (p=0,978). Наше дослідження надало докази того, що демографічні, імунологічні та клінічні характеристики матерів з інфекцією гепатиту В не відігравали значної ролі у вертикальній передачі інфекції новонародженим, а також тяжкості подальшої інфекції. Ми також припустили можливість того, що плацента виступає джерелом інфекції при ВП. Потрібне подальше лонгітудинальне дослідження з більшими розмірами вибірки, щоб показати точні предиктори передачі інфекції від інфікованих матерів їхнім дітям.*

Hepatitis B virus (HBV) is a serious global health issue, especially among Asian countries. Around 257 million people are infected by HBV, worldwide [1]. HBV infection can present as an acute, chronic or even fulminant hepatitis. Hepatocellular carcinoma and liver cirrhosis can occur as long-term outcomes of HBV infection, as well [2]. One of the main causes of chronic hepatitis is mother to child transfer which is also known as vertical transfer (VT) [3]. Despite providing early vaccination as well as HBV immunoglobulin in order to prevent neonates from developing chronic infection, immunoprophylaxis fail to inhibit HBV infection in up to 1-10% of infants [4, 5, 6, 7, 8]. Currently, there is no definite explanation for this failure, meanwhile it is assumed that it can be attributable to the high maternal viral load leading to intra-uterine infection ,or just the absence of adequate response in neonates who receive the vaccine [7, 9].The neonates infected through VT have a 90% risk of developing chronic infection which is mostly due to the immune response of the children compared with adults [10].

Intrauterine transmission (IUT) of HBV is the main route of VT (13-44%), which is defined as all sorts of transmission happening prior to the onset of labor. Some of the suggested mechanisms for IUT are placental infection, transplacental leakage, germline transmission, and transmission by peripheral blood mononuclear cells. Other means of VT include intrapartum and breastfeeding transmission [11, 12]. There are several studies investigating the risk factors of VT. It has been reported that factors like vaginal delivery [13], prolonged labor [14], and amniocentesis [15] can play a major role in VT. On the other hand, HBV viral factors such as HBV pre-S/S gene mutations and Serum HBV-DNA level have been indicated as reliable markers for predicting VT [16, 17, 18, 19]. Although there are several studies regarding the VT mechanism and its risk factors, none of these studies succeeded in explaining this process completely. On the other hand, as genetic factors are among the important factors affecting VT of HBV, and there was no such study evaluating VT and its risk factors in eastern Iran. We conducted this study aiming at investigating VT mechanism and risk factors in this region.

MATERIALS AND METHODS OF RESEARCH

The present study was a descriptive-analytic cross-sectional study on HBS Ag positive pregnant women, which was conducted from March 2018 to March 2020 in Amir-Al-Momenin Hospital in Zabol, Sistan-and-Baluchestan province, Iran. In this study, all pregnant women with HBV referred to the hospital for delivery during the above period were included in the study. Among them, pregnant mothers with various underlying diseases, hepatitis C, immunodeficiency, and/or family history of hereditary immunodeficiency diseases and patients with a variety of fetal abnormalities or fetal death were excluded. Finally, 43 infants born to HBS antigen positive mothers were evaluated. General characteristics, including maternal age, gravidity, and parity, as well as the date of delivery were documented. This project was approved by the ethics committee of Zabol University of Medical Sciences, and informed consent was obtained from patients prior to their enrollment.

Laboratory Investigation

After obtaining the patients' informed consent, a 5-cc blood sample was taken from each of them. All samples were tested for HBV markers (HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, and HBV-DNA) and anti-HCV by enzyme-linked immunosorbent assay (ELISA).

The commercial enzyme immunoassay kits used were as follows: HBsAg and anti-HBs (Hepanosticka Biomerieux, Boxtel, The Netherlands), anti-HBc (Dia.Pro Diagnostic BioProbes, Milan, Italy), anti-HCV (Biorad, Segrate, Italy). Liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and Alkaline Phosphatase (ALP)] were also determined in all of the patients. To investigate latent hepatitis infection, HBV-DNA was extracted from all samples using the DNA extraction kit, High Pure Viral Nucleic Acid kit (Roche Diagnostics GmbH, Mannheim, Germany). Then HBV-DNA was determined quantitatively by real-time PCR using the artus HBV RG PCR kit (QIAGEN, Hamburg, Germany) on the Rotor-Gene 3000 real-time thermal cycler (Corbett Research, Sydney, Australia). The analytical detection limit of this kit was 20 IU/ml.

DNA Amplification

For all samples, Nested PCR was performed with surface antigen primers including external (S1, S2) and Internal (S6, S7) by Taq DNA Polymerase kit. The sequence and size of the primers are given in the figure below (Figure). The second-round PCR products were transferred to 1% gel electrophoresis. Their positive sequence samples were determined, and their nucleotide sequence was determined bilaterally by ABI sequencer 3130Xi, and the mutations in this fragment were identified.

Primer	Gene	Seq 5' to 3'	Base
S1	Surface	5'-CCTGCTGGTGGCTCCAGTTC-3'	20
S2	Surface	5'-CCACAATTCKTTGACATACTTTCCA-3'	25
S6	Surface	5'-GCACACGGAATTCCGAGGACTGGGGACCCTG-3'	31
S7	Surface	5'-GACACCAAGCTTGGTTAGGGTTTAAATGTATACC-3'	34

Sequence and size of hepatitis B surface gene primers

Statistical analysis

The correlation between categorical variables was estimated using the Spearmen correlation coefficient. All statistical analyzes were performed using SPSS version 22 software. Age, Liver enzyme, and other laboratory and demographic information were expressed as mean ± standard deviation. The Chi-square test and Fisher's exact test were used to compare categorical data. The significance level was set at $p<0.05$. The prognostic value was expressed as odds ratios (OR) and corresponding 95% confidence interval (CI).

RESULTS AND DISCUSSION

Totally 43 infants of HBS antigen positive mothers were investigated 25 (58.1%) of whom were boys and mean (SD) age of them was 3.6 (2) months. The youngest and oldest infants were one and 10 months old, respectively. Mothers were in average 30.2±6.3 years old ranging from 14 to 44 years.

Of the studied mothers, 21 (71%) experienced normal vaginal delivery. Most of them were Iranian (74.4%) and the others were Afghan residents. Only 3 (9.7%) mothers reported a history of anti-viral treatment. Exclusive breast feeding was reported by 19 (44.4%) of mothers while 3 (9.7%) were feeding their neonates just by formula milk.

HBe antibody and HBe antigen were found in 25 (62.5%) and 2 (5%) of mothers, respectively. The prevalence of HBs antigen positive children was 16 (37.2%), while 27 (62.8%) of them were HBS negative. HBe antibody and HBe antigen were positive in 28 (70%) and 1 (2.5) of the infants respectively.

Positive and negative HBs antigen newborns did not have any significant difference regarding gender (p=0.405), type of delivery (p=0.086), mother's nationality (p=0.130), history of antiviral therapy (p=0.452) and feeding type (p=0.338) (Table 1).

Table 1

Demographic and clinical characteristics of newborns with and without positive HBs antigen

Characteristics			Infant's HBS Antigen		P value
			negative	positive	
gender	female	number	10	8	0.405
		%	37.40	50	
	male	number	17	8	
		%	62.96	50	
Type of delivery	NVD	number	18	9	0.086
		%	81.82	56.25	
	Cesarean	number	4	7	
		%	18.18	43.75	
nationality	Iranian	number	18	14	0.130
		%	66.67	87.5	
	Afghan	number	9	2	
		%	33.33	12.5	
History of Drug use	no drug	number	18	9	0.452
		%	94.74	81.82	
	drug history	number	1	2	
		%	5.26	18.18	
Type of breast feeding	breast milk	number	14	5	0.338
		%	70	45.45	
	replacement feeding	number	2	1	
		%	100	9.09	
	mixed feeding	number	4	5	
		%	20	45.45	

As demonstrated in table 2, frequencies of positive maternal HBe antibody among newborns with and without HBS antigen were 11 (68.7%) and 14 (58.33%) respectively (p=0.505). Corresponding figures for HBe antigen were zero and 2 (8.33%) respectively (p=0.508). There was no significant difference between the newborns with and without hepatitis B infection regarding maternal age (p=0.216), duration of the infection in mother (p=0.892), AST (0.779), AL (0.449) and ALP (0.065) (Table 3).

Table 2

Maternal immunological factors of the HBs antigen positive and negative infants

Maternal factors			Infant's HBS antigen		P value
			negative	positive	
Hbe Antibody	negative	number	10	5	0.505
		%	41.67	31.25	
	positive	number	14	11	
		%	58.33	68.75	
Hbe Antigen	negative	number	22	16	0.508
		%	91.67	100	
	positive	number	2	0	
		%	8.33	0	

Comparing demographic and biochemical factors between children with and without hepatitis B infection showed that just mean ALP was significantly higher among HBS antigen positive newborns (p=0.017). Other factors were not differed between the two groups (Table 4). As demonstrated in table 5, crude and adjusted odds ratios for maternal positive HBe antigen were 0.60 (p=0.708) and 0.55 (p=0.662), respectively. The corresponding figures for positive HBe antibody in mothers were 1.57 (p=0.506) and 1.34 (p=0.702), respectively.

Table 3

Maternal characteristics of HBS antigen positive and HBS antigen negative children

Maternal factors	Infant's HBsAg	Number	Mean	Std. Deviation	P value
Maternal age	negative	18	30.65	6.47	0.532
	positive	16	29.38	6.22	
Duration of the infection	negative	15	8.75	7.46	0.619
	positive	13	11.77	11.32	
AST	negative	16	14.85	7.74	0.897
	positive	13	14.15	4.77	
ALT	negative	16	3.85	2.30	0.685
	positive	13	4.38	2.53	
ALP	negative	16	198	92	0.067
	positive	13	144.92	52.06	

Table 4

Demographic and biochemical characteristics of the newborns with and without hepatitis B infection

Infant factors	Infant's HBsAg	Number	Mean	Std. Deviation	P value
age	negative	7	3.89	2.52	0.724
	positive	6	3.17	.41	
AST	negative	13	31.75	14.94	0.659
	positive	12	42.92	41.43	
ALT	negative	13	5.56	3.93	0.444
	positive	12	6.75	4.09	
ALP	negative	13	180	88.5	0.017
	positive	11	238.73	143.97	

Viral load

Positive viral load was observed in 7 (16.28%) of neonates which was vanished after three months in all infants. Although the frequency of positive viral load at birth in neonates of positive HBe antibody mothers was higher than that among those with negative HBe antibody mothers, this difference was not significant (p=0.819). Conversely, frequency of positive viral load at birth for neonates of positive HBe antigen was lower than that among those with negative antigen mothers, this difference was also non-significant (p=0.542) (Table 6).

Table 5

Crude and adjusted associations between maternal HBe antigen/antibody and hepatitis B infection vertical transmission

Maternal factors	crude odds ratio (p value)	95% CI	Adjusted* odds ratio (p value)	95% CI
Hbe antigen	0.60 (0.708)	0-8	0.55 (0.662)	0-7.55
Hbe antibody	1.57 (0.506)	0.41- 5.96	1.34 (0.702)	0.30-5.92

Note: Controlling for the effect of maternal nationality and type of delivery

Mothers with positive viral load during pregnancy delivered newborns with positive HBS antigen much more often than mothers with negative HBS antigen. However, this difference was not statistically significant (p=0.642). Although positive viral load was more common in neonates delivered from positive viral load mothers, the observed difference also remained non-significant (p=0.978). Crude and adjusted odds ratios for having positive HBS antigen or positive viral load at birth were also non-significant (Table 7).

Table 6

Neonatal viral load based on the immunological characteristics of mother

			Maternal HBe antibody		p value	Maternal HBe antigen		p value
			negative	positive		negative	positive	
Viral load at birth	negative	no	13	21	0.819	32	2	0.542
		%	86.67	84		84.21	100	
	positive	no	2	4		6	0	
		%	13.33	16		15.79	0	
	Total	no	15	25		38	2	
		%	100	100		100	100	

Table 7

Maternal viral load and its association with hepatitis B infection at birth

		maternal viral load		P value	Crude OR (p value)	95% CI	Adjusted* OR (p value)	95% CI
		Negative no (%)	Positive no (%)					
Neonatal HBS antigen	Negative (n=19)	17(56.67)	2(40)	0.642	1		1	
	Positive (n=16)	13(43.33)	3(60)		1.85(0.489)	0.32-10.48	1.70 (0.577)	0.26- 11.10
Neonatal Viral load	Negative (n=36)	31(83.78)	5(83.33)	0.978	1		1	
	Positive (n=7)	6(16.22)	1(16.67)		1.03(0.978)	0.10- 10.49	0.89 (0.922)	0.08- 9.32

Notes: OR – Odds ratio, CI – confidence interval, Controlling for the effect of maternal nationality and type of delivery.

Mean liver enzymes of the HBS antigen positive newborns were the same among those delivered from mothers with negative and positive viral load. That was the case for neonates of mothers with positive and negative HBe antibody, as well (Table 8).

Finally, we did not find any evidence of mutation in the S gene of the HBV which causes considerable changes in the α determinant area of HBS antigen.

We found that hepatitis B infection was vertically transferred from carrier mothers with positive HBe antigen the same as those with negative HBe antigen. Although having HBe antigen, increased the risk of developing hepatitis B infection in the newborn (18%), this association was not statistically significant.

Table 8

Severity of the newborn infection (HBS antigen positive neonates) based on the maternal factors

Maternal factors		Newborn liver enzymes		
		AST Mean (SD)	ALT Mean (SD)	ALP Mean (SD)
Viral load	negative	47(44.54)	6.80 (4.47)	249 (158)
	Positive	22.50(4.95)	6.50 (2.12)	194 (46.67)
	P value	0.451	0.930	0.722
HBe antibody	negative	48.80 (65.26)	7.60 (5.59)	203 (29)
	Positive	38.71 (16)	6.14 (2.97)	259 (181)
	P value	0.290	0.568	0.635

On the other hand, mothers with positive HBe antibody had transferred hepatitis B infection to their newborns the same as those with negative HBe antibody indicating that although positive maternal HBe antibody caused approximately 60% increased risk of hepatitis B vertical transmission, the observed association was also not significant in our study. Meanwhile, Boucheron et al. in their recent systematic review and meta-analysis indicated that a positive HBe Ag test can predict vertical transmission in spite of infant immunoprophylaxis with a sensitivity of 99.5% and a specificity of 62.2%.That was not consistent with our findings which showed that vertical HBV transmission was similar in mothers with and without HBe antigen .However, they mentioned that they could not evaluate the effects of different HBV genotypes on the performance of HBe antigen [20]. Dwivedi et al reported that mother to child transmission of hepatitis B infection is directly associated with the hepatitis B virus replicative status of mother. They found that 76.4% of positive HBe antigen mothers compared

with 23.6% of HBe negative mothers transmitted hepatitis B infection to their neonates. That was not in keeping with our findings which showed that vertical HBV transmission was similar in mothers with and without HBe antigen [21]. Therefore, in contrast to the recent evidences reporting high frequency of maternal HBe antigen as the main cause of HBV vertical transmission in the endemic regions [22], it seems that in the study area other factors should also be considered as the routes of transmission.

We also observed that hepatitis B infection vertical transmission occurred with the same rate after vaginal or cesarean delivery. However, previous researches reported the influence of delivery mode on HBV transmission with controversies [23]. Deng et al. in a more recent study indicated that cesarean section might decrease the vertical transmission of HBV in pregnant women with HBV DNA$\geq 10^7$ copies/mL [24]. Moreover, mothers of different age or different treatment durations had no different chance of hepatitis B infection vertical transmission.

In addition, Iranian mothers showed the same rate of infection transmission compared to Afghan mothers. Although refugees and immigrants are expected to be more suspected to transmit infection due to low quality of care, it seems that low sample size of Afghan participants makes our finding prone to bias. Investigating the viral load in neonates at birth showed that mothers with positive HBe antigen compared to those with negative antigen delivered newborns with similar viral load rates. In addition, viral load was the same in neonates of mothers with positive or negative HBe antibody indicating that HBe antigen or antibody cannot predict the degree of viral load in neonates. We also observed that although having a positive viral load during pregnancy was associated with more than two folds increased risk of HBV infection at birth, the observed association was not statistically significant. It demonstrates that viral load status of pregnant mothers with hepatitis B infection, cannot be a reliable predictor of neonatal infection at birth. Meanwhile, Boucheron et al. reported that HBV DNA levels higher than f 5 30 $\log_{10}$ IU/mL increases the risk of vertical transmission [20]. It should be noted that some neonates with positive viral load were delivered from mothers with negative viral loads indicating some other probable sources of infection such as placental infection. Chen et al. in their study evaluated individual cell layers of placenta and found HBV DNA, HBsAg as well as HBcAg in these cells. Their results could be indicative of the presence of infection in placenta. They also reported this type of infection in 31% of their patients as the main cause of vertical transmission [25]. In our study, viral load was vanished during the first three months of life which was much shorter than that reported in the previous literature. These differences might be due to the fact that none of our mothers with hepatitis B infection had S mutant. Similar liver enzymes of mothers giving birth to infants with and without hepatitis B infection indicates that probably liver function during pregnancy cannot be a predictor for hepatitis B infection vertical transfer.

In the present study, we found that mothers with positive viral load or positive HBe antibody, delivered infected newborns with the same levels of liver enzymes indicating that maternal factors did not affect the severity of the hepatitis B infection in their newborns.

In conclusion, our study provided evidences regarding that demographic, immunologic and clinical characteristics of mothers with hepatitis B infection did not play considerable role in the vertical transmission of the infection to the newborns as well as the severity of the following infection. We also suggested the possibility of placenta acting as a source of infection in VT. Further longitudinal studies with larger sample sizes are needed to show the exact predictors of transmission of the infection from infected mothers to their children.

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