

Efficacy of Post-Exposure Prophylaxis in Infants Born to HBsAg Positive Mothers in Iran; Is It Authentic?

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Abstract

Background: Hepatitis B infection is a universal concern. This infection can lead to chronic liver disease and hepatocellular carcinoma. Neonates born to HBsAg-positive mothers are at high risk of chronic hepatitis B virus (HBV) infection, especially for HBeAg-positive mothers or neonates who have not received hepatitis B immunoglobulin (HBIG) and HBV vaccines.

Objectives: The aim of this study was to evaluate the efficacy of post-exposure prophylaxis in these infants to prevent infection.

Patients and Methods: Thirty-eight infants born to HBsAg-positive mothers between September 2006 and September 2013 were followed. The investigation evaluated whether the standard prevention protocol of neonatal HBV transmission including HBIG at birth and receiving three doses of vaccine at birth and 2 and 6 months of age was performed, followed by post-vaccination tests (evaluation of HBsAg and HBsAb titer at 9 to 18 months of age) to determine subsequent infection. HBsAb titer ≥ 10 was considered as criterion for effectiveness of the prophylaxis procedure. The acquired data were analyzed using SPSS software (Version 18). The results are reported in descriptive tabulations.

Results: Ninety seven percent (97%) of infants received HBIG at birth in the hospital. Generally, all of them received the first, second and third doses of vaccine at birth, 2 months, and 6 months after birth, respectively. Information for 35 mothers infected with HBV and 38 infants was available. The mean age of the mothers was 30.3 years. The results indicated that 20% of mothers were HBeAg positive. HBsAg was positive in one (2.6%) infant born to an HBeAg-positive mother. Around 94% of infants' HBsAb titers were ≥ 10 , and 5.8% were reported as non-responders.

Conclusions: The vertical transmission prevention program used in the study population in Tehran, which had an appropriate sample size, is effective. Additional doses of the vaccine can be useful in raising the effectiveness of immunoprophylaxis for infants at high risk of HBV infection. Also, emphasis must be set on post-vaccination testing.

Keywords: Hepatitis B Virus (HBV), HBV Vertical Transmission Prevention, HBsAg, HBeAg, Hepatitis B Immunoglobulin (HBIG)

1. Background

Chronic hepatitis B virus (HBV) is endemic in many areas of the world, including Asia, Africa, and the Pacific islands (1, 2). HBV infection is a major cause of morbidity and death throughout the world due to cirrhosis, liver failure, or liver cancer (3). Perinatal mother-to-child transmission (or perinatal vertical transmission) is the most important factor in the persistence of the HBV as endemic, and it is the common route of infection due to blood exchange during the childbirth process (4, 5). Depending on maternal HBV viral load and hepatitis B type e antigen (HBeAg) status and in the absence of effective immunoprophylaxis, the rates of perinatal HBV transmission are approximately 20% to 95% (6, 7). Ninety percent of HBeAg-positive mothers transmit HBV infection to their offspring compared to only 10% - 20% of HBeAg-negative mothers (8). The chance

of chronic HBV infection in newborns infected with HBV perinatal transmission is 90%, while risk of development of chronic HBV infections through infected adults is less than 10% (9). Twenty-four percent of adults who were infected at birth will die because of HBV-related liver disease (10).

Screening pregnant women for HBV, administering HBV vaccine, and administering hepatitis B immune globulin (HBIG) at birth for newborns of infected mothers are effective ways of preventing perinatal transmission that could result in markedly reduced prevalence of HBV infection in the whole population (11, 12). Despite the adequate administration of hepatitis B immune globulin and HB vaccine at birth, around 5% to 10% of perinatal vertical transmissions of HBV could not be completely eliminated (13, 14). Moreover, administration of antivirals in late pregnancy for mothers with high viral loads has been shown to be an effective method of preventing perinatal transmis-

sion (7).

Effectiveness of postnatal immunoprophylaxis indicated that HBV vertical transmission of infection from mothers to their newborns occurs generally during childbirth or the perinatal period rather than during pregnancy. As a result, some factors related to childbirth such as prolonged labor (13), mode of delivery (15, 16); prematurity (17), premature rupture of membranes (18), maternal-fetal hemorrhage (19), and breastfeeding might be associated with an increased risk of mother-to-child HBV transmission.

The prevalence of hepatitis B in pregnant women has been determined by the presence of hepatitis B surface antigen (HBsAg) in blood samples (20). Prevalence of hepatitis B is highly variable and is dependent on region, even within a country (21, 22). In a study in Northern Iran (Amol), its prevalence rate among pregnant women was reported as 0.42% (23). The recommended components of perinatal HBV prevention programs also differ by region (24, 25). Studies in different countries have shown that the percentage of HBsAg infections has been decreased by vaccination and injection of immunoglobulin in newborns (26-30). The combination of vaccination and immunoglobulin is more effective than using just one of the two (31). Failure of immunoprophylaxis could be high in mothers with positive HBeAg and high levels of HBV DNA (32). Serologic results of newborns of HBsAg-positive mothers after receiving immunoglobulin and three doses of vaccine showed that 3% of those with HBeAg mothers were HBsAg positive (33). In a study in Iran, 38.7% of newborns with HBsAg-positive and HBeAg-positive mothers became HBsAg positive, even after receiving immunoglobulin and vaccination (34). In another study, just 45.1% of infants produced appropriate levels of antibody after receiving immunoglobulin and vaccination (35). However in a study in northern Iran (Amol) passive-active immunoprophylaxis was highly effective among high risk babies and 88.4% of children became anti-HBs positive (23). Because the results of prophylaxis efficacy studies in Iran differ from results of other studies around the world and in different regions of Iran, we were provoked to study the effectiveness of prophylaxis after exposure in infants born to positive HBsAg-positive mothers.

2. Objectives

This study aimed to determine the efficacy of vaccines and immunoglobulins in the prevention of hepatitis B in infants born to HBsAg-positive mothers. The results of this study verify the effectiveness of prophylaxis after exposure to prevent HBV transmission by the perinatal method.

3. Patients and Methods

In this sectional study, newborns were selected from pregnant women who were positive for HBsAg and who had been referred to Imam Khomeini hospital between September 2008 and September 2013. Thirty-five mothers were selected, of whom three had twins pregnancy, resulting in 38 newborns entering the study. None of these mothers had hepatitis D.

3.1. Performance

According to national and international instructions, all pregnant women must be screened for hepatitis B by measuring the level of HBsAg during the third trimester. Routinely, levels of HBV-DNA and HBeAg have been measured in pregnant women with hepatitis B who are referred to hepatitis clinics. In the case of high viral load, they should be treated with anti-viral drugs such as lamivudine and tenofovir. In the first 12 to 24 hours after delivery, 0.5 mL of hepatitis B vaccine and immunoglobulin were injected separately into gluteal muscle. All newborns in this study, at the age of 9 to 18 months, or 1 to 3 months after receiving the last of three vaccinations, were checked for HBsAg and HBsAb. Newborns were divided into three groups: the first group received immunoglobulin and three complete doses of vaccine; the second group received incomplete immunoprophylaxis with immunoglobulin and fewer than three doses of vaccine, or just vaccination; the third group received no immunoprophylaxis.

In all pregnant women referred to Imam Khomeini hospital in Tehran, prophylaxis effectiveness was assessed by HBsAb. $\text{HBsAb} \geq 10$ was considered positive and $\text{HBsAb} < 10$ was considered negative. Results of prophylaxis were interpreted as follows: positive HBsAg was considered as a non-effective result for prophylaxis, negative HBsAg and positive HBsAb were considered as effective, both negative HBsAg and HBsAb were considered as borderline, and those newborns without post-vaccination tests were considered as an unknown group.

Effectiveness of immunoprophylaxis was evaluated according to various variables such as mothers' age, viral load level, viral treatment before or during pregnancy, and mothers' positive or negative HBeAg. Prophylaxis effectiveness was a dependent variable, while mothers' age, delivery type, newborns' age at birth, number of births, age at pregnancy, method of prophylaxis, lamivudine consumption during pregnancy, viral load, quantitative HBV-DNA, and HBeAg were independent variables. Information about demographic, independent and dependent variables was gathered from questionnaires attached to

records. In addition, more information about the effectiveness of prophylaxis was acquired from parents through phone calls.

HBsAg and HBsAb testing were done using ELISA assays with sensitivity of 100% and 98.5%, respectively. HBV-DNA testing was done using polymerase chain reaction (PCR), which detects viruses at concentrations of more than 50 copies per mL.

3.1.1. Inclusion and Exclusion Criteria

Mothers with positive HBsAg during pregnancy and newborns at least 9 months of age by the end of the study were entered into the study. Mothers with positive HIV or HCV were excluded from the study.

3.2. Ethics

Patients' information was recorded and kept confidential. No money was received from patients under the study for tests pertaining to the plan. Other issues of the declaration of Helsinki were also taken into consideration.

3.3. Data Analysis

Quantitative and qualitative data were analyzed and reported using SPSS software (version 18) as average \pm standard deviation in number and percent.

4. Results

4.1. Prophylaxis Effectiveness According to Independent Variables

From September 2006 to September 2013, 79 pregnant women with positive HBsAg were referred to the Hepatitis clinic of Imam Khomeini hospital complex, a 1000-bed referral educational hospital in Tehran. Forty-one women were eliminated due to incomplete data about their infants in the clinic and no availability of information over the phone. Two cases of abortion and one case of simultaneous Hepatitis C were also eliminated.

At the end, 35 mothers entered the study, of whom three bore twins. Thus, 38 newborns were investigated. None of the mothers had hepatitis D. The average age of mothers was 30.4 ± 6.0 (range, 19 - 41) years. Average number of live deliveries by the mother was 2.1 ± 1.3 with a range of 1 to 6 deliveries. Four (11.4%) mothers had history of one abortion each. The average gestational age of newborns at the moment of birth was 37.9 ± 1.2 s (range, 36 - 41) weeks, and the average weight was 3061.3 ± 622.3 (range, 1800 - 4300) gr. None of the newborns had immunodeficiency disease.

After prophylaxis, HBsAg and HBsAb were assessed 17 months after birth, except for one infant (with unknown

effectiveness) in whom HBsAg testing was not performed. In the other 37 infants, HBsAg tests were done, and 1 test was HBsAg-positive and 37 tests were HBsAg-negative. Of the 36 infants with positive HBsAb test, 1 was HBsAb negative and 35 were HBsAb-positive. In other words, of the 38 infants included in this study, prophylaxis was effective in 35 (HBsAg = negative, HBsAb > 10); in one infant it was non-effective (HBsAg = positive); in one infant it was borderline (HBsAg = negative, HBsAb < 10); and in one infant effectiveness was unknown. The effectiveness of prophylaxis in relation to the independent variables is presented in [Table 1](#). These results show that there was premature rupture of membranes among mothers of 4 (10.5%) of the newborns, but prophylaxis in all of these infants was effective.

Of the 38 mothers whose newborns showed effective immunization, 17 (48.6%) had education levels under high school diploma, 15 (40.9%) had high school diploma or equivalent education, and 3 (8.6%) were university graduates. Mothers of 3 newborns with borderline, non-effective, and unknown immunization had an education level under high school diploma.

Of the 35 newborns who showed effective immunization, 15 (42.9%) were born per vaginal and 20 (57.1%) by cesarean section. The newborn with borderline immunization was also born by cesarean section, and those with non-effective and borderline immunization were born per vagina.

History of hepatitis among family members of newborns showed that the grandmothers of 3 (7.9%) newborns with effective immunization were HBsAg positive. Also, the fathers of 3 newborns, including 2 (66.7%) effective and 1 (33.3%) unknown, were positive for HBsAg. The grandmothers and fathers of the 2 newborns with hepatitis and the newborn with borderline effectiveness were not HBsAg positive. Four (10.5%) newborns with effective immunization had other family members, including a grandfather, maternal uncle or aunts, who were HBsAg positive. Moreover, 2 newborns who showed effective prophylaxis had family members who may have had hepatitis B. Among 21 mothers with more than 1 child, 4 (19%) mothers had other children with hepatitis B. Three (15.8%) of the newborns with effective prophylaxis had siblings with hepatitis B, while there were no siblings with hepatitis B of the other 16 (84.2%) newborns with effective prophylaxis. Also, there were siblings with hepatitis B of the newborn with borderline effectiveness, and no siblings with hepatitis B of the newborn with unknown effectiveness. In addition, the newborn with hepatitis B had no siblings.

Table 1. Prophylaxis Effectiveness in Relation to Mothers' Condition and Independent Variables^a

Mother's Condition	Effective	Borderline	Non-Effective	Unknown	Total
Education					
< Diploma	17 (48.6)	1 (100)			20 (52.6)
Diploma and associate degree	15 (42.9)				15 (29.5)
> Undergraduate	3 (8.6)				3 (7.9)
Delivery type					
Vaginal	15 (42.9)		1 (100)	1 (100)	17 (44.7)
Cesarean	20 (57.1)	1 (100)			21 (55.3)
Premature rupture of membranes					
Positive	4 (11.4)				4 (10.5)
Negative	31 (88.6)	1 (100)	1 (100)	1 (100)	34 (89.5)
Hepatitis B of the mother					
Positive	3 (8.6)				3 (7.9)
Negative	32 (91.4)	1 (100)	1 (100)	1 (100)	35 (92.1)
Hepatitis B of spouse					
Positive	2 (5.7)			1 (100)	3 (7.9)
Negative	32 (91.4)	1 (100)	1 (100)		34 (89.5)
Suspicious	1 (2.9)				1 (2.6)
Hepatitis B of other family members					
Positive	2 (11.4)		1 (100)		3 (10.5)
Negative	32 (82.9)	1 (100)		1 (100)	34 (84.2)
Suspicious	1 (5.7)				1 (5.3)
Hepatitis B of sibling					
Positive	3 (15.8)			1 (100)	4 (19)
Negative	16 (84.2)	1 (100)			17 (81)

^aValues are expressed as No.(%).

4.2. Prophylaxis Effectiveness According to Mothers' Hepatitis B Markers, Diagnosis Time, and Treatment

Effectiveness of prophylaxis related to diagnosis and treatment of mothers' hepatitis during pregnancy is presented in Table 2. HBV-DNA in 28 (84.8%) mothers was positive, while in 5 (15.2%) mothers it was negative, and in 2 mothers it was not recorded. Twenty-five (89.3%) newborns of those mothers with positive HBV-DNA showed effective prophylaxis, while newborns with non-effective, borderline, and unknown effectiveness were from mothers with positive HBV-DNA. Average amount of HBV-DNA was $6,299,759.6 \pm 13,490,001.7$ IU with a maximum of 5,582,857.14 IU and minimum of 2.5 IU. Average HBV-DNA in mothers whose newborns showed effective prophylaxis was $4,274,906.4 \pm 12,316,683.8$ IU. Level of viral load of mothers with unknown, borderline, and non-effective

prophylaxis in their newborns was 137,569, 1,482, and 40,731,263.8 IU, respectively.

Results of PCR in 34 mothers were available: in 10 (29.4%) mothers PCR was performed in the first trimester, in 9 (26.5%) PCR was performed in the second trimester, and in 15 (44.1%) it was performed in the third trimester. In the mother of the newborn with hepatitis, the PCR test was done in the third trimester. Of the 38 newborns in the study, hepatitis B in 9 (23.7%) mothers was diagnosed in the first trimester, in 12 (31.6%) it was diagnosed in the second trimester, and in 9 (23.7%) it was diagnosed in the third trimester, and 8 (21.1%) of the mothers had it before pregnancy. In the mothers of one newborn with hepatitis and one with unknown effectiveness, hepatitis was diagnosed in the third trimester. Also, the hepatitis treatment of mothers was considered in this study. Eight (21.1%)

Table 2. Newborns' Prophylaxis Effectiveness According to Mother's Hepatitis B Status^a

Status	Effective	Borderline	Non-Effective	Unknown	Total
Diagnosis of hepatitis B in pregnancy					
Before pregnancy	9 (25.7)				9 (23.7)
First trimester	11 (31.4)	1 (100)			12 (31.6)
Second trimester	9 (25.7)				9 (23.7)
Third trimester	6 (17.1)		1 (100)	1 (100)	8 (21.1)
PCR implementation time					
First trimester	10 (32.3)				10 (29.4)
Second trimester	8 (25.8)	1 (100)			9 (26.5)
Third trimester	13 (41.9)		1 (100)	1 (100)	15 (44.1)
DNA PCR					
Positive	25 (83.3)	1 (100)	1 (100)	1 (100)	28 (84.8)
Negative	5 (16.7)				5 (15.2)
Anti-Viral drug					
Yes	6 (17.1)		1 (100)	1 (100)	8 (21.1)
No	29 (82.9)	1 (100)			30 (78.9)
Beginning time of anti-viral drugs					
First trimester	1 (16.7)				1 (12.5)
Second trimester	1 (16.7)				1 (12.5)
Third trimester	4 (66.6)		1 (100)	1 (100)	6 (75)

^aValues are expressed as No.(%).

of the mothers were treated with anti-viral drugs during pregnancy. In one (12.5%) mother, treatment was started during the first trimester. In one (12.5%), treatment was started during the second trimester, and in 6 (75%), treatment was started during the third trimester. Mothers of the newborn with hepatitis and with unknown effectiveness started treatment in the third trimester. The mother of the newborn with borderline effectiveness had not received anti-viral treatment.

Serologic tests of mothers are presented in Table 3. From 30 mothers with available HBeAg tests, 24 (80%) were negative and 6 (20%) were positive. The mother of the one newborn with hepatitis, and the mother of the infant with unknown prophylaxis effectiveness were HBeAg positive. Among newborns with effective prophylaxis, 4 (12.9%) mothers were BeAg positive and 27 (87.1%) mothers were HBeAg negative. Also, of 29 available HBeAb tests, 21 (72.4%) were positive and 8 (27.6%) were negative, and of these 29, 28 had newborns with effective prophylaxis. No information on the HBeAb test of the mother of neonate with hepatitis was available. Sixteen HBcAb tests were available, of which 14 (87.5%) were positive and 2 (12.5%) were negative.

It is noticeable that 15 of these newborns showed effective prophylaxis. No information was available from mother of neonate with hepatitis. Furthermore, 15 HBsAb tests were accessible, of which 1 (6.7%) case was positive and 14 (93.3%) were negative. Thirteen of them had newborns who showed effective prophylaxis, and 12 (92.3%) of these mothers were negative for HBsAb. No information was available for the HBsAb test of the mother of neonate with hepatitis.

4.3. Prophylaxis Effectiveness According to Newborn Condition

Table 4 presented, 11 (28.9%) newborns were preterm, 26 (68.4%) were at term, and 1 (2.7%) newborn was post-term statue. All of the pre-terms, the post-term, and 23 of the term newborns showed effective prophylaxis. The newborn with hepatitis B and those with borderline and unknown effectiveness were born at term. Eight (21.1%) of the newborns had low birth weight (LBW), lower than 2500 gr, and 30 (78.9%) weighed more than 2500 gr. Neither the newborn with hepatitis B nor the one with unknown prophylaxis effectiveness was categorized in the LBW group. From 34 newborns with effective prophylaxis, 7 (20%) were LBW and 28 (80%) weighed more than 2500 gr. Moreover, 31 (81.6%) of the newborns were breastfed and 7 (18.4%) were

Table 3. Results of Hepatitis Serological Tests in the Mothers Under Study^a

Serologic Test	Positive	Negative
HBe-Ag	6 (20)	24 (80)
HBe-Ab	21 (72.4)	8 (27.6)
HbC-Ab	14 (87.5)	2 (12.5)
HBs-Ab	1 (6.7)	14 (93.3)

^aValues are expressed as No.(%).

fed with formula. The one with hepatitis was breastfed. Also, the prophylaxis' performance was incomplete in just one (2.6%) newborn; nonetheless, the result was effective.

5. Discussion

Immunization of infants born to mothers with HBsAg is the best way to prevent HBV vertical transmission. Our results demonstrated that immunoprophylaxis with immunoglobulin and vaccination significantly decreased HBV transmission, similar to the results of Koyama et al. (26). Also, in a study by Lee et al., hepatitis B occurrence among newborns who received either vaccine or immunoglobulin or both was lower compared to those newborns who did not receive vaccine or immunoglobulin; the combination of immunoglobulin and vaccine is more effective than vaccine alone (31).

The mother of the only newborn with hepatitis B in our study was positive for HBeAg. According the studies of Wu et al., positive-HBeAg is almost indicative of replicative virus and increases the probability of HBV transmission to 66% to 93%. Also, there was a significant correlation between higher load of HBV-DNA and intrauterine transmission (29). The mother of the newborn with hepatitis B in our study showed higher viral load. Thus, in order to diminish the perinatal transmission, consumption of anti-viral drugs is proposed. Also, it is better to inject immunoglobulin, along with vaccine, in newborns with HBeAg-positive mothers. It has been shown that the probability of HBV transmission decreased to 0.8% when immunoglobulin was combined with vaccine (36).

According to Evans et al., some of the newborns of HBeAg- positive mothers were infected, even though they had received immunization vaccines (27). In our study, one newborn with complete prophylaxis was infected. Despite 20% of mothers being HBeAg-positive, infection was successfully prevented in 97.3% of newborns. Our results are in agreement with the centers for disease control (CDC), which proposed one dose of immunoglobulin and regular vaccination to prevent HBV infection in newborns of HBsAg positive mothers with an effectiveness of 85% to 95%

(37). In another study, 204 newborns with HBsAg-positive mothers received immunoglobulin and three doses of vaccine, of whom six were HBeAg-positive mothers (33). Our results are compatible with these findings. Also, one newborn had received only three doses of vaccine (without immunoglobulin) and remained free of infection. This result implies that the efficacy of vaccination alone in preventing infection is 75% (38), although the combination of immunoglobulin and vaccine is more effective (31).

5.1. Conclusion

The investigation of vertical transmission in the population sample in Imam Khomeini Complex hospital in Tehran showed that prevention of such transmission is possible. Immunoprophylaxis treatments were effective in preventing HBV transmission from mothers to infants. Moreover, an additional dose of vaccine could be more effective for those infants who are at higher risk of HBV infection to increase the immunoprophylaxis impact. Also, post-vaccination tests must be recommended for all infants to evaluate the effectiveness of this measure.

Table 4. Newborns' Prophylaxis Effectiveness According to Their Status^a

Status	Effective	Borderline	Non-effective	Unknown	Total
Nourishment by breastfeeding					
Yes	29 (82.9)	1 (100)	1 (100)		31 (81.6)
No	6 (17.1)			1 (100)	7 (18.4)
Low birth weight					
Yes	7 (20)	1 (100)			8 (21.1)
No	28 (80)		1 (100)	1 (100)	30 (78.9)
Maturity					
Pre-term	11 (31.4)				11 (28.9)
Term	23 (65.7)	1 (100)	1 (100)	1 (100)	26 (68.4)
Post-term	1 (2.9)				1 (2.6)
Prophylaxis quality					
Complete	34 (97.1)	1 (100)	1 (100)	1 (100)	37 (97.4)
Incomplete	1 (2.9)				1 (2.6)

^aValues are expressed as No. (%).

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