Annals of Neonatology Journal

OPEN ACCESS
ISSN: 2636-3596

Original Article

The Delayed Immune Response of Infants of Diabetic Mothers to Hepatitis B Vaccine: A prospective Case-Control Study

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DOI: 10.21608/anj.2021.65423.1022

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Abstract

Background: Infants of diabetic mothers (IDMs) have a significantly greater risk for perinatal morbidity, death, and altered immunological response. The aim of this study to evaluate the immune response of IDMs for hepatitis B virus (HBV) vaccine and to compare them with infants of non-diabetic mothers as a control group.

Materials and Methods: The inclusion criteria were met by 150 newborns, 100 IDMs, and 50 non-diabetic mothers as controls. According to the WHO guidelines, all neonates who met the inclusion criteria received HBV vaccine during the first 24 hours of age and at 1 and 6 months of age. Furthermore, at 9, 12, and 24 months of age, hepatitis B surface antigen (HBsAg), hepatitis B virus surface antibodies (anti-HBs), and hepatitis B virus core antibodies (anti-Hbc) were measured.

Results: IDMs had significantly higher birth weight when compared to infants of the non-diabetic mothers (3.6 ± 0.4 kg and 3.03 ± 0.5 kg, P-value 0.01). There was a significant difference between the response to anti-HBs between case group and control group at 9 months 7±12 mIU/dL versus 20±23 mIU/dL (P-value < 0.0001). However, anti-HBs antibodies levels follow-up at 12 and 24 months showed no significant differences between the case and control groups.

Conclusion: At 9 months of age, post HBV vaccination, there was a delayed immune response for HBV vaccine was present in IDM compared to infants of non-diabetic mothers. However, IDM became immune at follow-up at 12 and 24 months of age.

Keywords: Infants of diabetic mothers, Immune response, Hepatitis B vaccine.

Introduction

Hepatitis B surface antigen (HBsAg) was first identified as "Australia Antigen" by Blumberg et al. in 1963 [1]. Later research revealed that this protein is a component of the "serum hepatitis" virus (hepatitis B virus). About 257 to 291 million people worldwide are affected by chronic hepatitis B virus (HBV) infection, which is associated with severe clinical morbidity such as hepatocellular carcinoma and chronic liver diseases. In the United States of America, 1.59 million persons have chronic HBV infection [2]. Egypt is moderately endemic for HBV, where the prevalence of HBsAg is estimated to be 1.2-1.6% among the general population [3].

The HBV vaccine is the cornerstone of HBV prevention. The World Health Organization (WHO) advocated for the global adoption of universal childhood immunization in 1992 [2]. The HBV vaccination offers a defense against the infection and its side effects, including liver cirrhosis and hepatocellular carcinoma. This makes it the first vaccine against cancer, preventing chronic liver diseases, and decreased maternal-fetal viral transmission occurring at birth [4]. A course of three vaccine injections was given; the first dose was given within the first 24 hours of life, the second dose was given at one month, and the third dosage was given at the sixth month of age [5].

Immunological memory is necessary for long-term protection against HBV infection [6]. More than 95% of immunocompetent newborns, children, and young adults have protective antibody levels after receiving the full course of vaccinations [2]. However, little information is known about the strength and duration of immunological memory of HBV vaccine in immunocompromised individuals, including premature infants [7], people with AIDS [8], people with diabetes type 1 (DM) [9], and others. IDM had immunological abnormalities when compared to infants born to healthy mothers, such as lower total lymphocytes [10],

increased expression of interleukin (IL)-6, and transforming growth factor beta (TGF-β) [11]. However, it is unknown how maternal DM affects the neonatal immune response to vaccinations. Therefore, this study aimed to compare the immune response of IDM to neonates of healthy mothers after given full course of HBV and follow up immunological response to HBV vaccine at 9, 12, and 24 months of neonatal age.

Material and methods

In collaboration with the Department of Microbiology, Faculty of Medicine, Minia University, Egypt, and the Pediatrics Department, Faculty of Medicine, Sohag University, the current clinical study was performed in the neonatal intensive care unit (NICU) at the Pediatrics Department, Faculty of Medicine, Minia University, Egypt. The study took place from January 2017 to June 2019. Local ethical approval for the study was obtained from the Research Committee of the Faculty of Medicine at Minia University. Written informed consent was obtained from all parents of the children.

All IDMs (full term or preterm more than 34 weeks) born throughout the study period were included in the study. We exclude mothers who tested positive for the HBs antigen, infants who had not received three full doses of the HBV vaccine, premature infants weighing less than 2 kg or less than 34 weeks corrected gestational age, serious congenital malformations, severe perinatal hypoxia, twins, and erythroblastosis fetalis. During the study period, 100 IDMs met the inclusion criteria. a 50 additional newborns of non-diabetic mothers who were born during the study period were taken as a control group. Both the cases and the control groups were drawn from the same population characteristics. Mother's HBsAg screen result was mandatory before enrolled in the study.

According to the American Diabetes Association [12], DM type 1, type 2, and gestational diabetes were diagnosed as the following. I) fasting blood sugar reading ≥126 mg/dL. II) Blood glucose level ≥ 200 mg/dL two hours after ingesting 75 grams of oral glucose.

Women who are pregnant and met one or both of the above criteria and have no prior history of DM are diagnosed as gestational diabetics [13]. Additionally, third-trimester follow-up glycated HB (HbA1C) measurements were made for the study's diabetic mothers.

According to the Egyptian schedule for vaccination, all newborns who met the inclusion criteria received the HBV vaccine at 0, 1, and 6 months of age [14]. A full maternal and neonatal history was taken including age and sex, gestational age, mode of delivery, APGAR score, causes neonatal admission to NICU, duration of diabetes, and medications used for control. All newborns who were included underwent thorough general and local examinations, and measurements like weight, length, and vital signs were noted.

Additionally, before each neonate was discharged, 2 ml of venous blood was collected under strict aseptic conditions and divided into two tubes. The second tube was left in the incubator for 30 minutes, centrifuged at 3000 rpm for 10 minutes, and then the separated serum was collected for liver enzymes, urea, and creatinine which measured by colorimetric method using commercial kits. The first tube contained EDTA for CBC which was done by (Roche HITACHI Cobas C-311 Auto-Analyzer System).

At 9, 12, and 24 months of age, infants' immune responses were assessed following a full course of HBV vaccination administered according to schedule. Every time, the obtained samples were centrifuged for 15 minutes at 1000 rpm after being allowed to clot for two hours at room temperature or overnight at 4°C. Hepatitis B surface antigen (HBsAg), hepatitis B viral surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) assessments were performed on samples that had been stored at -20°C or -80°C.These measurements each time was done by ELISA Kit DEIA002, Creative Diagnostic NY, USA

Ethical approval and consent to participate

Local ethical approval for the study was obtained from the Research Committee of the Faculty of Medicine at Mina University, Egypt. Written informed consent was obtained from all parents of the children.

Statistical analysis

The Statistical Package for Social Science (SPSS) version 21 operating system was used to perform all statistical analyses. Quantitative data were represented as mean, standard deviation, median, and range. Data were subjected to a student t-test to compare the means of the two groups. Mann-Whitney's test was used when the data were not normally distributed. The Chi square test or Fisher's exact test was used to compare qualitative data that were given as numbers and percentages. If the probability level (P-value) was less than 0.05, it was considered significant.

Results

In total, 150 neonates met the inclusion criteria and were included in this study.

In which 100 IDMs as a case group and 50 neonates of non-diabetes mothers a control group. There was a significant difference between the weight of the case group compared to the control group (3.6 ± 0.4 kg and 3.03 ± 0.5 kg, P-value 0.01). However, there were no other significant differences in maternal or neonatal differences between the case group and control group, even for maternal age (P-value = 0.26), mode of delivery duration (P-value= 0.43), as shown in Table 1. Furthermore, IDMs had higher hemoglobin (17.4 ± 1.3) gram/dL and hematocrit (55.5± 16.4%) compared to control group hemoglobin (15.5 ± 2.0) gram/dL and hematocrit (46± 17.2%), (both P-value 0.01). Moreover, as shown in Table 2, no significant difference between the case and control group as regards other CBC parameters, and serum of AST, ALT, urea, and creatinine.

Comparison between cases and control groups regarding hepatitis B virus serology follow-up after vaccination, there was a significant difference between the response to anti-HBs between the case group and control group at 9 months 7±12 mIU/dL

versus 20±23 mIU/dL (P-value <0.0001). However, anti-HBs follow-up at 12 and 24 months have shown no significant differences between the case and control group as shown in Table 3. Furthermore, no cases in the case group or control group had HBsAg or anti-HBc positive initially at 9 months or during follow-up at 12 and 24 months of age as shown in Table 3.

Discussion

The immune response of infants to different vaccines still a question especially in immunocompromised children [15]. IDM had some immunological abnormities which could affect their immunity [10]. In this study, we found that the immune response of IDM after a full course of HBV vaccine by measuring anti-HBs was significantly lower at 9 months when compared to an infant of non-diabetic mothers. However, IDM developed a protective immunity by the increased titer of anti-HBs at 12, 24 months of age. Furthermore, no positive HBs antigen or anti-HBc patients between the case and control group. Moreover, IDM had a higher birth weight, hemoglobin, and hematocrit level when compared to the control group. IDMs have significantly increased rates of spontaneous abortion, stillbirth, congenital abnormalities, neonatal mortality and morbidity [16]. According to the current findings, there was no significant difference between the groups in terms of sex distribution, mother age, mode of delivery, or APGAR score. However, we believed that this is important to ensure the homogenization of the studied groups to get accurate results from the comparison between groups. Moreover, we found that when compared to the control group, IDMs had significantly higher birth weights, hemoglobin levels, and hematocrit. These data agree with other reports about fetal macrosomia and polycythemia in IDMs due to neonatal hyperinsulinemia [17].

HBV vaccine is highly effective in preventing HBV infection and is recommended for all infants, adolescents, and adults at risk for HBV infection [18]. WHO recommended vaccine schedules for hepatitis B protection at birth that provide a birth dose will avoid most perinatal

infections and provide early protection from horizontal transmission [19, 20].

It is well-known that the presence of anti-HBs is typically taken as a sign of HBV immunity and recovery [19, 21]. A person who has received a full course of HBV vaccination also develops anti-HBs. A person is immune to HBV if they have a positive anti-HBS test result (> 10 mIU/mL) [15]. Anti-HBs were above (> 10 mIU/mL) in this study's follow-up at 12 and 24 months, with the exception of 9 months following vaccination.

Different interesting suggestions were offered as explanations for why IDMs' early HBV vaccination immunity was compromised. Roll et al. [10] investigation into the effects of diabetes mothers on the development of their newborns' immune systems. They found that compared to non IDMs, IDMs had considerably lower percentages of total lymphocytes. However, according to Mrizak et al. [11] gestational diabetes can alter the placental and neonatal immune systems. They found an increased expression of interleukin (IL)-6, toll-like receptor (TLR) 4, and transforming growth factor-beta mRNA in the placenta. Another study by Atègbo et al. [22] discovered that the serum of macrocosmic infants had low levels of IL-10 and increased amounts of T helper type 1 cytokines.

Additionally, Mehta and Anna [23] found a decreased functional activity of neutrophils in the cord blood of IDMs. According to Franca et al. [24], diabetes mothers had lower colostrum levels of IgA and IgG and blood levels of IgG and IgM than non-diabetic mothers. These findings suggested that hyperglycemia alters the synthesis of antibodies in pregnant women and may reduce immunoglobulin production, which may have a negative impact on IDMs' immunity. This could account for the IDMs' early decreased immunity to the HBV vaccine at the age of 9 months. In agreement with our result, Abd el Aziz et al. [25] reported that infants of IDMs had delayed response to HBV vaccine at 9 months of life.

Furthermore, Lee et al. [19] at 12 months of life follow-up after HBV vaccine, 94% of children were surface antibody-positive (anti-HBs ?10 IU/L) but negative for anti-HBc, suggesting that, they had been successfully

vaccinated and were uninfected. A small proportion (1%) had no evidence of response to the vaccine. These agree with our result as we found that at 12 and 24 months both IDMs and infant of non-diabetics mothers had a significant level of anti-HBs with negative HBs antigen and anti-HBc. However, the HBV vaccine did not, in general, give a 100% protection against HBV infection as children with anti-HBs <10 IU/L rise from 1% in the first year after vaccination to 4% in 2-4 years, and up to 25% in 7 years or later [6]. Therefore, the risk of infection with positive anti-HBc rise to 2.7% by year 7 after vaccination [21]. In this study, we did not found any positive cases in IDMs or control group as all infants had anti-HBc and HBs antigen negative initially and at follow-up.

The limitation for this study was as follows: we measured anti-HBs, HBs antigen, and anti-HBc at 9, 12, and 24 months, prolonged follow-up should be done in further research. We include only IDMs with their mother HBs antigen negative, further researches include positive HBs antigen mother needed.

Conclusion

We found that the immune response of IDM after a full course of HBV vaccine by measuring anti-HBs was significantly lower at 9 months when compared to the infant of non IDMs. However, there was no significant difference in anti-HBs between the case and control group at the age of 12, 24 months. Furthermore, no positive HBsAg or anti-HBc cases between the case and control group. Moreover, IDM had a higher birth weight, hemoglobin, and hematocrit level when compared to the control group.

Acknowledgements

The authors thank http://proof-reading-services.com for language editing.

Author's contributions

AMA, GTS, AME, RAM equally contributed in the study concept, design, supervision, methodology, statistical analysis and data collection. RAM wrote the first manuscript. MSM performed the investigations and laboratory workup and wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript for publication.

Conflict of interest

Authors declare they have no conflict of interest

Funding

The manuscript funded only from the authors.

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Abbreviations

Anti-HBc: Hepatitis B core antibodies; Anti-HBs: Hepatitis B virus surface antibodies; DM: Diabetes mellitus; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; IDMs: Infants of diabetic mothers; WHO: World health organization.

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Table (1): Comparison between studied groups regarding the demographic data

Variable	Case group (n=100)	Control group (n=50)	P value
Sex			
Male	45 (45.0%)	21 (42.0%)	0.70
Female	55 (55.0%)	29 (58.0%)	
Weight (kg)			
Mean ± SD	3.6 ± 0.4	3.03 ± 0.5	0.01*
Maternal age (year)			
Mean ± SD	28.1 ± 5.0	27.2 ± 4.9	0.26
Mode of delivery			
SVD	32 (32.0%)	18 (36.0%)	0.60
CS	68 (68.0%)	32 (64.0%)	
Gestational age Weeks (Mean ± SD)	36±3.3	37±4.4	0.12
APGAR score			
1 Min (Median (range)	8 (7-9)	8 (6-9)	0.8
5 Min (Median (range)	10 (7-10)	10(8-10)	0.75
Preeclampsia (Yes)	30 (30%)	14 (28%)	0.90
PROM >18 hours (Yes)	10 (10%)	6 (12%)	0.76
HBA1C			
Median and range	6.5(5.5-9.6)		
Median	7.1±1.6		
Type of diabetes			
Gestational diabetes	53 (53%)		
Type 1 diabetes	12 (12%)		
Type 2 diabetes	35 (35%)		

**significant;*

Table (2): Comparison between studied groups regarding the laboratory data.

Variable	Group (I) Cases (n=100)	Group (II) Control (n=50)	P value
HB (g/dl) Mean ± SD	17.4 ± 1.3	15.5 ± 2.0	0.01*
Hematocrit (%)	55.5± 16.4	46± 17.2	0.01*
WBCs $*10^3$ U/L Mean ± SD	7186 ± 3330	7842 ± 2146	0.161
Platelets $*10^3$ U/L Mean ± SD	230.8 ± 73.4	239.1 ± 97.1	0.559
AST (U/L) Mean ± SD	25.2 ± 4.9	23.9 ± 4.7	0.111
ALT(U/L) Mean ± SD	29.1 ± 4.9	28.1 ± 5.2	0.182
Urea (mg/dL) Mean ± SD	21.9 ± 3.78	20.9 ± 3.85	0.853
Creatinine (mg/dL) Mean ± SD	0.67 ± 0.17	0.65 ± 0.11	0.531

**significant*

Hb: hemoglobin; WBC: white blood cells; AST: Aspartate transaminase; ALT: Alanine transaminase

Table (3): Comparison between cases and control groups regarding hepatitis B virus serology follow up after vaccination.

Item	HBs antigen	Anti-HBs	Anti-HBc
9 months			
Case group (N=100)	Negative	7±12	Negative
Control group (N=50)	Negative	20±23	Negative
P value		< 0.0001	
12 months			
Case group (N=97)	Negative	235±110	Negative
Control group (N=47)	Negative	265±45	Negative
P value		0.07	
24 months			
Case group (N=94)	Negative	138±95	Negative
Control group (N=45)	Negative	165±60	Negative
P value		0.08	

NB: HBs antigen: Hepatitis B surface antigen; Anti-HBs Hepatitis B surface antigen antibodies; Anti-HBc: Hepatitis B core antibodies.

Citation: Gamal T. Soliman; Mahmoud S. Mahmoud; Abdel-Azeem M. El-Mazary; Ahmed M. Ali; Ramadan A. Mahmoud. "The Delayed Immune Response of Infants of Diabetic Mothers to Hepatitis B Vaccine: A prospective Case-Control Study". *Annals of Neonatology Journal* 2021; 3(2): 145-159 -. doi: 10.21608/anj.2021.65423.1022