The Barriers to Neonatal Hepatitis B Vaccination in Israel: A Prospective Study

Elena Fridman MD MSc[1,2*], Liran Peretz-Aizenman RN MN[3*] and Abed N. Azab PhD[2]

[1]Department of Neonatology, Assuta Ashdod Medical Center, Ashdod, Israel
[2]Department of Clinical Biochemistry, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
[3]Maccabi Health Care Services, Petah Tikva, Israel

ABSTRACT: **Background:** Opposition to neonatal Hepatitis B vaccination is a growing trend in Israel.

Objectives: To assess the sociodemographic factors and attitudes associated with non-vaccination of term singleton newborns.

Methods: This prospective, pair-matched, controlled trial was conducted in a tertiary university-affiliated hospital. Data on maternal sociodemographic parameters, delivery, and infant care practices were gathered. Knowledge and references of Hepatitis B virus (HBV) vaccination, vaccination schedule, and health government policies were assessed. A follow-up telephone survey was completed at the age of 7 weeks postpartum regarding vaccine catch-up rate.

Results: Mothers in the study group were mostly Jewish white middle class married multiparous women with some higher education. Hepatitis B serology was not tested in most. Higher rates of rooming-in and exclusive breastfeeding were observed. Knowledge about HBV was stated, multiple sources of information were significantly associated with newborn non-vaccination. Many objected to the timing of the vaccine and its necessity. Multiple medical encounters are viewed as missed opportunities.

Conclusions: Multiple sources of vaccine information are associated with non-vaccination. Medical encounters prior and post-delivery should be used for vaccination education and may improve vaccination coverage.

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KEY WORDS: Hepatitis B, non-vaccination, newborn, prenatal education, vaccination catch up

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Hepatitis B is an infectious disease caused by the Hepatitis B virus (HBV) that affects the liver. Infection at birth is associated with high rate of chronic HBV (90%), cirrhosis, and hepatocellular carcinomas [1]. Since 1982 the infection can be prevented by vaccination. The recombinant antigen vaccine was widely examined and proved safe in the neonatal period with very few, if any, side effects. Vaccination is recommended by the World Health Organization (WHO) on the first day of life. The scheduling of the first vaccine dose is planned to reduce the rate of vertical HBV infection, being the only efficient route to decrease childhood prevalence of chronic HBV [2,3].

Israel harbors an intermediate HBV prevalence, with 1.5–7% Hepatitis B surface antigen positive patients in the adult population [4]. The Israeli national immunization program for HBV follows that of the United States, and since 1992 all newborns are vaccinated during the initial nursery hospitalization regardless of the mother's disease and immunization status. Such an approach has been effective in reducing global burden of liver diseases in Europe and the United States [5].

Despite overwhelming scientific evidence that vaccines are beneficial, there is a growing body of parents opposing this vaccination schedule. Anti-vaccinations groups urge the parents to actively deny HBV vaccination at birth, stating that the vaccine is unnecessary for most healthy newborns. Such negative campaigns undermine the authority of the Ministry of Health and have been previously associated with higher rates of under vaccination, higher incidence of infectious diseases outbreaks, and poor global health [6].

Our study was designed to assess parental information, attitudes toward healthcare guidelines, and sources of parental education regarding the HBV vaccine, and to perform a follow-up survey to estimate the rate of catch-up immunization and health practices in this population.

PATIENTS AND METHODS

This prospective pair matched, controlled trial was conducted in the neonatal department at the Rabin Medical Center. The study was approved by the institutional research ethics board. The study population included mothers of healthy term singleton babies who gave birth between October 2014 and October 2016, and who refused to vaccinate their newborn during the initial hospital stay. The hospital policy is to obtain a written refusal to standard procedures such as HBV vaccination from the parent, after a detailed explanation about HBV vaccination and its importance is provided by a physician in the nursery

*The first and second authors contributed equally to this study

upon admission of the newborn. Mothers with unknown HBV status close to delivery are individually advised about the importance of HBV vaccination for their infant.

The research questionnaire was constructed based on the WHO with sections on sociodemographic parameters, knowledge, and practice toward childhood immunization [7-10]. The level of trust in medical providers and self-perceived knowledge about HBV were tabulated as high (affirmative: 4 to 5 statements, uncertain: 3, or low: 1 to 2 statements, in the questionnaire). A composite score formulating maternal attitudes toward childhood vaccinations was calculated based on 10 Likert-type scale questions (scores < 20 were considered low, non-opposing attitudes; > 30 as high level of conflict toward childhood immunizations).

The control group consisted of women who decided to participate in the research and did not oppose the vaccination. They were pair-matched to the study group by gestational age, birth weight, and mode of delivery.

The infant's immunization status, as well as procedures provided during nursery care, were recorded in the medical discharge letter. Adherence to routine immunization schedule is recommended to all discharged infants. A follow-up telephone survey was completed at the age of 7 weeks postpartum regarding vaccine catch-up rate and infant care practices.

STATISTICAL ANALYSIS

Statistical analysis was performed with MedCalc statistical software for Windows, version 12.7.7 (MedCalc Software Ltd, Ostend, Belgium). Student's *t*-test and one-way analysis of variance (ANOVA) were used for comparison of continuous variables and the Chi-square test for discrete variables. Multivariate logistic regression analysis was used to evaluate risk factors associated with non-vaccination based on univariate analysis. A *P* value of < 0.05 was considered significant.

RESULTS

Rabin Medical Center is a tertiary university affiliated medical center. The annual number of deliveries was approximately 8500 during the years sampled. Between October 2014 and October 2016, 80 women who declined routine HBV vaccination for their newborns signed a refusal form. Fifty women were included in the study group. Based on inclusion criteria, a control group was recruited (n=45). The sociodemographic parameters of the cohorts are described in Table 1. There was no significant difference between the groups as to gravidity, parity, marital status, occupation, or medicine-related occupation. Many defined themselves as religious (26% study vs. 35.6% control group non-significant). Maternal or familial incidence of chronic medical conditions, fertility treatments, or gestation related complications were not associated with vaccine denial.

Gestation, delivery, and neonatal data during hospitalization are listed in Table 2. No differences as to prenatal care,

Table 1. Maternal demographics and perinatal medical data

	Study group N=50	Control group N=45	*P* value
Maternal age years	33 ± 5.8	31.7 ± 5.14	NS
Education Partial high school education Full high school education (12 years) Higher education (› 12 years)	 0 5 (10) 45 (90)	 0 5 (11) 40 (89)	NS
Health related occupation	6 (12)	5 (11)	NS
Religious propensity Secular Some religious observance Ultraorthodox Other/ Non defined	 34 (68) 13 (26) 1 (2) 2 (4)	 24 (53.3) 16 (35.6) 0 5 (11.1)	NS
Ethnic background Ashkenazi Jew Sephardic Jew Mixed ethnicity Jew Arab Other	 26 (52) 11 (22) 12 (24) 1 (2) 0 (0)	 14 (31) 20 (44) 7 (15) 2 (4) 2 (4)	NS
Marital status Married Single/ divorced	 46 (92) 4 (8)	 43 (95) 2 (4)	NS
Place of Birth (Israel inborn)	45 (90)	38 (84)	NS
Chronic diseases	13 (26)	6 (13)	NS
Chronic medication	11 (22)	6 (13)	NS
Order of gravidity	2 ± 3.1	3 ± 3.6	NS
Order of parity	2 ± 3.3	2 ± 3	NS
Primipara	17 (34)	9 (20)	NS
Previous HBV vaccination Stated Documented	 41 (82) 2 (4)	 33 (73) 3 (6.7)	NS
Pregnancy follow-up Extended Partial None	 42 (84) 8 (16) 0	 39 (87) 6 (13) 0	NS

Values are presented as n (%) or as mean ± standard deviation
HBV = Hepatitis B virus, NS = nonsignificant

Table 2. Obstetric and neonatal data

	Study group N=50	Control group N= 45
Mode of delivery Spontaneous delivery Assisted delivery Caesarean delivery	 37 (74) 5 (10) 8 (16)	 36 (80) 2 (4) 7 (16)
Epidural anesthesia	32 (64)	31 (69)
Male Gender	29 (58)	25 (56)
Birth weight	3356 ± 361	3376 ± 325
1 minute Apgar score	9 ± 1	9 ± 1
5 minute Apgar score	10 ± 0.2	10 ± 0.5
Abnormal neonatal weight loss*	2 (4)	1 (2)
Phototherapy	5 (10)	1 (2)
Feeding difficulties	1 (2)	0 (0)
Maternal length of hospital stay	3.4 ± 0.72	3.4 ± 0.75
Neonatal length of hospital stay	3.7 ± 1.4	3.6 ± 0.75

*Abnormal neonatal weight loss › 10%
All *P* values were nonsignificant Values are presented as n (%) or as mean ± standard deviation

mode of delivery, epidural anesthesia, 1 and 5 minute Apgar scores, or length of hospital stay were found. All women had some antenatal care, most (84%) received extended antenatal counseling (including triple test, sonographic imaging, fetal growth monitoring, and screening for gestational diabetes). Past HBV vaccination was declared by 82% of the study group and 73% of the control group, although none had proper documentation of immunization doses. Only two women had HBV serology tested during gestation. None had updated serology tests prior to delivery. None of the women were aware of the waning immunity or the possibility of insufficient Hepatitis B antibody levels post-vaccination.

Experienced parents were queried about their infant care practices for previous offspring. No difference in previous mode of delivery, low birth weight infants, or neonatal period complications such as feeding difficulties or hospital admissions were noticed. Significantly lower rates of vaccination were prevalent in the study group (40% vs. 100% control group, $P < 0.001$). We found no differences as to previous breastfeeding rates and duration. Mothers in the study group declared a more naturalistic approach to infant care, and in that group there were higher rates of rooming-in and exclusive breastfeeding during the initial nursery hospitalization [Table 3].

Mothers who declined the vaccination felt knowledgeable about the HBV vaccine based on their declaration. The mothers in the study group made more inquiries about the Hepatitis B vaccine during pregnancy and most consulted multiple sources [Table 3]. Fewer women in the study group discussed immunization guidelines with a member of the medical staff prior to delivery (6% study group vs. 18% control group). Most stated that they were well informed about the Hepatitis B prevalence, routes of transmission, and the importance of HBV vaccination. Some consulted alternative medicine literature or providers, social media, friends, and family members. The control group indicated significantly lower information and knowledge scores.

Most mothers in the study group stated a high level of trust in the government and health care policies in their commitment to ensure their infant's health. Most of them had routine pregnancy follow-up, opted to deliver in a hospital setting, and did not decline other medical preventive services such as neonatal bathing, vitamin K prophylaxis, and routine ophthalmic care to prevent ophthalmia neonatorum. Only a few communicated a firm disbelief in medical authorities. Statements directed to evaluate a general approach toward vaccinations showed significantly higher composite scores opposing vaccinations in the study group. Vaccine safety, effectiveness, importance, perceived risk of infectious diseases they are intended to prevent, and being unnatural were found as reasons for opposing vaccination in open-ended as well as closed scale-based questions (37.5 compared with 19 in the control group, P value < 0.001).

Table 3. Maternal attitudes toward newborn-related care and Hepatitis B virus vaccination

	Study group N=50	Control group N= 45	*P* value
Intent to breastfeed	49 (98)	36 (80)	0.004
Intent to breastfeed exclusively	33 (66)	11 (24)	‹ 0.001
Rooming-in during initial hospitalization	33 (66)	9 (20)	‹ 0.001
Vitamin K administration	47 (94)	45 (100)	NS
Ophthalmia neonatorum prophylaxis	50 (100)	45 (100)	NS
Newborn bath refusal	5 (10)	0 (0)	0.05
Intent to visit mother-child clinic	48 (96)	45 (100)	NS
Trust in the health system and medical providers High level of trust Uncertain Distrust toward medical providers	 43 (86) 3 (6) 4 (8)	 44 (98) 1 (2) 0 (0)	0.04
Hepatitis B advice-giver Medical provider Internet websites Family/ friends Alternative medicine Several sources None of the above	 3 (6) 5 (10) 9 (18) 1 (2) 30 (60) 2 (4)	 8 (18) 2 (4) 0 (0) 0 (0) 6 (13) 29 (65)	‹ 0.001
Basic knowledge regarding HBV vaccination High level of knowledge Uncertain / low level of knowledge	 42 (84) 3 (6)	 17 (38) 21 (46)	‹ 0.001
Arguments against HBV vaccination (combined score)	37.5 ± 7.2	19 ± 5	‹ 0.001
Intent to implement full vaccination program Intend Uncertain No	 30 (60) 5 (10) 15 (30)	 42 (93) 3 (7) 0 (0)	‹ 0.001
Timing of Hepatitis B vaccination at delivery is obtrusive	41 (83)	4 (9)	‹ 0.001
Hepatitis B vaccine is unnecessary at delivery	35 (70)	6 (13)	‹ 0.001
Concerns about the potential adverse effects of vaccine	12 (24)	9 (20)	NS

Values are presented as n (%) or as mean ± standard deviation
HBV = Hepatitis B virus, NS = nonsignificant

The majority of women in the study group (83%) described that the timing of first vaccination at such an early age was unnecessary and highly traumatic to the baby, and that it was based on health ministry convenience. Some 60% stated that they intend to complete the vaccination program at later date (most indicated 1 year of age as appropriate to commence HBV vaccination). Most planned to comply with routine well-child appointments (tipat halav) (96%). We found low incidence of vaccine uncertainty. Only 10% of women stated they did not have a well formulated decision as to future vaccination of their newborn and this rate did not differ from the control group.

Multivariate analysis showed that previous non-vaccination (odds ratio [OR] 9.2, 95% confidence interval [95%CI] 7.6–92.3), multiple sources of advice regarding vaccination (OR 3.6, 95%CI 2.55–20.62), and high scores of opposition toward immunization (OR 1.2, 95%CI 1.02–7.38) were all significantly associated with non-vaccination.

FOLLOW-UP TELEPHONE SURVEY

We had a high follow-up response rate (92% in the study group and 100% in the control group). The naturalistic approach still prevailed at 7 weeks post-delivery, with higher rates of exclusive breastfeeding and bed sharing in the study group [Table 4].

Most of the mothers in the study group had routine well-child appointments (tipat halav). Most children had at least one conventional medicine encounter by the time of the telephone survey (96% study and 100% control group). Lower adherence to vitamin D supplementation was noted in the study group [Table 4]. While 60% of women stated intent to administer immunizations to their children at a later date in their initial hospitalization questionnaire, only 33% percent did so up to the telephone survey. This concurs with the fact that many women stated that they plan to vaccinate their children at 1 year of age.

Table 4. Follow-up survey at 7 weeks post delivery

	Study group* N= 46	Control group N= 45	*P* value
Exclusive breastfeeding	33 (72)	11 (24)	‹ 0.001
Pacifier use	35 (76)	34 (75)	NS
Bed sharing	19 (41)	0 (0)	‹ 0.001
Fever illnesses	6 (13)	5 (11)	NS
Neonatal post discharge hospital admissions	6 (13)	5 (11)	NS
Mother-child clinic appointments	1.89 ± 1.33	2.33 ± 1.13	NS
Pediatrician encounters	2.08 ± 1.85	1.57 ± 1.23	NS
Conventional medicine encounters post discharge	44 (96)	45 (100)	NS
HBV vaccination at 7 weeks	15 (33)	43 (96)	‹ 0.001
Vitamin D (doses per week)	5.51 ± 2.35	6.46 ± 1.46	‹ 0.001

*Four women in study group did not participate in the follow-up
Values are presented as n (%) or as mean ± standard deviation
HBV = Hepatitis B virus, NS = nonsignificant

DISCUSSION

SOCIODEMOGRAPHIC FACTORS

Our study is another in a series of epidemiological and demographic analyses aimed to identify reasons for non-vaccination in Israel [5,11-16]. The sociodemographic characteristics were similar between the study and control groups. Previous reports associated younger maternal age, single households, lower income, lower education levels, ultra-Orthodox Jews, and minority ethnicities with incomplete child vaccination. These demographics were not represented in our study. Other reports from Israel described women who are likely to decline routine child vaccination as older, white, and well educated [14,15]. We found no correlation between religious observance, parity, maternal education, or medicine related occupation of the mothers and non-vaccination. A high proportion of women with higher formal education in our cohort may suggest that some sub-populations were not sampled in our study. Yet, the similarity of sociodemographic determinants empowers us to discuss the attitudes and beliefs that lead to the decision not to vaccinate newborns.

NATURALISTIC APPROACH

Infants in the study group were more likely to be exclusively breastfed and the mothers preferred rooming-in during initial hospitalization. Previous reports have highlighted the relationship of a "natural" approach to infant care and low vaccination rates [17]. Emphasis should be made to differentiate the rational desire for natural birthing processes and the need to seek full newborn immunization to ensure high health outcomes.

HEPATITIS B SEROLOGY

Based on the American Academy of Pediatrics HBV vaccination guidelines, an option for postponing the vaccine is given to mothers who know their negative status. Such a disclaimer is omitted from Israeli Center of Disease Control (CDC) guidelines [18]. Our study shows that while women cite their own immunization or non-exposure of the infant as reasons to prevent giving the vaccine to their newborn, none had an updated HBV immune status. None of the women knew the importance of waning immunity and possible decline of Hepatitis B antibody titers over time, becoming non-protective for their infant [1].

Routine screening of all pregnant women via HBs antigen performed in the delivery room may minimize the possible conflict of interest between the mothers and the caregivers, and offer a highly proficient screening method that will diminish possible unknowing vertical HBV transmission to optimal zero cases. Such a method embraces the maternal natural desires while making sure that neonatal safety comes first. However, such an approach may be economically costly and does not face the true issues of non-vaccination and low adherence to preventive care strategies [1,5].

Horizontal community-based transmission of HBV by non-sexual close contact in areas of intermediate endemicity is important. National statistics based on the Israeli Ministry of Health official report of the Childhood National Immunization Coverage Survey conducted in Israel in 2013 noted low coverage of HBV vaccine among adults, with only a minority of Israeli adults having been vaccinated against HBV [19]. As mothers declining neonatal HBV vaccination do not ensure their Hepatitis B protective antibody titers, their children are at risk for HBV infection through accidental exposure to bodily fluids, through open wounds, or by contact in childcare facilities. Delaying the first dose of HBV vaccine based on the non-exposure argument is risky as at least two doses are usually needed to supply sufficient immunity, and most children are enrolled in childcare facility during the first year of life.

Parents seek information about vaccinations from many sources. Most parents decide on the issue after researching the subject via social media and internet searches. While women feel knowledgeable and well informed about HBV vaccine, their information is misleading and leads to a sense of confidence in anti-vaccination messages. Multiple sources of immunization advice were significantly associated with non-vaccination in our study, similar to previous reports [20-23]. Our study demonstrated that only a few (6%) discussed immunization program with certified medical care providers.

Terms like shopping for healthcare and need for crosschecking of information all refer to the social pressures the future parents face in pursuit of a healthy child. While anti-vaccine messages are broadcasted aggressively, the official site of the Ministry of Health is not approachable enough and not explicit enough as to the reasons behind the early HBV vaccination policy. To overcome the dangerous trend of anti-vaccination campaigns, the medical community must supply counter information that encourages vaccinations.

ATTITUDES TOWARD VACCINATION

Maternal attitudes toward vaccination were important predictors of infant non-vaccination. Similar to previous reports, pain and vaccine unnecessity were cited as the most common reasons for vaccine opposition [6,7]. The majority of women in the study group described that the timing of first vaccination at such an early age as traumatic, unnecessary, and based on health ministry convenience. Sixty percent stated they intend to complete the vaccination program at a later date (most indicated 1 year of age as appropriate to commence HBV vaccination). Most mothers in the study group stated a high level of trust in the government and health care policies in their aim to insure infant health. Trust in a healthcare provider is associated with use and delivery of preventive services. Moreover, trust in the advice of a child's healthcare provider and the feeling that it is easy to communicate with that provider have been found as key factors associated with the parental belief that they had access to enough information to make a good decision about immunizing their child. Understanding concerns of parents and developing trusting and positive relationships are crucial in improving vaccination coverage [20-23]. High levels of trust, multiple medical encounters prior to delivery, and the intent to further complete the vaccination program expressed by the study group convinces us to view the multiple antenatal and postnatal medical encounters as missed opportunities to educate about immunizations (20).

Most women form and envision their infant care attitudes during late stages of gestation. Low level of hesitancy in our cohort supports the theory of planned behavior. We suggest that perinatal educational interventions may be a good opportunity to address the misinformation about vaccines, and may assist in the parental decision making toward vaccination. The prenatal care setting offers an opportunity to educate the prospective parents before the initiation of immunization series to their infants. Many high-income countries provide standardized immunization education [24]. Strong partnerships need to be established with the obstetricians or the midwives to make collaborative efforts to improve the parents' immunization knowledge and to increase the childhood vaccination coverage.

PREVENTIVE AND WELL CARE VISITS

Previous studies have clearly associated parental refusal to HBV vaccination as a predictor to further non-vaccination, poor adherence to other preventive services, and lower health standards [25]. Our study showed similar results. There were fewer routine checkups and lower adherence to vitamin D supplementation in the study group [Table 4]. When combined, most children in the study have had at least one conventional medicine provider encounter at the time of telephone survey (96% study and 100% control group). The high incidence of vaccine opposition witnessed by our study further highlights the need for intervention to increase vaccination coverage.

LIMITATIONS

Women included were those who consented and completed the questionnaire. Mothers with firm disbelief in conventional medicine were probably unwilling to cooperate and be included in the study. Our study may not accurately represent the motivations and beliefs of the entire vaccine non-complying population. We presume that the highly skeptical parents are harder to reach and suggest that the population included is the first tier that should be targeted by intervention strategies to improve the vaccination coverage. Low representation of minority and high risk sub-populations also limits the conclusions regarding non-vaccinating parents.

CONCLUSIONS

Active opposition to routine neonatal care is a concerning trend as it undermines the authority of the Ministry of Health as the optimal health provision regulator to the public. The common demographic variables in the study and control groups make this study well powered to detect the barriers that result in non-vaccination. Our study accentuates sociodemographic factors and personal perceptions associated with refusal for Hepatitis B immunization among low-risk term singleton parturients in central Israel. Knowledge gaps that may pose a risk to unknowing vertical HBV transmission are identified. Screening maternal disease and immunization status may be found as best approach to decrease the rate of vertical HBV infection.

The high follow-up rate was unique and sheds light on postnatal infant approaches among women who deny HBV vaccination to their newborn. Vaccination catch-up rate was evaluated. High utilization of medical services prior to delivery and postnatally is viewed as missed opportunities. We urge the

healthcare representatives to view every medical encounter as a possible intervention point to educate the parents about childhood immunization. Closer surveillance could assist in assessing the occurrence of refusal and any changes in the occurrence over time. Educational programs, decreasing missed opportunities to administer HBV vaccine, transparency, and increased information sharing may all be effective interventions to global health promotion.

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Correspondence

Dr. E. Fridman

Dept. of Neonatology, Assuta Ashdod Medical Center, Ashdod 7747629, Israel

Phone: (972-72) 339-8312, **Fax:** (972-72) 339-9444

email: slomovel@gmail.com

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Capsule

Sourcing brain abnormality

Disruptions in the transcription factor TCF4 lie at the root of Pitt-Hopkins syndrome (PTHS), which manifests with intellectual disability and disruptions in brain development. **Schoof** and co-authors generated mice with inducible and tissue-specific truncation of TCF4 to ensure that gene disruption occurs only in the central nervous system. The truncated protein lacks the DNA-binding domain of TCF4, a mutational hotspot for PTHS. Embryonic mice with this truncated TCF4 showed deficits in differentiation and migration of neural precursor cells. During postnatal development, Cajal-Retzius cells were misplaced and hippocampal development was disrupted. The corpus callosum, which is the fiber tract connecting the brain hemispheres, also developed poorly in these mice. These findings thus map the anatomical abnormalities that underlie this syndrome.

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Eitan Israeli