Immunogenicity of hepatitis B vaccination in preterm infants started soon after birth: the implications for prevention

Marisa M. Mussi-Pinhata*

Infections by the hepatitis B virus (VHB) that occur during infancy, acquired from a mother carrying the virus, account for 40% of all infections and are of great clinical and epidemiological relevance worldwide. Despite the acute infection being symptomatic in less than 10% of children, the development of a chronic infection and its consequences, after an acute infection, is inversely proportional to age of exposure. The risk of a chronic infection is at a maximum (70-90%) in children who acquire an infection during the perinatal period and it is these children that constitute the main virus reservoir for spreading the infection to other individuals.

See related article on page 113

The hepatitis B virus can be transmitted from mother to child during pregnancy. However, perinatal exposure to maternal blood and genital secretions is the most efficient means of transmission and can affect between 65 and 93% of newborn babies (NB) whose mothers are infected and carry the "e" antigen (HBeAg), while the risk of infection (0 to 19%) is lower in the absence of this marker. Even if children do not acquire a perinatal infection, they remain at risk of acquiring an infection by horizontal transmission by means of close contact with their mothers.

The measures available for perinatal VHB transmission prevention are highly effective. Data originating in Asian countries, with elevated endemicity of infection, indicate that full term NB given a combination of human hepatitis B hyperimmune immunoglobulin (HGIG) and the VHB vaccine soon after birth, present an effective level of protection of between 85 and 95%, even when the mother is HBe antigen positive and does not have anti-HBe antibodies. Even vaccination regimen using VHB vaccine in isolation during the perinatal period prevent 70 to 85% of vertical transmission cases, depending on the frequency of HBeAg markers in the population and also confer protection against post-natal infection.[1]

The protective efficacy of hepatitis B vaccination is associated with the development of anti-HBs antibody titers > 10 mUI/ml. Even when begun soon after birth, the recombinant vaccines that are currently available have proved themselves effective; virtually all full term NB, both when infants and children, exhibit seroconversion, irrespective of the system employed. However, promoting VHB infection prevention during infancy implies vaccinating preterm neonates whose immunological immaturity may interfere with the protective efficacy of the vaccine. While vaccination of premature babies can be delayed, it can become necessary to vaccinate as early as the first 12 hours postpartum if the child's mother is known to be positive for HBsAg or if her infectious status is unknown.

During the last 13 years, a number of different authors have studied the immunogenicity of different hepatitis B vaccination programs for premature neonates. There is evidence demonstrating that delaying vaccination for preterm children whose birth weights are less than 1,750 g, until they reach 2,000 g,[2] or until hospital discharge, at between 1 and 3 months of age[3] permits a similar post-vaccination response to that observed among full term NB to be triggered. This represents a safe alternative for NB whose mothers are not carrying hepatitis B, and has been the recommendation of the American Academy of Pediatrics, since 1994. Nevertheless, research into the immunogenicity of early vaccination (begun during the first few days of life) of preterm NB has been inconclusive with disagreement between the various studies available in published literature.

In the article by Sadeck & Ramos in this issue of the *Jornal de Pediatria* the authors investigate the immunogenicity of a vaccination protocol composed of three doses of recombinant vaccine, at routine dosage, administered on the day of birth, at one month and at 6 months to full term and preterm (gestational age < 37 weeks) neonates.[4] The two groups were compared b y means of testing for protective anti-HBs antibody levels (> 10 mUI/ml) before the third vaccine dose, at 9 months and at 12 months. Despite identifying a tendency, before the third dose was given, towards a lower frequency of protective antibody levels among preterm children, due to a reduced response to the first two doses from those whose gestational age < 34 weeks and/or, and more

* Professor, Department of Child Care and Pediatrics, School of Medicine of Ribeirão Preto, Universidade de São Paulo (USP), Ribeirão Preto, SP, Brazil.

importantly, those whose birth weight was < 1,500 g, these authors' data demonstrated no significant difference between the groups under study once the vaccination program was complete. After a global analysis of these results, we are able to conclude, as did the authors, that this trial indicates that preterm NB achieve satisfactory post-vaccination protective antibody levels. However, the methodological features of this and other studies that have returned similar results, should be observed. In general, these studies included NB from a wide gestational age and birth-weight range, with the majority of the members of the sample groups having gestational ages close to 36 weeks or birth weights close to 2,000 g.[5,6] In contrast, other studies that have performed early vaccination on larger numbers of preterm NB whose birth weights were < 1,500 g or gestational ages < 32 weeks,[2,3,7-9] including a study we performed of Brazilian children,[10] have identified significantly lower levels of immunogenicity among preterm NB after the complete course of vaccination was completed (60-77%) than among full term NB (98-100%). While the study made by Sadeck & Ramos was not designed for this end, it too identified a reduced frequency of post-vaccination protective antibody levels within the subgroup of preterm NB born weighing less than 1,500 g.[4]

What are the implications of reduced vaccination immunogenicity among preterm NB born at less than < 1,500-1,800 g and/or with a gestational age < 32-34 weeks for infant VHB infection prevention?

The first implication, pointed out by Sadeck & Ramos in the conclusions of their article, is the need for serological tests after the original three-dose vaccination when the preterm NB has been vaccinated during the first week of life because of the possibility that the child will need booster doses to achieve satisfactory anti-HBs antibodies. When it is not possible to test these levels, routine administration of a four-dose program is envisaged, aiming at achieving higher numbers of preterm NBs with protective levels of antibodies against postnatal infection. In our view, however, this is not the most significant implication and can be compensated for by delaying vaccination whenever possible.

It is in terms of the post-exposure perinatal prophylaxis of preterm NB that reduced immunogenicity raises important questions. Studies that demonstrate that the prophylactic program has an elevated protective efficacy against perinatal VHB transmission were performed on full term NB. There have been no studies of the efficacy for preterm NB in addition to a lack of detailed information on the importance of the immunogenicity of different vaccine doses on the protective efficacy, both early and late, of the prophylactic protocol. Based on studies of NB at high risk of acquiring VHB infections, that have demonstrated that high doses of vaccine antigens, when administered early, permit elevated antibody levels to be reached rapidly and provide protective efficacy rates of 98%, even without HGIG administration,[1] it is possible to conclude that the immunogenicity of the vaccine, including its initial doses, is a primary factor for successful VHB vertical transmission prevention. Taking into account that even those preterm NB that responded to vaccination exhibit lower post-vaccination antibody levels that also take longer to produce[8,10] (Sadeck & Ramos also demonstrated the same effect among their subgroup of low weight and gestational age NB), it can be supposed that the protective efficacy of the classically employed prophylactic program is inadequate for preterm NB. There are clear indications that further information is required to improve assessment of what prophylaxis is ideal for such NB, making the use of HGIG mandatory in such cases to compensate for the reduced response to initial vaccine doses.

Current Brazilian Health Ministry guidelines for hepatitis B prevention indicate systematic hepatitis B vaccination during the first 12 hours postpartum. Furthermore, while recommending concurrent anti-hepatitis HGIG administration for NB weighing < 2,000 g or whose gestational age < 34 weeks, this organ dispenses with the indication for systematic antibody testing of mothers. This part of the recommendation, while adequate for full term NB, appears inadequate to us from the point of view of optimizing prevention measures since it makes the ideal prophylaxis for preterm NB impossible. We know that a majority of infected expectant mothers are not identified by high infection risk clinical indicators. It could be argued that in regions of Brazil with low infection endemicity, such as the South, there would be no significant repercussions from the lack of maternal serological testing since VHB infection in these regions is primarily of adolescents and adults. Nevertheless, as the prevalence of VHB carriers increases through the country in the direction from South to North, and since in regions with intermediate to elevated endemicity infection occurs primarily during infancy, failure to identify infected expectant mothers and failure to administer HGIG to preterm NB results in children from these regions being left unprotected.

Will there be other alternatives in future? Yet to be studied with preterm NB is a new, three-antigen, recombinant vaccine, which includes pre-S1 and pre-S2 proteins in addition to the S protein and which induces higher titers more rapidly in people with little or no response to the single-antigen recombinant vaccine.[11] This may be a viable alternative for preterm NB as well since they need rapid protection against VHB infection after perinatal exposure.

References

1. Poovorawan Y, Sanpavat S, Pongpunglert W, Chumdermpadetsuk S, Sentrakul P, Vandepapeliere P, et al. Long-term efficacy of hepatitis B vaccine in infants born to hepatitis B antigen-positive mothers. Pediatr Infect Dis J. 1992;11:816-21.
2. Lau YL, Tam AY, Ng KW, Tsoi NS, Lam B, Lam P, et al. Response of preterm infants to hepatitis B vaccine. J Pediatr. 1992;121:962-5.
3. Faldella G, Allessandroni R, Magini GM, Perrone A, Sabatini MR, Vancini A, et al. The preterm infant's antibody response to a combined diphtheria, tetanus, acellular pertussis and hepatitis B vaccine. Vaccine. 1998;16:1646-9.

4. Sadeck LSR, Ramos JLA. Resposta imune à vacinação contra hepatite B em recém-nascidos pré-termo, iniciada no primeiro dia de vida. J Pediatr (Rio J). 2004;80:113-8.
5. Del Canho R, Grosheide PM, Gerards LJ, Heijtink RA, Schalm SW. Hepatitis B vaccination and preterm infants. Pediatr Infect Dis. J 1993;5:407-8.
6. Belloni C, Chirico G, Pistorio A, Orsolini P, Tinelli C, Ronidini G. Immunogenicity of hepatitis B vaccine in term and preterm infants. Acta Paediatr. 1998;87:336-8.
7. Patel DM, Butler J, Feldman S, Graves GR, Rhodes PG. Immunogenicity of hepatitis B vaccine in healthy very low birth weight infants. J Pediatr. 1997;131:641-3.
8. Losonsky GA, Wasserman SS, Stephens I, Mahoney F, Armstrong P, Gumpper K, et al. Hepatitis B vaccination of premature infants: a reassessment of current recommendations for delayed immunization. Pediatrics. 1999;103:E14
9. Sood A, Singh D, Mehta S, Midha V, Kumar R. Response to hepatitis B vaccine in preterm babies. Indian J Gastroenterol. 2002;21:52-4.
10. Freitas da Motta MS, Mussi-Pinhata MM, Jorge SM, Tachibana Yoshida CF, Sandoval de Souza CB. Immunogenicity of hepatitis B vaccine in preterm and full term infants vaccinated within the first week of life. Vaccine. 2002;20:1557-62.
11. Zuckerman JN, Zuckerman AJ. Recombinant hepatitis B triple antigen vaccine: Hepacare. Expert Rev Vaccines. 2002;1:141-4.

Corresponding author:
Marisa M. Mussi-Pinhata
Departamento de Puericultura e Pediatria
Faculdade de Medicina de Ribeirão Preto da Univ. de São Paulo
CEP 14049-900, Campus USP, Ribeirão Preto, SP, Brazil
Tel.: + 55 (16) 602.2479 – Fax: +55 (16) 602.2700
E-mail: mmmpinha@fmrp.usp.br