Hepatitis B Vaccination of Premature Infants: A Reassessment of Current Recommendations for Delayed Immunization

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ABSTRACT. Objective. Current American Academy of Pediatrics and United States Public Health Service Immunization Practices Advisory Committee recommendations for hepatitis B immunization in premature infants weighing <2 kg at birth born to hepatitis B surface antigen (HBsAg)-negative mothers are to delay the initiation of vaccination until such infants reach 2 kg or until 2 months of age. This proposal to delay vaccination at birth in these low-risk infants was based on limited studies not conducted in the United States. We sought to reassess current recommendations to delay administration of hepatitis B vaccine in low-risk premature infants by determining the immunogenicity of early hepatitis B vaccination in a US population and identifying variables associated with poor immunogenicity.

Methods. A total of 148 infants <37 weeks' gestation born to mothers negative for HBsAg were recruited at birth and stratified to three birth weight groups: <1000 g, 1000 to 1500 g, and >1500 g. Recombinant hepatitis B vaccine was administered within the first week of life, at 1 to 2 months of age, and at 6 to 7 months of age. Serum obtained at birth and after the second and third doses of vaccine was tested for antibody to HBsAg. Variables associated with poor response were sought prospectively by collecting demographic and clinical data.

Results. A total of 118 subjects (83%) completed the study. Postsecond dose sera were available for 117 infants and postthird dose sera were available for 112 infants. The seroprotection rate (attaining ≥10 mIU/mL HBs antibody) after two doses was low (25%) regardless of birth weight; infants weighing <1000 g at birth had the poorest response (11%). The seroprotection response rate after three doses of vaccine increased with birth weight (11% at birth; infants weighing <1500 g at birth (groups 1 and 2) had lower rates of response (52% and 68%, respectively) than did infants weighing >1500 g at birth (group 3; 84% response rate). The seroprotection response rate of group 3 infants after three doses of vaccine, although low, could not be differentiated from the response rates reported for full-term infants using 95% confidence intervals. Of all infants who did not achieve protective levels of antibody after three doses of vaccine, 96% (26/27) weighed <1700 g at birth. The geometric mean HBs antibody levels in responders were 88 and 386 mIU/mL after two and three doses, respectively. Of 36 children with a birth weight >1500 g, 33 (91%) achieved levels of HBs antibody >100 mIU/mL after three doses of vaccine, compared with 25/35 (71%) of infants with birth weight <1500 g.

Using logistic regression analysis, nonresponders were more likely than were responders to have been treated with steroids (26% vs 9%) and to have had a low birth weight (1037 g vs 1455 g). In addition, the seroresponse rate of black infants was more likely than that of white infants to be associated with poor weight gain (falling off 2 percentile ranks in weight) in the first 6 months of life: 22% of black and 60% of white children who failed to gain weight adequately responded to vaccination, compared with 92% of black and 70% of white children who were growing adequately. Of interest, the only infant with a birth weight >1700 g who did not make protective levels of specific antibody after three doses of vaccine was 2300 g at birth, but had inadequate weight gain in the first 6 months of life.

Conclusions. This study supports current recommendations of the American Academy of Pediatrics and the Centers for Disease Control and Prevention for delaying the initiation of hepatitis B immunization beyond the first week of life for premature infants at low risk for hepatitis B infection, particularly in newborns weighing <1700 g at birth. In addition, we have identified variables other than birth weight that were associated with an inadequate immune response to early hepatitis B vaccination in premature infants, such as poor weight gain in the first 6 months of life and steroid use in the first few months of life. Pediatrics 1999;103(2). URL: http://www.pediatrics.org/cgi/content/full/103/2/e14; premature hepatitis B, early vaccination.

ABBREVIATIONS. HBsAg, hepatitis B surface antigen; AAP, American Academy of Pediatrics; CI, confidence interval; GM, geometric mean; ANOVA, analysis of variance.

Although vaccines effective in preventing hepatitis B infection have been licensed since the early 1980s, their use in infants before 1992 had been limited primarily to those high-risk infants born to mothers identified as hepatitis B carriers. This selective vaccination strategy had little impact...
on the control of hepatitis B infections, preventing only ~3% of the 250 000 new cases of hepatitis B each year. In 1992, both the American Academy of Pediatrics (AAP) and the United States Public Health Service Immunization Practices Advisory Committee recommended hepatitis B immunization of all infants born in the United States regardless of maternal status as the most feasible approach to reach the goal of total elimination of hepatitis B disease.3,4

Although full-term infants can be immunized in the immediate newborn period, with the second and third doses following at 1 to 2 months of age and 6 to 18 months of age, respectively, the optimal time to initiate immunization in premature infants born of hepatitis B surface antigen (HBsAg)-negative mothers has not yet been determined. Since 1994, the AAP has recommended delaying the start of hepatitis B immunization in such low-risk premature infants weighing <2 kg at birth until they reach 2 kg or until 2 months of age.5 This revision derived from limited data from Hong Kong and Thailand demonstrating lower immunogenicity of the hepatitis B vaccine in premature infants vaccinated at birth.6,7

We reevaluated the basis for this revised recommendation in a US population for several reasons. Confirmation was needed because the recommendations were based on studies performed in populations from hepatitis B endemic areas where chronic carriage is prevalent. Such study populations may be biased for immune hyporesponsiveness to HBsAg.8 In fact, a European study of HBsAg vaccination of premature infants at birth did not find lowered immunogenicity, although extremely low birth weight infants were not evaluated.9 Therefore, we wanted to evaluate a US population and include infants weighing <1000 g at birth. In addition, under current recommendations, infants born prematurely of HBsAg-positive mothers and mothers of unknown status continue to receive the first dose of hepatitis B vaccine in the first few days of life. Finally, if our study did confirm lowered immunogenicity of hepatitis B vaccine in premature infants, we sought to identify other factors associated with poor responses. Such an analysis might help to define important host characteristics in the premature infant population relevant for the development and use of future candidate vaccines targeted for administration in the newborn period.

METHODS

Subjects

Newborn infants <37 weeks’ gestation admitted to the neonatal intensive care units of the University of Maryland Medical Center and Mercy Medical Center and their mothers were recruited for this study after meeting eligibility requirements and after written informed consent was obtained. Gestational age was determined by the attending neonatologist’s assessment of obstetric dates and the new Ballard score.10 Infants were excluded from the study if the mother was HBsAg-positive or had unknown hepatitis B carrier status at the time of delivery, were positive for human immunodeficiency virus or had a known immunodeficiency, or if the infant had clinical infection at the time of vaccination, had thrombocytopenia (platelet count <70 000) or a coagulopathy, had a major birth anomaly or chromosomal abnormality, had received immunoglobulin therapy before study entry or during the study, or were small for gestational age (birth weight less than the 10th percentile adjusted for gestational age). This study was approved by the institutional review boards of both participating hospitals.

Eligible infants were enrolled into one of three birth weight groups: <1000 g, 1000 to 1500 g, or >1500 g. This prospective stratification by birth weight was done to ensure sufficient numbers of very low birth weight infants in the study. The following information was obtained at enrollment of each subject: birth weight, gestational age, gender, race, twinning information, maternal age, maternal complications during pregnancy and delivery, maternal and paternal race, and ethnicity. Medical information on each infant also was obtained, including discharge weight, weight at 6 to 7 months of age, ventilator requirements, number of episodes of sepsis, receipt of blood products, and clinical problems after discharge. This information was extracted from medical charts. Percentile ranks of weight by age of each child were determined at birth, discharge, and 6 to 7 months of age using premature infant growth charts.

Vaccination

Three 2.5-μg doses of recombinant hepatitis B vaccine, Recombivax HB (Merck & Co, Inc, West Point, PA) were administered to each infant by intramuscular injection in the anterior portion of the thigh. The first dose was given within the first 7 days of life; the second and third doses were given at 1 to 3 months and at 6 to 8 months of age, respectively. At least 4 months elapsed between administration of the second and third doses. Vaccine was supplied in two lots (0996W and 0798A). Those children who did not attain protective levels of antibody after three doses of vaccine (<10 mIU/mL of anti-HBsAg) were offered a fourth dose of vaccine at 9 to 12 months of age. Fifth or sixth doses were given at least 3 months apart at 15 to 24 months of age if the previous doses did not produce protective antibody levels. Vaccine was stored at 4°C until use.

Reactogenicity data (vaccination site reactions, irritability, fever [rectal temperatures >38°C], and temperature instability) were recorded for each child for 3 days after each vaccination dose. These data were extracted from the medical record if the infant received the vaccine in hospital or obtained passively from reports of caretakers if the child received any vaccinations after hospital discharge.

Serologic Evaluation

A predelivery maternal blood sample collected for blood typing was used to determine the hepatitis B antibody and antigen status of the mother. One to two milliliters of blood was collected from each infant before the first immunization, and 1 month after the second and third immunizations. If a fourth vaccine dose was required, an additional blood sample was obtained 1 month after that dose. Serum was extracted and the sample frozen at −20°C until assayed. Levels of HBs antibody were quantitated by enzyme immunoassay at the Hepatitis Branch of the Centers for Disease Control and Prevention (AUSAB, Abbott Laboratories, Abbott Park, IL). All samples from each subject were assayed at the same time. Seroprotection was defined as those serum samples having HBs antibody ≥10 mIU/mL.

Statistical Analysis

Sample size determinations were based on existing data from full-term infants first vaccinated between 0 and 2 months of age who received a 2.5-μg dose of Recombivax HB, estimating that 50% and 95% of such infants achieve protective levels of antibody after the second dose and third dose, respectively.11 We sought to recruit 50 infants in each birth weight group. This sample size would allow us to generate a minimum observed seroprotection rate for the postdose two and postdose three of 40% and 89%, respectively, for which the 95% confidence interval (CI) include the 50% and 95% seroprotection rates, respectively, for full-term infants.

Seroprotection rates after the second and third doses of vaccine in each birth weight group were compared with historical data for inborn infants using 95% CI.11 Analysis of independent variables and seroconversion was performed using the Fisher’s exact test. The Wilcoxon rank sum test or t test was used to evaluate the relationship between continuous variables and birth weight groups. Comparisons were Bonferroni-adjusted for multiple com-
parisons. Multivariate analysis of the relationship between demo-
graphic and clinical prognostic variables and seroprotection rates
was performed using logistic regression analysis. The indepen-
dent variables included in the initial model were maternal age,
gestational age, gender, race (black/white), birth weight group,
weight gain at discharge, weight gain at 6 to 7 months, intraven-
tricular hemorrhage, intubation, sepsis, postnatal steroid use, and
the following interactions: race × weight gain at 6 to 7 months;
race × sepsis; weight gain at 6 to 7 months × sepsis; sepsis ×
steroid use. To obtain the final model, we removed individual
terms that were not statistically significant and whose absence
from the model did not qualitatively influence the relationship
between the remaining terms and the dependent variable. Chil-
dren with weight gain at discharge and at 6 to 7 months were
defined as children whose weight did not fall below the 2nd
percentile ranks on premature growth chart curves between birth and discharge, or
between discharge and 6 to 7 months of age, respectively. Pro-
longed intubation defined children who were intubated ≥21 days.

RESULTS

Of the 148 infants recruited for participation in this study in the newborn period, 4 (3%) died, 3 (2%) withdrew from the study, and 23 (16%) were lost to follow-up after receiving only one dose of vaccine. All but one of the deaths occurred in the first month of life, and all were attributable to extreme prematurity or complications of extreme prematurity (mean birth weight, 780 g). Of the 118 children who remained in the study, 102 (86%) completed all three doses of vaccine and provided all postimmunization blood specimens. The remainder received two doses of vaccine with follow-up postimmunization sera.

Birth weights of the 118 study infants ranged from 448 to 2580 g (mean, 1366 g). Their mean gestational age was 30 weeks (range, 22 to 35 weeks). Clinical characteristics of these infants, grouped by birth weight, are listed in Table 1. There were no differences between the three birth weight groups in gender or racial distribution, number of subjects who were part of multiple births, or the number of subjects suffering intraventricular bleeds among birth weight groups. Infants in the very low birth weight group (group 1) were more likely than were the other two groups to have prolonged intubation (≥21 days)

Table 1. Characteristics of Study Participants*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>&lt;1000 g (n=35)</th>
<th>1000–1500 g (n=31)</th>
<th>&gt;1500 g (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean birth weight, g (range)</td>
<td>761 (448–990)</td>
<td>1230 (1010–1500)</td>
<td>1846 (1510–2580)</td>
</tr>
<tr>
<td>Mean gestational age at birth, wk (range)</td>
<td>25.3 (22–28)</td>
<td>29.3 (26–35)</td>
<td>32.2 (29–35)</td>
</tr>
<tr>
<td>Number female (%)</td>
<td>16 (46)</td>
<td>14 (45)</td>
<td>33 (63)</td>
</tr>
<tr>
<td>Number nonwhite (%)</td>
<td>26 (74)†</td>
<td>20 (65)</td>
<td>28 (54)</td>
</tr>
<tr>
<td>Number receiving dexamethasone (%)</td>
<td>14 (40)‡</td>
<td>1 (3)§</td>
<td>0‡</td>
</tr>
<tr>
<td>Number with an episode of sepsis (%)</td>
<td>17 (49)†‡</td>
<td>8 (26)‡</td>
<td>2 (4)¶</td>
</tr>
<tr>
<td>Number requiring mechanical ventilation past 3 weeks of age (%)</td>
<td>12 (34)¶§</td>
<td>2 (6)¶</td>
<td>0§</td>
</tr>
<tr>
<td>Number with intraventricular hemorrhages (%)</td>
<td>9 (26)</td>
<td>10 (32)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Member of multiple birth (%)</td>
<td>8 (23)</td>
<td>10 (32)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>Length of stay in hospital, d (range)</td>
<td>84,6** (42–139)</td>
<td>45,1** (13–128)</td>
<td>20** (5–92)</td>
</tr>
<tr>
<td>Mean weight at 6–7 mo, g (range)</td>
<td>5258†† (2120–7650)</td>
<td>6272 (3842–8109)</td>
<td>6765†† (3546–8958)</td>
</tr>
</tbody>
</table>

* Probabilities have been Bonferroni-adjusted for multiple comparisons.
† Includes one Asian/white infant and 2 Hispanic infants.
‡ P < .001 for comparison between group 1 and groups 2 and 3 (Fisher’s exact test).
§ P < .001 for comparison between group 1 and group 3 (Fisher’s exact test).
¶ P < .001 for comparison between group 1 and group 3 (Fisher’s exact test).
# P = .01 for comparison between group 1 and group 2 (Fisher’s exact test).
** P < .01 for comparison between group 1 and group 3 (Fisher’s exact test).
‡‡ P < .001 for comparison between groups 1 and 3, Wilcoxon test.

for ventilatory support, to have received dexameth-
asone postnatally, and to have been hospitalized ≥2 months. Infants with <1500 g birth weight (groups 1 and 2) were more likely to have had an episode of sepsis postnatally than were larger infants.

The 30 children who withdrew or were lost to follow-up were not statistically different from those who finished the study in gestational age, race, or gender. However, the majority of children (21/30) who did not complete the study were in the highest birth weight group (>1500 g) (P = .03).

Safety

Active surveillance in hospital for vaccine reactions occurred for all subjects after the first dose, for 58% (66/113) of enrollees after the second dose, and for no subject after the third dose. No infant had any local reactions noted after any intramuscular injection. There were no instances of fever or temperature instability or episodes of sepsis within 3 days of vaccination.

Immunogenicity

Seven infants had detectable HBs antibody before receiving their first vaccination; all but 1 had decreasing antibody or complete loss of maternal antibody before the third vaccination, which allowed for inclusion in the analysis of immunogenicity. In addi-
tion, 4 infants had no detectable HBs antibody at birth, although their mothers were HBs antibody-positive before delivery; all were extremely premature, with gestational ages ranging from 23 to 28 weeks.

Of the study infants who completed the three-dose vaccination schedule, 70% (71/102) achieved protective levels of HBs antibody; 1 additional infant sero-
converted but did not attain protective levels. Only 23/111 (21%) infants achieved protective levels of antibody after two doses of vaccine.

The seroprotection response rates by birth weight
group in our premature infants and historical data for full-term infants for comparison purposes are presented in Table 2. The seroprotection rates after two doses of vaccine in premature infants was low regardless of birth weight; infants weighing <1000 g at birth had the poorest response (11%). The 95% CI for seroprotection rate after two doses of vaccine for each weight group did not overlap the seroprotection rate reported for full-term infants. The seroprotection response rate after three doses of vaccine increased with birth weight. Infants weighing ≤1500 g at birth (groups 1 and 2) had lower rates of response than did infants in group 3 with a birth weight of >1500 g ($P = 0.01$, Bonferroni-adjusted Fisher’s test) and rates were different from those reported for full-term infants using 95% CI. However, the seroprotection response rate of group 3 infants after three doses of vaccine could not be differentiated from the reported response rates of full-term infants. Of all infants who did not achieve protective levels of antibody after three doses of vaccine, 96% (26/27) weighed <1700 g at birth (Fig 1).

The geometric mean (GM) HBs antibody levels after two and three doses of vaccine was 88 and 386 mIU/mL, respectively. The magnitude of HBs antibody achieved in responders by birth weight group is presented in Table 2. There was no difference between birth weight groups in the GM antibody levels after two or three doses of vaccine ($P > .05$, analysis of variance [ANOVA]). In the majority of infants (65%), the GM antibody level after two doses of vaccine was <100 mIU/mL. However, 33 of 36 (91%) children who weighed >1500 g at birth achieved levels of HBs antibody >100 mIU/mL after three doses of vaccine, compared with 25/35 (71%) of infants who weighed <1500 g at birth ($P = .006$, Fisher’s exact test).

### Analysis of Variables Contributing to Lowered Immunogenicity

Univariate and multivariate analyses of the factors associated with the lack of protective immune responses after vaccination are presented in Table 3. Using univariate methods, maternal age, gender, race, or the development of intraventricular hemorrhages was not associated significantly with poor seroprotection rates after three doses of vaccine. However, gestational age, birth weight, birth weight <1700 g, prolonged ventilatory support, an episode of sepsis, treatment with steroids, and poor weight gain at discharge and at 6 to 7 months of age were associated with poor seroprotection rates after three doses. Logistic regression analysis indicated that low birth weight was predictive of poor seroprotection response after vaccination, as was steroid use. In a subanalysis of infants who weighed <1700 g at birth, sepsis also was a factor associated with poor seroprotection rates ($P = .04$; data not shown).

There was a significant effect of the interaction between race and poor weight gain at 6 to 7 months of age and seroprotection rates after three doses of vaccine. Only 2 of 9 black children (22%) with poor weight gain at 6 to 7 months of age reached protective levels of antibody, compared with 45 of 49 black children (92%) who had adequate weight gain at 6 to 7 months of age ($P = .003$, two-tailed Fisher’s exact test). In contrast, 6 of 10 white children (60%) who failed to gain weight achieved protective antibody levels, compared with 21 of 30 white children (70%) who had adequate weight gain ($P > .05$, two-tailed Fisher’s exact test). This apparent racial difference in immunogenicity was not attributable to birth weight differences because there was no difference in the birth weights between black and white infants who did not grow well (GM birth weights, 922 g and 1141 g, respectively; $P = .12$, ANOVA).

### Effect of Subsequent Doses of Hepatitis B Vaccine in Nonresponders

Of the 29 children who did not seroconvert after three doses of vaccine, 14 received additional doses of vaccine. The fourth dose of vaccine was given at a mean of 12.5 months of age (range, 10 to 14 months). After receiving a fourth dose of vaccine, 7 of the 14 (50%) children seroconverted, (GM, 119 mIU/mL; range 6.4 to 1426 mIU/mL); all but one of these responders achieved protective levels. All nonresponders to this fourth dose weighed <1500 g at birth. Of the remaining 7 children, 3 were lost to follow-up, 3 required a fifth dose (given at a mean of

<table>
<thead>
<tr>
<th>TABLE 2. Seroprotection Rates (HBs antibody levels ≥10 mIU/mL) in Premature Infants by Birth Weight Group After Two and Three Doses of Recombivax HB, Vaccine*</th>
<th>Birth Weight</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1000 g</td>
<td>1000–1500 g</td>
<td>&gt;1500 g</td>
<td>Full-term†</td>
<td></td>
</tr>
<tr>
<td>Seroprotection rate (%) 95% CIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After second dose</td>
<td>4/34 (12) 03%, 28%</td>
<td>8/29 (28) 13%, 47%</td>
<td>11/48 (23) 12%, 37.4%</td>
<td>(58)</td>
<td></td>
</tr>
<tr>
<td>After third dose</td>
<td>16/31 (52)‡ 33%, 70%</td>
<td>19/28 (68)‡ 48%, 84%</td>
<td>36/43 (84)‡ 69%, 93%</td>
<td>(98)</td>
<td></td>
</tr>
<tr>
<td>After two or three doses</td>
<td>19/35 (55) 37%, 71%</td>
<td>22/31 (71) 52%, 86%</td>
<td>47/52 (90) 79%, 97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM HBs antibody, mIU/mL (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After second dose</td>
<td>52 (20–96)</td>
<td>112 (22–375)</td>
<td>918 (23–517)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After third dose</td>
<td>222 (25–2900)</td>
<td>373 (64–2325)</td>
<td>562 (27–3326)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 95% Upper and lower CIs and GM HBs antibody levels given; all probabilities have been Bonferroni-adjusted for multiple comparisons.

† Historical data obtained from West (11).
‡ Seroprotection rates rate of premature infants in birth weight groups <1500 g was lower than that achieved by infants with birth weights >1500 g ($P = .01$, Fisher’s exact test).
§ There was no difference between birth weight groups in the GM antibody levels after two or three doses of vaccine ($P = .01$ or $P = .12$, ANOVA, respectively).

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DISCUSSION

This is the first study in a US population to evaluate the response of early hepatitis B vaccination in the premature infant and to characterize the factors associated with a poor immune response. Our study confirms that low birth weight is an important variable in determining the success of early vaccination of these infants. Premature infants weighing <1500 g at birth responded poorly to an early hepatitis B vaccination regimen compared with full-term historical control infants, with response rates increasing as birth weight increased. Our data are less clear for premature infants with birth weights between 1500 g and 1700 g. Although we were unable to show a significant difference in response rate after three doses of vaccine between this largest birth weight group and full-term historical control infants, this birth weight group had lower seroprotection response rates compared with full-term infants (84% and 98%, respectively). Additional analysis of this largest birth weight group revealed that all but one of the vaccine nonresponders weighed <1500 g at birth, resulting in a seroprotection response rate of 96% in infants weighing >1700 g at birth. In addition, after three doses of vaccine, 98% of infants weighing >1700 g at birth who attained protective levels of HBs antibody.

TABLE 3. Relation of Various Subject and Demographic Variables With Achievement of Seroprotective Levels (≥10 mIU/mL) of HBs Antibody

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infants With Seroprotective Antibody</th>
<th>Infants Without Seroprotective Antibody</th>
<th>P Value *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 77)</td>
<td>(n = 27)</td>
<td>Univariate Analysis</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>18</td>
<td>52</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Steroid use (%)</td>
<td>9</td>
<td>26</td>
<td>.05</td>
</tr>
<tr>
<td>Female (%)</td>
<td>52</td>
<td>44</td>
<td>.66</td>
</tr>
<tr>
<td>Race/black (%)</td>
<td>65</td>
<td>44</td>
<td>.09</td>
</tr>
<tr>
<td>Weight gain at hospital discharge (%)</td>
<td>74</td>
<td>44</td>
<td>.008</td>
</tr>
<tr>
<td>6-7 Months weight gain (%)</td>
<td>89</td>
<td>50</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intraventricular hemorrhage (%)</td>
<td>27</td>
<td>33</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prolonged intubation (%)</td>
<td>38</td>
<td>78</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Birth weight &lt;1700 g (%)</td>
<td>1</td>
<td>99</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mean maternal age (y)</td>
<td>27</td>
<td>29</td>
<td>.10</td>
</tr>
<tr>
<td>Mean birth weight (g)</td>
<td>1455</td>
<td>1037</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean gestational age (wk)</td>
<td>31</td>
<td>28</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race × 6/7 months weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race × sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis × 6/7 months weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis × steroids</td>
<td></td>
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</tbody>
</table>

* Univariate statistical analysis performed using Fisher’s exact test for discontinuous variables and Wilcoxon test for continuous variables; multivariate analysis used logistic regression.
† For infants with birth weights <1700 g, this variable gave a P = .04.
ND indicates not done.
achieved levels $\geq 100$ IU/mL, levels associated with long-lasting immunity.\textsuperscript{12}

For the most part, our data support the current AAP and Centers for Disease Control and Prevention advisory panel recommendations for delaying the initiation of hepatitis B vaccination in premature infants weighing $<2$ kg.\textsuperscript{3} Two kilograms was chosen by the advisory committees based on then available information demonstrating that delaying vaccination of premature infants weighing $<1500$ g at birth until the attainment of $2$ kg resulted in an acceptable protective seroresponse rate compared with a similar birth weight group of premature infants vaccinated at birth.\textsuperscript{5–7} It was unclear from these studies whether the delay in vaccination rather than birth weight itself was the important determinants of seroresponse to vaccination. Our study suggests that birth weight itself is an important variable and that premature infants weighing $>1700$ g might be vaccinated successfully starting in the first week of life. One potential benefit to the early initiation of vaccination would be to increase vaccine compliance because the first dose would be given before discharge. However, two points of caution must be made for practitioners contemplating this change: 1) this study was not designed specifically to compare the immunogenicity of an early vaccination schedule in premature infants weighing $>1700$ g at birth with full-term infants; and 2) our data show that the entire three-dose schedule must be completed for most large birth weight premature infants to achieve protective levels of antibody. Less than 25% of such infants had protective levels of antibody after two doses of vaccine. This finding can be compared with a recent study evaluating the immunogenicity of the same hepatitis B formulation given to premature infants starting at 5 weeks of age (mean weight, 2203 g at vaccination); 66% of such infants achieved protective levels of antibody after two doses.\textsuperscript{13}

Our study demonstrates that birth weight is not the only factor contributing to the lowered immunogenicity of early hepatitis B vaccination in the premature infant. More than half of infants weighing $<1700$ g at birth respond well to three doses of hepatitis B vaccine; steroid use, sepsis, and poor weight gain in the first 6 months of life were associated with poor antibody responses. The only infant with a birth weight $>1700$ g who did not attain protective levels of specific antibody after three doses of vaccine was $2300$ g at birth, but had inadequate weight gain in the first 6 months of life. Clearly, under current AAP recommendations, this infant's birth weight would not have been a deterrent to early initiation of vaccination. Both black and white children who failed to gain weight during the first 6 months of life had decreased rates of response to vaccination compared with children who were gaining weight adequately. However, a significant association of poor weight gain and low immunogenicity was seen only in black infants. Although it has been suggested that genetic differences influence the response to the hepatitis B vaccine, environmental and other host factors could contribute to the immunogenicity of this vaccine.\textsuperscript{14} Previous studies evaluating antibody responses of the premature infant to other pediatric vaccines have not evaluated our study variables to any great extent, so it is difficult to estimate the overall contribution of their results to the immunologic competence of the premature infant. Poor nutritional status and growth have been linked with increased morbidity and mortality secondary to diarrheal disease in developing countries.\textsuperscript{15} Nutritional or growth impairment in Haitian infants (gestational ages unknown) did not affect their response to measles vaccine at 6 months of age.\textsuperscript{16} However, in two studies evaluating the response of preterm infants to \textit{Haemophilus influenzae} conjugate vaccines starting at 2 and 4 months of age, low weight for age at the time of administration of vaccine was associated significantly with poor immune responses.\textsuperscript{17,18}

It is unclear whether premature infants with poor weight gain would respond better if hepatitis B vaccine initiation were delayed. Data from studies of full-term infants suggest that delaying hepatitis B immunization from birth to 2 months of age results in a higher magnitude of antibody response rather than in a change in seroresponse rate.\textsuperscript{19} In contrast, recent data in premature infants suggest provocatively that delay in the initiation of vaccination may be important for successful immunization.\textsuperscript{13} In this latter study, premature infants were vaccinated when a weight of 2 kg was achieved. There were more vaccine nonresponders among larger birth weight premature infants who took a shorter time to achieve the prespecified weight of 2 kg (and therefore were vaccinated at an early postnatal age) compared with lower birth weight infants. Clearly, the relative contributions of postnatal age, immunologic development, growth, and nutritional factors to vaccine immunogenicity in the premature infant need to be explored further.

At present, our data would suggest that until additional information is forthcoming, premature infants vaccinated immediately after birth who have been given steroids should have HBs antibody levels determined after the third vaccination. It also would seem prudent for practitioners to determine the HBs antibody levels after three doses of vaccine in all low-risk premature infants who are falling off their weight curves regardless of when vaccination is initiated.

Another question raised by this study is whether our results have implications for premature infants at risk for perinatally acquired hepatitis B infection. For such high-risk infants, the AAP currently recommends administration of the first dose of vaccine and hepatitis B immunoglobulin within a few hours of birth, followed by an additional three doses of vaccine by 6 months of age; specific antibody levels would be determined after the last dose to ensure that a serum HBs antibody protective level is achieved.\textsuperscript{20} Our study results cannot be extrapolated to these at-risk infants because they receive passively administered protective antibody and because the AAP-recommended dose of this vaccine formulation for infants born of HBsAg-positive mothers is double that used for low-risk infants. Vaccine dose has been
shown to influence the magnitude of the immune response to hepatitis B vaccine in full-term infants. However, in addition to the data derived from our study suggesting that there are innate and iatrogenic factors associated with decreased active immunity associated with early hepatitis B vaccination, passive protective antibody levels may be reduced in hospitalized premature infants who receive multiple transfusions and sustain losses from continued blood sampling. Clearly, additional information is needed to assess current prophylaxis recommendations for these high-risk low birth weight premature infants.

In summary, in the premature infant, low birth weight, steroid use, and poor weight gain in the first 6 months of life are associated with decreased immunogenicity after three doses of hepatitis B vaccine when vaccine is initiated in the first week of life. Our data support the current recommendations for delay in the start of hepatitis B vaccination in premature infants at low risk for perinatally acquired hepatitis B infection, especially in infants with birth weights of <1700 g.

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