Comparison of Infantile Hemangiomas in Preterm and Term Infants: A Prospective Study

Infantile hemangiomas (IH) occur more frequently in premature infants.1,2 To our knowledge, studies comparing the clinical features of IH in term and preterm infants have not been reported. Results of the demographic and clinical characteristics of our prospective cohort study of children with IH have previously been reported.3,4 The current study compares the characteristics of IH in preterm and term infants within this cohort.

Methods. Data on gestational age (GA) was available for 1047 patients who were enrolled at the sites in the United States and formed the basis of the study. Preterm infants were defined as those with a GA of less than 37 weeks, and term infants were those with a GA of 37 weeks and greater.

Results. Demographic and clinical characteristics are summarized in the Table. Two hundred and fourteen subjects were preterm (20%), and 73 of these had a gestational age of 32 weeks or less (7%). Factors associated with preterm birth included a higher reported incidence of pre-eclampsia, placental anomalies, and use of infertility treatments than in term counterparts ($P < .001$). The female to male ratio was less pronounced in premature infants (1.85) than in term infants (2.62) ($P = .04$). No differences were noted in the age when IH was first noted or age at the time of presentation to a specialist. The mean (SD) number of hemangiomas was inversely related to GA: 1.37 (0.78) in term infants; 1.60 (1.15) in preterm infants with a GA of 33 to 36 weeks; and 1.83 (1.17) in preterm infants with a GA of 32 weeks or less ($P < .001$).

Forty percent of preterm infants had 2 to 5 lesions vs 24.5% of term infants ($P < .001$), and 7.5% of preterm infants had more than 5 lesions compared with 3% for term infants ($P < .001$) (Figure). Analysis of birth weight association alone showed that lower birth weight also correlated with increased numbers of IH ($P < .001$). Localized hemangiomas were more common than either segmental or indeterminate subtypes in both preterm and term groups; however, there was no significant difference in the incidence of segmental hemangiomas in preterm infants (14.6%) and term infants (18.1%) ($P = .24$). Anatomic location differed, with facial involvement being more common in term infants ($P = .005$). There was no difference in the incidence of complications (eg, visual compromise, ulceration, or cardiac or airway compromise), and need for treatment did not differ, nor did the treatment techniques used in those infants requiring treatment.

Comment. While previous studies have confirmed the higher incidence of IH in premature infants, to our knowledge, this is the first study to address whether characteristics of IH differ between term and preterm infants. The most notable differences found were the increased number of hemangiomas in preterm infants and the decreased female to male ratio (Figure and Table). The recent suggestion for a role of endothelial progenitor cells in IH development could help explain both the increase in frequency and numbers of hemangiomas in preterm infants because these progenitor cells might be more likely

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preterm Infants $&lt;37$ Weeks</th>
<th>Term Infants $&gt;37$ Weeks</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, No.</td>
<td>214</td>
<td>833</td>
<td>NA</td>
</tr>
<tr>
<td>Birth weight, mean, kg</td>
<td>2.1</td>
<td>3.4</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>Female to male ratio</td>
<td>1.85</td>
<td>2.62</td>
<td>NA</td>
</tr>
<tr>
<td>Maternal age, y</td>
<td>30.4</td>
<td>29.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>34.1</td>
<td>4.6</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>Placental anomalies</td>
<td>16.8</td>
<td>7.4</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>Infertility treatments</td>
<td>22.1</td>
<td>7.3</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>Maternal preeclampsia</td>
<td>21.7</td>
<td>9.3</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>Maternal CVS</td>
<td>4.3</td>
<td>3.5</td>
<td>.54</td>
</tr>
<tr>
<td>Age hemangioma noted, mo</td>
<td>1.9</td>
<td>2.1</td>
<td>.77</td>
</tr>
<tr>
<td>Age at presentation to specialist, mo</td>
<td>5.2</td>
<td>5.4</td>
<td>.30</td>
</tr>
<tr>
<td>Subjects with complications</td>
<td>23.4</td>
<td>18.5</td>
<td>.12</td>
</tr>
<tr>
<td>Subjects requiring treatment</td>
<td>39.3</td>
<td>37.7</td>
<td>.69</td>
</tr>
</tbody>
</table>

Abbreviations: CVS, chorionic villus sampling; NA, not applicable.

*Unless otherwise indicated, data are reported as percentage of subjects.

Figure. Comparison of the frequency of multiple infantile hemangiomas in preterm and term infants. Multiple infantile hemangiomas occur more frequently in preterm infants ($P < .001$).
to be present and in higher numbers in an immature fetus than in a mature one. This hypothesis might also help explain the decrease in female to male ratio noted, with prematurity offsetting whatever factors (as yet unknown) cause a female predominance.

Because premature infants have greater numbers of hemangiomas, a higher percentage overall are of the localized subtype, but there is no significant difference in the per-patient incidence of segmental hemangiomas between term and preterm infants. Segmental hemangiomas appear to arise as an error in neural crest development as early as 4 to 8 weeks GA, and their occurrence is thus less likely to be affected by prematurity delivery. The higher incidence of multiple-gestation pregnancies, placental anomalies, and preeclampsia in the preterm group is predictable because these factors are associated with preterm birth regardless of the presence of IH. However, a more causal relationship cannot be completely discounted. These pregnancy-related morbidities could hypothetically lead to an imbalance toward proangiogenic factors as responses to a hypoxic environment, either via the expression of growth factors, such as insulin-like growth factor 2, or via hypoxia-inducible factor 1α, which is upregulated in proliferating hemangiomas.

Limitations of the study include an ascertainment bias due to the nature of the study sites (pediatric dermatology practices) and the reliance on parental recall vs obstetrical data to determine perinatal history. Nevertheless, several findings should provide assistance to clinicians in managing preterm infants with IH. Hemangiomas did not differ in the time they were first noted or when they were first seen by specialists, suggesting that actual rather than adjusted GA can be used to predict growth characteristics. And although hemangiomas are more common in preterm infants, they do not appear to behave either more or less aggressively than in term infants: nor were differences noted in complication rates or need for treatment.

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COMMENTS AND OPINIONS

Anatomic Transitions and the Histopathologic Features of Melanocytic Nevi

In their letter, Braun et al1 reported a case of an acral melanocytic lesion that exhibited a completely benign dermoscopic pattern but was histopathologically diagnosed as melanoma in situ. As previously noted,2 despite benign clinical features, melanocytic nevi located in transition sites between glabrous and non-glabrous skin and in interdigital areas often histopatho-