Nucleated red blood cells in infants of mothers with asthma

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OBJECTIVE: The purpose of this study was to evaluate whether the absolute nucleated red blood cell and lymphocyte count is elevated in term, appropriate-for-gestational-age infants born to women with asthma.

STUDY DESIGN: We compared absolute nucleated red blood cell counts taken during the first 12 hours of life in two groups of term, vaginally delivered, appropriate-for-gestational-age infants; one group was born to mothers with active asthma during pregnancy (n = 28 infants), and the other group was born to control mothers (n = 29 infants). Asthma severity was classified according to the National Asthma Education and Prevention Program. We excluded infants of women with diabetes mellitus, hypertension, alcohol, and tobacco or drug abuse and infants with fetal heart rate abnormalities, hemolysis, blood loss, or chromosomal anomalies.

RESULTS: There were no differences between groups in birth weight, gestational age, maternal age, gravidity, parity, maternal analgesia during labor, 1- and 5-minute Apgar scores, and infant sex. The hematocrit level, red blood cell count, absolute nucleated red blood cell count, and corrected leukocyte and lymphocyte counts were significantly higher in the asthma group than in the control group. The platelet count was not significantly different between groups. The absolute nucleated red blood cell count correlated significantly with the asthma severity score ($r^2 = 28\%, P < .001$). Backward stepwise multiple regression that included Apgar scores and gestational age showed a significant correlation of absolute nucleated red blood cell count with the presence of asthma and its severity ($P < .001$).

CONCLUSION: At birth, term appropriate-for-gestational-age infants born to mothers with asthma have increased circulating absolute nucleated red blood cell and lymphocyte counts compared with control infants.

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Key words: Asthma, nucleated red blood cells, term infants

Material and methods

We prospectively studied two groups of term infants (38-41 weeks of gestation by last menstrual period, confirmed by early ultrasound scans), appropriate for gestational age (by Lubchenco intrauterine growth charts) who were born vaginally at the Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, between January 1, 1998, and December 31, 2001. Infants were recruited whenever three of the authors (Y. L., D. M., G. S. M.) were on call. Group 1 consisted of 28 infants of mothers with asthma; group 2 consisted of 29 control infants of mothers who did not have asthma. Asthma severity was classified according to National Asthma Education and Prevention Program; the absence of asthma was given a score of 0, mild intermittent asthma was given a score of 1, mild persistent asthma was given a score of 2, moderate persistent asthma was given a score of 3, and severe persistent asthma was
given a score of 4. In both groups we excluded those infants with other factors that were associated with potential increase in absolute nucleated RBC counts, as described by us and others, such as infants born to women with gestational or insulin-dependent diabetes mellitus; pregnancy-induced hypertension; abruptio placentae or placenta previa; any maternal heart, kidney, other lung, or other chronic condition; drug, tobacco, or alcohol abuse; perinatal infections (eg, fever, leukocytosis, signs of chorioamnionitis); abnormal electronic intrapartum monitoring; infants with low Apgar scores (<8 at 1 or 5 minutes); or infants delivered with the assistance of forceps or vacuum. We also excluded infants with perinatal blood loss, meconium-stained amniotic fluid, hemolysis (blood group incompatibility with positive Coombs test), or chromosomal anomalies.

Capillary blood samples for complete blood cell counts were collected from the infant within 12 hours of birth and analyzed according to laboratory routine with an STK-S counter (Coulter Corporation, Hialeah, Fla). Differential cell counts were performed manually, and absolute nucleated RBC counts were counted per 100 white blood cells (WBC). We showed previously that leukocyte counts and absolute nucleated RBC numbers are not independent; thus, the traditional expression of nucleated RBCs as their number per 100 WBCs might introduce a significant bias. Therefore, we expressed the number of nucleated RBCs as an absolute number rather than per 100 leukocytes; both WBC and lymphocyte counts were expressed as corrected for the presence of nucleated RBCs.

Our local Institutional Review Board approved the study. Because all newborn infants in our hospital are screened routinely for polycythemia with complete blood count by 12 hours of life, the requirement for informed consent was waived.

Statistical analysis included the Kruskal-Wallis test because of nonnormal distribution of absolute nucleated RBCs and backward stepwise regression analysis. Spearman ranked correlation was used to test the correlation between the absolute nucleated RBC count and the severity of asthma score. The comparison of the two groups on categoric data was accomplished with \( \chi^2 \) tests. Data are reported as mean ± SD or median (range). A probability value of <.05 was considered significant.

### Results

In the asthma group, 20 women were diagnosed with mild intermittent asthma, 2 women were diagnosed with mild persistent asthma, 5 women were diagnosed with moderate asthma, and 1 woman was diagnosed with severe persistent asthma. There were no differences between groups in birth weight, gestational age, maternal age, gravidity, parity, maternal analgesia during labor, 1- and 5-minute Apgar scores, and infant sex (Table). The hematocrit levels, RBC counts, absolute nucleated RBCs, and corrected leukocyte and lymphocyte counts were significantly higher in the asthma group than in the control group (Table). The platelet count was not significantly different between groups (Table). Multiple backward regression analysis that used the nucleated RBC count as the dependent variable and the asthma status, Apgar scores, and gestational age as independent variables showed that the absolute nucleated RBC count correlated only with the asthma status \( (P < .001) \). Moreover, in simple linear regression, the absolute nucleated RBC

### Table. Demographic and hematologic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mothers with asthma ( (n = 28) )</th>
<th>Control mothers ( (n = 29) )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)*</td>
<td>3245 ± 295</td>
<td>3297 ± 348</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age (wk)*</td>
<td>39.7 ± 0.9</td>
<td>39.4 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>12</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>43</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Maternal age (y)*</td>
<td>28.9 ± 4.1</td>
<td>28.4 ± 6.3</td>
<td>NS</td>
</tr>
<tr>
<td>Gravidity†</td>
<td>2 (1-8)</td>
<td>1 (1-9)</td>
<td>NS</td>
</tr>
<tr>
<td>Parity†</td>
<td>1 (1-6)</td>
<td>1 (1-5)</td>
<td>NS</td>
</tr>
<tr>
<td>Epidural analgesia during labor (No.)</td>
<td>25 (89%)</td>
<td>26 (97%)</td>
<td>NS</td>
</tr>
<tr>
<td>Apgar score†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-min</td>
<td>9 (9-10)</td>
<td>9 (8-10)</td>
<td>NS</td>
</tr>
<tr>
<td>5-min</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit level*</td>
<td>0.65 ± 0.06</td>
<td>0.61 ± 0.07</td>
<td>.018</td>
</tr>
<tr>
<td>RBCs ( \times 10^9/L )*</td>
<td>6.3 ± 0.7</td>
<td>5.7 ± 0.7</td>
<td>.002</td>
</tr>
<tr>
<td>WBCs: corrected ( \times 10^9/L )*</td>
<td>28.4 ± 6</td>
<td>23.0 ± 9</td>
<td>.005</td>
</tr>
<tr>
<td>Platelets ( \times 10^9/L )*</td>
<td>261 ± 73</td>
<td>283 ± 81</td>
<td>NS</td>
</tr>
<tr>
<td>Absolute lymphocyte count: corrected ( \times 10^9/L )*</td>
<td>6.6 ± 1.9</td>
<td>5.2 ± 1.9</td>
<td>.014</td>
</tr>
<tr>
<td>Absolute nucleated RBCs ( \times 10^6/L )†</td>
<td>633 (0-8749)</td>
<td>223 (0-2546)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NS, Not significant.

*Data are expressed as mean ± 1 SD.
†Data are expressed as median (range).
count correlated significantly with the severity of asthma score ($r^2 = 28\%, P < .001$).

Comment

We found that maternal asthma during pregnancy is associated with an increase in nucleated RBC and lymphocyte counts (both markers of chronic intrauterine hypoxia$^{6,7,9,21-25}$) in term appropriate-for-gestational-age infants. Moreover, hematocrit levels were also elevated significantly in the asthma group. We excluded small-for-gestational-age infants, an important confounding variable. We also excluded infants with other factors that were associated with a potential increase in absolute nucleated RBC counts, including preterm labor with histologic placental signs of chorioamnionitis,$^{19}$ maternal smoking,$^{8}$ meconium-stained amniotic fluid,$^{20}$ hemolysis, chromosomal anomalies,$^{18}$ maternal diabetes mellitus,$^{7,19}$ and potential neurologic insults.$^{9,22}$ Furthermore, we showed that the absolute nucleated RBC count correlated with the severity of the asthma score. We believe that our study unequivocally shows that maternal asthma is an independent risk factor for an increased newborn absolute nucleated RBC counts.

The mechanism by which maternal asthma increases circulating neonatal absolute nucleated RBC counts is unknown. A likely explanation is relative fetal hypoxia. In our study, this relative hypoxia was of sufficient duration and/or intensity to cause an increase in hematocrit level. Other previously reported indicators of fetal hypoxia in infants of mothers with asthma include a decrease in birth weight and a subsequent increase in low birth weight and small for dates deliveries.$^{1,2}$ In our study, by design, weights were similar between the two groups because we excluded small-for-gestational-age infants from both groups. Theoretically, maternal medications could also cause an increase in nucleated RBC counts. This is unlikely because patients used inhaled bronchodilators (albuterol) and at times inhaled steroids, which are not known to affect erythropoiesis.

The mechanism of elevation of neonatal lymphocyte counts in hypoxic fetuses has been reported by others and us$^{8,23-24}$; in this study, corrected lymphocyte counts were elevated in the infants born to mothers with asthma compared with the control infants. To date, there is no known explanation for this elevation in lymphocyte counts. Furthermore, the corrected WBC count was higher in the asthma group by approximately 1.4 $\times 10^9$/$L$, although the lymphocyte count was higher only by approximately 1.4 $\times 10^9$/$L$. Thus, the elevation in WBC counts was contributed to by both an elevation of lymphocytes and an elevation of granulocytes. We have no clear explanation for this observation.

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