Developmental Hematopoiesis in Normal Human Fetal Blood

By François Forestier, Fernand Daffos, Nicole Catherine, Michèle Renard, and Jean-Paul Andreux

Using an easy and safe procedure for fetal blood sampling in utero, we studied 3,415 fetuses for prenatal diagnosis. Retrospectively, 2,860 normal blood samples, performed from the 18th week of gestation to the end of pregnancy, were selected. Differentials were evaluated in 732 cases. Burst-forming unit erythroid (BFU-E) and erythropoietin (Epo) were measured in 27 and 183 cases, respectively. Total nucleated cell and platelet counts did not change from the 18th to the 30th week of gestation. The lymphocytes represented the main population and the decrease of normoblastic cells made up for the increase in neutrophils. The increase of red blood cells and hemoglobin was substantial during the studied period. At mid trimester threefold more BFU-E were obtained than at birth. Epo levels remained stable throughout the pregnancy and no correlation was found between Epo and gestational age. These normal values of fetal erythropoiesis will improve our knowledge of physiology and provide a better insight into developmental hematopoiesis. © 1991 by The American Society of Hematology.

Table 1. Evolution of Hematologic Values of 2,860 Normal Fetuses During Pregnancy (mean ± SD)

<table>
<thead>
<tr>
<th>Week of Gestation</th>
<th>Total WBC Counts (×10^9/L)</th>
<th>PLT (×10^9/L)</th>
<th>RBCs (×10^12/L)</th>
<th>Hb (g/100 mL)</th>
<th>Ht (%)</th>
<th>MCV (fl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-21 (n = 760)</td>
<td>4.68 ± 2.96</td>
<td>2.57 ± 0.42</td>
<td>234 ± 57</td>
<td>2.85 ± 0.36</td>
<td>11.69 ± 1.27</td>
<td>37.3 ± 4.32</td>
</tr>
<tr>
<td>22-25 (n = 1,200)</td>
<td>4.72 ± 2.82</td>
<td>3.73 ± 2.17</td>
<td>247 ± 59</td>
<td>3.09 ± 0.34</td>
<td>12.2 ± 1.6</td>
<td>38.59 ± 3.94</td>
</tr>
<tr>
<td>26-29 (n = 460)</td>
<td>5.16 ± 2.53</td>
<td>4.08 ± 0.84</td>
<td>242 ± 69</td>
<td>3.46 ± 0.41</td>
<td>12.91 ± 1.38</td>
<td>40.88 ± 4.4</td>
</tr>
<tr>
<td>&gt;30 (n = 440)</td>
<td>7.71 ± 4.99</td>
<td>6.40 ± 2.99</td>
<td>232 ± 87</td>
<td>3.82 ± 0.64</td>
<td>13.84 ± 2.21</td>
<td>43.65 ± 7.2</td>
</tr>
</tbody>
</table>

*Including normoblasts.
Table 2. Some Aspects of Fetal Differential Counts From 18 to 30 Weeks of Gestation of 752 Normal Fetuses

<table>
<thead>
<tr>
<th>Week of Gestation</th>
<th>Lymphocytes (%)</th>
<th>Neutrophils (%)</th>
<th>Eosinophils (%)</th>
<th>Basophils (%)</th>
<th>Monocytes (%)</th>
<th>Normoblasts (% WBCs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-21 (n = 186)</td>
<td>66 ± 7</td>
<td>6 ± 4</td>
<td>2 ± 3</td>
<td>0.5 ± 1</td>
<td>3.5 ± 2</td>
<td>45 ± 86</td>
</tr>
<tr>
<td>22-25 (n = 230)</td>
<td>87 ± 6</td>
<td>6.5 ± 3.5</td>
<td>3 ± 3</td>
<td>0.5 ± 1</td>
<td>3 ± 2.5</td>
<td>21 ± 23</td>
</tr>
<tr>
<td>26-29 (n = 144)</td>
<td>86 ± 6</td>
<td>8.5 ± 4</td>
<td>4 ± 3</td>
<td>0.5 ± 1</td>
<td>3 ± 2.5</td>
<td>21 ± 67</td>
</tr>
<tr>
<td>&gt;30 (n = 172)</td>
<td>68.5 ± 15</td>
<td>23 ± 15</td>
<td>5 ± 3</td>
<td>0.5 ± 1</td>
<td>3 ± 2</td>
<td>17 ± 40</td>
</tr>
</tbody>
</table>

Table 3. BFU-E in Normal Fetuses, Cord Blood (at birth), Adult Bone Marrow, and Peripheral Blood (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Extreme Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal blood (n = 27)</td>
<td>160</td>
<td>107</td>
<td>80-460</td>
</tr>
<tr>
<td>Cord blood at birth (n = 9)</td>
<td>48</td>
<td>19</td>
<td>12.96</td>
</tr>
<tr>
<td>Adult bone marrow (n = 10)</td>
<td>16</td>
<td>9</td>
<td>5.43</td>
</tr>
<tr>
<td>Adult peripheral blood (n = 10)</td>
<td>3.6</td>
<td>3</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Results expressed per 10⁵ cells.

The data of differential counts for 732 normal fetuses (Table 2) indicated that lymphocytes represented the main population (around 80%). The decrease in normoblastic cells, ranging from 45% to 17%, made up for the increase in neutrophils from 6% to 23%. Eosinophils, basophils, and monocytes remained stable in percentage.

Data concerning BFU-E/10⁵ cells are shown in Table 3. We obtained 160 BFU-E ± 107 for the fetuses (mean ± SD), 48 ± 19 at birth (cord blood), 16 ± 9 in adult bone marrow, and 3.6 ± 3 BFU-E in the adult peripheral blood. A graph of BFU-E versus gestation is presented in Fig 1. We did not observe any correlation between Hb, erythroblasts, or RBCs and BFU-E.

Epo. The extreme values of the measurements of 163 fetal Epo ranged from 0 to 12 with a mean of 1.6 ± 2.5 mIU/mL, and Fig 2 represents Epo versus gestational age. No correlation was observed (Spearman coefficient: 0.062; P > .2).

RESULTS

The means and standard deviations of the main hematologic parameters are shown in Table 1. To better assess the evolution of the hematopoietic system, four groups were considered: (1) 18 to 21 weeks of gestation, (2) 22 to 25 weeks of gestation, (3) 26 to 29 weeks of gestation, and (4) from the 30th week to birth.

WBCs started at 4.68 × 10⁹/L at the 18th week of gestation to reach 7.71 × 10⁹/L at the 30th week. We observed a gradual decrease of MCV during this same period from 131 to 114 fl, and an increase in Hb (11.69 in the first group v 13.64 g/100 mL in the fourth group). RBCs and Ht are progressively increased from 2.85 to 3.82 × 10¹²/L and from 37.3% to 43.55%, respectively. We did not observe any change in the platelet counts, which remained comparable with adult values (around 245 × 10⁹/L).

DISCUSSION

Hematopoietic progenitors are first observed in the yolk sac. Some experiments suggest that an intact yolk sac is required for subsequent fetal hematopoiesis, because progenitors from the vascular system of the yolk sac apparently migrate into and colonize the fetal liver. Fetal bone marrow erythropoiesis begins between the 16th and 18th week, as liver hematopoiesis is challenged by hepatocyte proliferation. The first morphologically recognizable platelets appear in the fetal circulation at 8 to 9 weeks of gestation and the circulating platelet concentration is similar to those of adults and is achieved by or before 18 weeks of gestation. Neutrophils are the last of the fetal blood cells to appear and the macrophages are probably the first. Our data confirmed that previously published, but they

![BFU-E/10⁵ Cells](image-url)
were measured in a larger population. WBCs and neutrophils are much lower at 18 to 21 weeks than at the end of pregnancy \( (4.68 \pm 2.96/7.71 \pm 4.9 \times 10^3/L) \), and that may suggest that, should such subjects be exposed to bacteria or parasites, their defenses would be deficient because of the very low neutrophil count, ie, \( 28 \times 10^3/L \) at the beginning of pregnancy.

Fetal hematopoietic progenitors differ in several aspects from the marrow-derived adult progenitors. These differences include their rapid cycling rate, the constantly and rapidly expanding pool size, in vivo differentiation almost exclusively along the erythroid pathway, accelerated in vitro maturation time, greater sensitivity to Epo, and decreased sensitivity to granulocyte-macrophage colony-stimulating factor.

There have been few studies on BFU-E in fetuses and the data are heterogeneous due to the methods used for cell isolation, culture, and to the way data are expressed. Some results are given for \( 10^5 \) seeded cells and others per milliliter of blood. Our results are in good agreement with those obtained by Partanen et al, using the same method with adult bone marrow; by Migliaccio et al, who cultured 20 to 30 BFU-E per \( 10^3 \) mononucleated cells in perinatal blood; and by Shekhter-Levin et al in neonatal cord blood. It appears that the early second trimester has the highest BFU-E level. At mid-gestation, the proportion of BFU-E is approximately three times that of neonatal cord blood and 10 times that of adult bone marrow.

The level of Epo in fetal sera during the second and third trimesters of pregnancy is extremely low and, surprisingly, we did not observe any increase in Epo level at different gestational ages. We only observed elevations of Epo in cases of Rh alloimmunization and in some cases of severe intrauterine growth retardation (data not shown). All these new data confirm the fundamental differences between the hematopoietic systems of fetal and adult subjects.

In conclusion, it has been possible to establish normal hematologic reference values from a very large group of 2,680 normal fetuses during the second and third trimesters of pregnancy. We confirmed our previous data (obtained from a smaller group) and we added some new information about erythroid progenitors and Epo levels. It may provide better understanding of fetal hematopoiesis, wiser usage of blood retrieved from the umbilical cord at delivery to restore abnormal hematopoiesis, and directions for the administration of Epo in premature newborns.

REFERENCES

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