Cord Blood Erythropoietin and Markers of Fetal Hypoxia

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To investigating the relationship between cord blood erythropoietin and clinical markers of fetal hypoxia.

Abstract

Objective: To investigating the relationship between cord blood erythropoietin and clinical markers of fetal hypoxia

Methods: Erythropoietin (EPO) concentrations in umbilical venous blood were measured from 80 neonates with low-risk and different risk factors by radioimmunoassay (RIA). The relation between EPO concentration and clinical markers of fetal asphyxia was evaluated.

Results: Median EPO concentrations were 29mU/mL, in infants with no risk factors or complications during pregnancy (n=23). In infants with complicated pregnancy and no complication during labor the median level of EPO was 68mU/ml (n=25) Infants showing abnormal FHR pattern during labor had median EPO levels of 42mU/ml (n=13) while infants showing umbilical blood acidosis showed a median EPO levels of 76mU/ml.

Using multiple regression, we found that the erythropoietin concentration correlated significantly (p<0.01) with fetal growth retardation and umbilical acidosis but not with gestational age, abnormal fetal heart rate (FHRT) pattern or Apgar score at 5 minutes.

Conclusion: Elevated Erythropoietin concentrations in umbilical venous blood may indicate prolonged fetal hypoxia.

Introduction

More than forty years have passed since Virigina Apgar introduced her score to evaluate the condition of the newborn (1). Although not meant primarily for this purpose, the score has become the most widely used indicator of perinatal asphyxia. Nevertheless, it is still difficult to determine the presence, duration and extent of fetal hypoxia. Certain abnormal fetal heart rate patterns are considered to indicate imminent fetal risk (2). Whether meconium stained amniotic fluid is related to fetal distress is controversial (3). Umbilical arterial pH is widely used as an indicator of fetal hypoxia. All of these are indirect markers. Moreover, neurologic outcome seems to correlate poorly with acidosis at birth (4,5), low Apgar score or meconium stained amniotic fluid (5). Therefore, additional markers are required to distinguish between acute and chronic fetal hypoxia.

Erythropoietin production is stimulated by hypoxia in adults (6) and fetuses (7,9). Because this glycoprotein does not cross the placenta (10,11) elevated cord blood concentration should be a marker of fetal hypoxia. Increased cord EPO concentrations have been found in maternal diabetes (12,14), maternal hypertension (12,15) and acute fetal hypoxia (15,16). Fetal polycythemia frequently occurs in intrauterine growth retardation and increased levels of EPO have been reported in pathological pregnancies possibly associated with placental insufficiency (17). Severe anemia was accompanied by increased EPO concentration (18). Elevated EPO in these cases suggested that prolonged intrauterine hypoxia is an important factor among these fetuses.

This study was conducted to investigate the relationship between erythropoietin concentration in umbilical venous blood and the indirect markers of fetal hypoxia (Apgar score, Abnormal FHR...
pattern, Meconium stained amniotic fluid, Umbilical arterial pH and blood gases).

**Subjects and Methods**

Eighty pregnant women with singleton pregnancy were selected for this study. Thirty women had no complications during pregnancy and fifty women had one or more complications during pregnancy; 19 (38%) had pregnancy induced hypertension and/or pre-eclampsia; 11 (22%) had Diabetes mellitus; 6 (12%) had both Diabetes and hypertension; 8 (16%) had rheumatic heart disease and 6 (12%) had vaginal bleeding during pregnancy.

Forty-six (57.5%) infants were delivered spontaneously; 20 (25%) by Caesarian section before the onset of labor; 10 (12.5%) by Caesarian section after the onset of labor and 4 (5%) vaginally by operative means (forceps or ventous).

The infants' birth weight was nearly normally distributed with a range of 1050 to 4700gm. Seven (8.75%) weighed below the tenth percentile for gestational age (20).

The gestational age ranged from 33 to 42 completed weeks; 22 (27.5%) were born before completed 37 weeks and 58 (72.5%) were term infants. Sixteen infants (20%) were transferred to our neonatal intensive care unit after birth, 12 for prematurity; 3 because of hypoglycemia and one because of pulmonary maladaptation.

Based on clinical signs of fetal distress, we defined four groups of infants:

1- Low-risk group (n=23) singleton term newborns (37-42 completed weeks) with no event detected that could lead to fetal hypoxia during pregnancy e.g. maternal diabetes, hypertension, vaginal bleeding, preterm labor, rupture of the membranes more than 24 hours before delivery or heart disease. Also there was no signs of fetal distress during labor e.g. meconium stained amniotic fluid, abnormal FHR pattern; umbilical pH below 7.20 or need for special care after birth

2- Complicated pregnancy (n=25+ with events detected during pregnancy that can lead to fetal hypoxia and no signs of fetal distress.

3- Abnormal FHR pattern and/or meconium stained amniotic fluid (n=13) during labor but no umbilical acidosis.

4- Umbilical acidosis (n=19); umbilical arterial pH below 7.20 with or without abnormal FHR pattern

Erythropoietin was measured by competitive binding double antibody radioimmuno-assay technique (RIA)(20). Using Commercial Kit of Incstar-EPO trace, 125 I (Incstar Corporation, Stillwater, Minnesota USA).

Fetal heart rate was continuously recorded during labor using IM76 intrapartum fetal monitor (advanced Medical System Inc.) All recordings were evaluated retrospectively during the last 40 minutes of the first stage of labor by the same obstetrician who classified FHR according to that of MacDonald et al (21).

Blood gases and pH were analyzed in umbilical arterial blood drawn by needle puncture immediately after birth. An ABL30 blood gas analyzer (Radiometer, Copenhagen, Denmark) was used.

To determine the relationship between EPO concentration in umbilical venous blood and clinical findings we performed multiple regression analysis and reported the results as statistically significant at p<0.05. All calculations were done with the SPSS-statistical package (SPSS Inc. Chicago,..n).

**Results**

Table 1 shows values of EPO, pH and blood gases in low-risk group and other groups. Significant difference between mean EPO in low-risk group and other groups was found.

Erythropoietin concentrations did not correlate significantly with umbilical arterial oxygen pressure (PO2) and carbon dioxide pressure (PCO2) and correlate significantly with umbilical arterial pH
Table 2 shows the Erythropoietin concentrations of low-risk group in our study and other studies.

Erythropoietin concentration in preterm infants [median 55mU/ml; range 29-160] were not different from those in term infants [median 72.5mU/ml; range 29-150]. However, EPO concentrations were markedly higher in small for gestational age infants (p<0.01) below the tenth percentile than in average gestational age infants [median 62.4mU/ml Vs median34mU/ml]. Infants who need special care had higher EPO concentrations than well infants [median 53.6mU/ml Vs 29mU/ml] p<0.04.

Table 3 presents results of EPO concentration in low-risk group and the other three groups with clinical signs of fetal distress. The four groups differ significantly with regard to EPO concentration in umbilical venous blood (p<0.01). No infant in the low-risk group had an EPO above 58mU/ml. On the other hand, several infants with complicated pregnancy or umbilical acidosis had EPO levels above 300mU/ml.

The median EPO concentration increased with decreasing umbilical arterial pH (p<0.01).

Using multiple regression analysis we evaluated gestational age and factors related to fetal distress; fetal growth retardation, abnormal FHR pattern, umbilical arterial blood pH and Apgar score at 5 minutes.

Erythropoietin concentration correlated significantly with fetal growth retardation (p<0.01) and with umbilical arterial pH. The levels of EPO did not correlate with gestational age, abnormal FHR pattern or Apgar score at 5 minutes.

Discussion

Levels of EPO in umbilical venous blood observed in our low-risk group is comparable to those measured in other studies, however, inclusion and exclusion criteria for control groups are not comparable in all of these studies (table 2).

Like Widness et al (13, 14, 22), Ruth et al (15,17), Forestier et al (23) and Maier et al (24) we found no difference in EPO concentrations between preterm and term infants. These results contrast to those of Thomas et al (11) and Ekardt et al (25), who reported an increase with progressing gestational age. However, the latter studies involved only infant in an advanced stage of gestation (36-43 weeks).

In contrast to Ekardt et al (25), who observed no differences in EPO levels between average for gestational age (AGA) and small for gestational age (SGA) infants in the absence of fetal distress, we found increased EPO levels in SGA infants, suggesting a prolonged period of hypoxia. This agrees with Ruth et al (15) and Maier et al (24) who found a correlation between cord blood EPO levels and the degree of fetal growth retardation.

Whereas adults produce EPO in the kidney, the main production site during fetal life is thought to be the liver in animals (7), as well as in human beings. Widness et al (26) observed that EPO concentrations in the cord blood of infants with Potter syndrome were similar to those in healthy term infants. Furthermore, they found no difference between a nephric infants and those with severe renal disease. They concluded that nearterm human kidney is not important for fetal erythropoietin synthesis.

We found no relation between erythropoietin concentration in umbilical venous blood and umbilical arterial PO2. This in agreement with the observations of Teramo et al (12), Widness et al (14) and Maier et al (24). This can be explained in that tissue oxygenation depends not only on arterial PO2 but also on the oxygen dissociation characteristic, which is influenced by acidosis. Furthermore, fluctuations in arterial PO2 occur more rapidly than those in serum erythropoietin concentration.

In healthy adults following exposure to hypobaric hypoxia, elevated serum EPO concentrations
decline with an average half-life of 5.1 hours (6). Ruth et al (15) found a shorter half-life in newborn infants, after cessation of a hypoxic stimulus serum EPO declined with a mean half life of 3.7 hours. Assuming that these results (15) obtained immediately after birth can be extrapolated to fetal life, we can detect a proceeding hypoxia by elevated EPO concentrations several hours after cessation, even when the PO2 returned to normal levels.

In our study EPO rose with increasing degree of acidosis. A negative correlation between cord blood EPO concentration and umbilical arterial blood pH has also been observed by Ekardt et al (25), Ruth et al (15), Termo et al (12) in infants of mothers with pre-eclampsia, and Widness et al (14) in infants of diabetic mothers, this was also observed by Maier et al (24) where they measured EPO by ELISA.

In our study EPO concentrations in umbilical venous blood were not related to umbilical arterial PCO2. Widness et al (8) demonstrated that prolonged hypoxia in fetal sheep was followed by metabolic acidosis and increased serum EPO. On the other hand they found that lactic acidosis without hypoxia did not stimulate Epo production.

Some of our infants with acidosis and/or other clinical signs of fetal distress had EPO concentrations within the range of low-risk group, which may reflect a delay between the start of a hypoxic stimulus and the increase of EPO in circulating blood. This delay suggests that there are no stores for rapid EPO release.

In adult rabbits, EPO began to rise 3 hours after exposure to hypobaric hypoxia (27). In fetal sheep, a progression increase in plasma EPO could be measured during the fourth hour of maintained hypoxemia. Ekardt et al (6) found the first significant increase 1.5 hours after exposure of healthy human adults to acute hypobaric hypoxia. If these results can be applied to human fetuses, elevated EPO levels in umbilical venous blood combined with arterial blood pH could help to distinguish between acute and prolonged fetal hypoxia.

Ruth et al (28) reported that a high cord blood EPO levels after normal pregnancy indicates an increased risk of cerebral palsy or death. We found that higher EPO concentration in infants who needed special care compared to those who did not. Preterm infants did not differ from term infants with regard to EPO concentrations, this finding can not be explained by the fact that preterm infants are more likely to need special care than term infants.

There is no standard diagnosis of fetal hypoxia. Sykes et al (29) noted that Apgar score does not usually reflect the degree of acidosis at birth. We found that abnormal FHR pattern during the last 40 minutes before delivery and Apgar score at 5 minutes were not closely correlated to EPO concentration in umbilical venous blood. Therefore, we concluded that abnormal FHR pattern may signal imminent fetal risk but does not indicate fetal hypoxia. We can identify infants with acidosis at birth, but further investigations are needed to determine the exact relation between EPO and the duration of fetal hypoxia in human fetuses.

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ±SD pH</th>
<th>Mean ±SD EPO</th>
<th>Mean ±SD PO2</th>
<th>Mean ±SD PCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.30(± 0.06)</td>
<td>28.04( ±13.7)</td>
<td>21.17(± 2.9)</td>
<td>33.78(± 7.5)</td>
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<tr>
<td>2</td>
<td>7.23(± 0.04)</td>
<td>73.84( ±29.6)</td>
<td>13.17(± 3.1)</td>
<td>51.38( ±5.7)</td>
</tr>
<tr>
<td>3</td>
<td>7.30(± 0.05)</td>
<td>43.92(± 26.1)</td>
<td>13.8(± 4.9)</td>
<td>41.91(± 9.6)</td>
</tr>
<tr>
<td>4</td>
<td>7.13(± 0.05)</td>
<td>109.57(± 86.4)</td>
<td>10.3(± 0.5)</td>
<td>53.5( ±5.6)</td>
</tr>
</tbody>
</table>

NS=not significant
**Table 2**

Cord blood EPO concentrations in current study and previous reports

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>No.</th>
<th>Value</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eckardt et al (26)</td>
<td>75</td>
<td>33.6/17-56</td>
<td>Median/95%CI</td>
</tr>
<tr>
<td>Ruth et al (16)</td>
<td>17</td>
<td>37/23/18-27,40/33-47</td>
<td>Median/95%CI-no labor, Median/95%CI-labor</td>
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<tr>
<td>Ruth et al (17)</td>
<td>9</td>
<td>20/6-39</td>
<td>Median/range</td>
</tr>
<tr>
<td>Teramo et al (13)</td>
<td>17</td>
<td>19.7/9.8-50.3</td>
<td>Median/range</td>
</tr>
<tr>
<td>Widness et al (14)</td>
<td>16</td>
<td>32/7-64</td>
<td>Median/range</td>
</tr>
<tr>
<td>Widness et al (23)</td>
<td>23</td>
<td>23/9.8-50.3</td>
<td>Median/range</td>
</tr>
<tr>
<td>Maier et al (25)</td>
<td>19</td>
<td>25.1/11.9-55.3</td>
<td>Median/range</td>
</tr>
<tr>
<td>Abdel Aziz et al (present study)</td>
<td>23</td>
<td>29/5-58</td>
<td>Median/range</td>
</tr>
</tbody>
</table>

CI= Confidence Interval

**Table 3**

Erythropoietin Concentration in umbilical venous blood in the 4 studied groups

<table>
<thead>
<tr>
<th>Group</th>
<th>No</th>
<th>Median mU/ml</th>
<th>Range mU/ml</th>
<th>Mean mU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Risk</td>
<td>23</td>
<td>29</td>
<td>5-58</td>
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<td>Complicated pregnancy</td>
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<td>68</td>
<td>30-160</td>
<td>73.84</td>
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<td>Abnormal FHR</td>
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<td>42</td>
<td>11-100</td>
<td>43.92</td>
</tr>
<tr>
<td>Umbilical acidosis</td>
<td>19</td>
<td>76</td>
<td>25-300</td>
<td>109.5</td>
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<tr>
<td>Abnormal FHR</td>
<td>13</td>
<td>42</td>
<td>11-100</td>
<td>43.92</td>
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<td>Abnormal FHR</td>
<td>19</td>
<td>76</td>
<td>25-300</td>
<td>109.5</td>
</tr>
</tbody>
</table>

Disclosures:

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