EFFECT OF MATERNAL ANEMIA AT HIGH ALTITUDE ON INFANT HEMATOCRIT AND OXYGENATION

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Abstract. Hematocrit levels were determined in 36 mothers living at high altitudes (3,750 meters) and their infant cord bloods to determine the effect of maternal anemia on the infant. The arterial oxygen saturation (SaO$_2$) and respiratory rate of the infants were also followed during the first four months of life. There was a negative correlation between maternal hematocrit and infant hematocrit ($r_s = -0.57$). Nineteen babies born to anemic women (hematocrit < 41%) had a significantly higher mean hematocrit (59.9%) than those born to non-anemic mothers (55.8%; $P = 0.003$). The SaO$_2$ levels and respiratory rates of infants were not different between infants born to non-anemic and anemic mothers. At high altitudes, infants from mothers with anemia have higher hematocrits than those born to non-anemic mothers.

INTRODUCTION

Fetal oxygenation is critically dependent on maternal oxygen supply. Findings of reduced infant birth weight and increased neonatal and infant mortality suggest that fetuses at high altitudes experience greater hypoxia than those at low altitudes.$^{1-4}$ However, infants born to Tibetan women native to the highlands had a higher birth weight than those of women native to lower altitudes, suggesting that genetic or physiologic adaptation may permit adequate oxygenation of fetuses at high altitudes.$^{5-8}$

In animal studies, maternal systemic and uteroplacental circulations are capable of adapting well to chronic maternal anemia, even in the case of acute anemia.$^{9,10}$ Studies at high altitudes are useful in evaluating the effect of maternal anemia on infant hematocrit values and oxygenation because the hypoxia of high altitude produces an exaggerated response compared with those seen at sea level. It must be emphasized that to date no studies have determined the effect in humans of maternal anemia on newborn oxygenation at high altitudes. In fact, the effect of maternal anemia in the newborn, even at sea level, is an inexplicably neglected area. We examined mothers’ hematocrit levels and compared them to those of their infants, and also observed arterial oxygen saturation (SaO$_2$) at birth. In addition, we monitored arterial oxygen saturation of the infants born at high altitudes during the first four months of life to determine the SaO$_2$ response of infants over time and with varying states of activity (awake, sleeping, and feeding) to evaluate the relationship between maternal anemia and neonatal oxygenation.

METHODS

Site. The study site was the EsSalud Hospital in La Oroya, Peru (altitude = 3,750 meters [12,300 feet]). This hospital only admits patients with social security insurance. These individuals usually have stable employment (miners, road workers, and employees) and are somewhat more affluent than the surrounding general population. They come from nearby towns that are at an altitude similar to La Oroya (between 3,500 and 4,000 meters).

Subjects. Women were eligible for the study if they were between 16 and 40 years of age, had normal results on a prenatal examination, and were expected to have a normal vaginal delivery. Patients were excluded for any of the following pre-delivery complications: pre-eclampsia, eclampsia (the occurrence in a woman with preeclampsia of seizures that cannot be attributed to other causes), maternal dystocia, placenta previa, or severe hemorrhage during the birth process. All women were of mixed (Mestizo) descent (Quechua native and Spanish). All were born at high altitudes (more than 3,000 meters) and lived at altitudes ranging from 3,500 to 4,000 meters throughout their lives. All deliveries occurred in the hospital. An experienced pediatrician evaluated all newborns, and only term infants (more than 37 weeks based on expected date of confinement) with a normal cardiopulmonary examination result and an Apgar score of eight or more were eligible for the study. Gestational age was determined by the method of Capurro and others using five physical examinations and two neurologic signs.$^{11}$ Low birth weight infants (< 2,500 grams) were excluded from the analysis.

After informed consent was obtained from the pregnant woman, a maternal history was taken that included place of residence, birthplace, and use of alcohol, drugs, or tobacco. The study protocol was reviewed and approved by the ethical committee at A.B. PRISMA (Lima, Peru) and the institutional review board of the Johns Hopkins Bloomberg School of Public Health (Baltimore, MD).

Study techniques. The mother’s hematocrit was measured within 12 hours prior to delivery, and the newborn hematocrit was measured in cord blood immediately post-delivery. The hematocrit levels were determined by the microcapillary method. Prevalence of anemia was estimated in pregnant women after correcting for the plasma volume expansion that occurs during pregnancy. Persons who fall below a set level of the fifth percentile of the non-anemic population, assuming a normal distribution, are considered to be anemic. We calculated the hemoglobin (Hb) cut-off for women of childbearing age at 3,750 meters using the model developed by Cohen and Haas$^{12}$ according to the following formula: Hb cut-off = mean Hb – [(0.061 × mean Hb) × 1.96] when the mean Hb (g/L) = $120 + 16.3 \times \exp(0.00038 \times (\text{altitude} - 1000))$. 


420
This model demonstrates the change in hematocrit of non-anemic women at different altitudes and predicts that at an altitude of 3,750 meters women of childbearing age have Hb cutoffs for anemia of 14.6 g/dL (hematocrit = 44%). However, the degree of hemodilution that occurs in pregnant women at high altitudes has not been defined. At this altitude, pregnant women in the second and third trimester were estimated to have an Hb level of 1 g/dL less than their level in the non-pregnant state.12 This gives an Hb cut-off for anemia of 13.6 g/dL (hematocrit = 41%). This hematocrit level of 41% was used for the comparison between high altitude anemic and non-anemic mothers.

Arterial oxygen saturation (SaO2) was measured by pulse oximetry with an N–20 pulse oximeter (Nellcor, Inc., Pleasanton, CA). An appropriately sized sensor was placed on the lateral foot to minimize postductal effects.13 None of the infants received supplemental oxygen at delivery or afterwards. Pulse oximetry studies were performed at varied activity levels at 10 minutes to 4 months of age (10 minutes, 2 hours, 6 hours, 12 hours, 24 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 2 months, 3 months, and 4 months) after birth. Each child was studied, if possible, while quietly awake, while feeding, and while quietly sleeping.14 A child was considered quietly awake when his eyes were open and he or she was not crying. Feeding was defined as actively sucking and swallowing from a breast or a bottle. Quietly asleep was defined by the clinical criteria of Prechtl:15 a relaxed state with eyes open but not moving, no swallowing, and no gross movements except occasional startles. The infants were observed for three minutes in a definable state before collecting data. The SaO2 levels were recorded on one-minute intervals for a total of 10 minutes during each of the three activities.6,13 Care was taken to ensure that the pulse rate displayed on the oximeter reflected the heart rate heard by stethoscope. Respiratory rate was counted by auscultation for a one-minute period during quiet sleep and the awake state only. Data was rejected when the infant’s activity was not clearly classifiable or when the pulse oximetry was less than 65% (two children on one occasion) because pulse oximetry readings of SaO2 less than 65% have been shown to be inaccurate.16 Infants were screened for respiratory illness before each home study; if fever or signs of lower respiratory infection were present, they were excluded from further study (one child on one occasion). Infants with nasal congestion alone were not excluded because in previous studies at high altitudes we demonstrated that children with upper respiratory infections had SaO2 readings similar to those of normal children.17

**Statistical analysis.** The chi-square or Fisher’s exact tests were used to compare differences in proportions. The Student t-test or Mann-Whitney U test was used to compare continuous variables. To evaluate a linear relationship between maternal and cord blood hematocrit, a Spearman’s correlation coefficient (r) was calculated. Two-related measures were analyzed using the Wilcoxon signed rank test. Analysis of slopes was performed for comparison of arterial oxygen saturation and respiratory rate for awake infants at different time intervals by the general linear models for repeated measures analysis in anemic and non-anemic women. All reported confidence intervals are 95% and all reported P values are two-sided. Statistical analyses were carried out using SPSS for Windows version 10.1 (SPSS Corporation, Chicago, IL).

**RESULTS**

The 36 mother-infant pairs included in the study remained in the area for the study period. None of the mothers or infants reported using medications, drinking alcohol, or smoking during their pregnancies or needed supplemental oxygen at any time. None of the mothers had meconium-stained fluid at delivery. The mean gestational age was 38.9 weeks (Standard error of the mean [SEM] = 0.2) by the method of Capurro and others.11 Of the 36 women, 19 (53%) were anemic with a mean hematocrit of 34.9% (SEM = 1.1) compared with 43.4% (SEM = 0.3) for the 17 non-anemic women (Table 1).

The newborns had a mean umbilical cord venous blood hematocrit of 57.9% (SEM = 0.7) (Table 1). There was a moderate negative correlation between maternal and cord blood hematocrit (r = -0.57, P < 0.0001) (Figure 1). The infants born to anemic mothers had a significantly higher mean hematocrit than did those born to non-anemic women (59.9%, SEM = 0.7 versus 55.8%, SEM 1.1, respectively (P = 0.003). One anemic mother had a newborn with polycythemia (hematocrit > 65%). There was no difference in

<table>
<thead>
<tr>
<th>Feature</th>
<th>All (n = 36)</th>
<th>Anemic (n = 19)</th>
<th>Non-anemic (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age in years*</td>
<td>28.1 (1.1)</td>
<td>28.1 (1.8)</td>
<td>28.2 (1.3)</td>
<td>0.975</td>
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<tr>
<td>Median parity (range)</td>
<td>2.3 (0–8)</td>
<td>2.6 (0–8)</td>
<td>1.9 (0–5)</td>
<td>0.676</td>
</tr>
<tr>
<td>Hematocrit %*</td>
<td>38.9 (0.9)</td>
<td>34.9 (1.1)</td>
<td>43.4 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)*</td>
<td>38.9 (0.2)</td>
<td>39.0 (0.3)</td>
<td>38.9 (0.3)</td>
<td>0.674</td>
</tr>
<tr>
<td>Median Apgar score (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 minute</td>
<td>8 (8–10)</td>
<td>8 (8–10)</td>
<td>8 (8–10)</td>
<td>0.526</td>
</tr>
<tr>
<td>At 5 minutes</td>
<td>9 (8–10)</td>
<td>9 (8–10)</td>
<td>9 (8–10)</td>
<td>0.445</td>
</tr>
<tr>
<td>Males, no. (%)</td>
<td>20 (56)</td>
<td>9 (47)</td>
<td>11 (65)</td>
<td>0.478</td>
</tr>
<tr>
<td>Mean birth weight (g)*</td>
<td>3,178 (56)</td>
<td>3,231 (78)</td>
<td>3,120 (79)</td>
<td>0.328</td>
</tr>
<tr>
<td>2,500–3,500 (%)</td>
<td>29 (81)</td>
<td>15 (79)</td>
<td>14 (82)</td>
<td>0.797</td>
</tr>
<tr>
<td>&gt;3,500 (%)</td>
<td>7 (19)</td>
<td>4 (21)</td>
<td>3 (18)</td>
<td></td>
</tr>
<tr>
<td>Cord blood hematocrit %*</td>
<td>57.9 (0.7)</td>
<td>59.9 (0.7)</td>
<td>55.8 (1.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Polycythemia (hematocrit &gt; 65)</td>
<td>1 (3)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0.999</td>
</tr>
</tbody>
</table>

* Values for continuous variables are given as the mean (standard error in parentheses).
SaO$_2$ or respiratory rate in awake or sleeping children, born to mothers with or without anemia, initially or over the four-month observation period.

The mean SaO$_2$ for both awake and asleep states among all the infants decreased through the first week ($P < 0.0001$, $P < 0.008$), then increased significantly ($P < 0.0001$, $P < 0.0001$) until four months of age (Figure 2). The same trend was found for infants born to both anemic mothers and those born to non-anemic mothers.

The SaO$_2$ levels for the infants while awake were significantly greater than for infants while feeding ($P < 0.02$) and while asleep ($P < 0.01$) at all ages studied. Respiratory frequency in awake infants decreased rapidly after delivery until the 24th hour of life, reaching a nadir at one week of age ($P < 0.0001$) and then remaining stable from two weeks to four months of age (Figure 3).

**DISCUSSION**

This study demonstrated a high prevalence of anemia in women giving birth to children of normal birth weight at high altitudes at a Peruvian Andean hospital. In these Peruvian women living at high altitudes, maternal anemia was not a risk factor for newborn anemia or hypoxemia.

Maternal anemia is common in both developed and developing countries, yet its effect on neonatal hematocrit levels has not been well explored. An article from Nigeria$^{18}$ and one from Turkey$^{19}$ demonstrated that low-altitude mothers that are anemic have neonates that are not anemic. Furthermore, the Turkish study demonstrated that maternal anemia present in women living at low altitudes was attended by increased fetal erythropoietin levels and increased erythropoesis.$^{19}$ Our study in Peru is the first to demonstrate that at high altitude maternal anemia does not adversely affect either the infant’s hematocrit or oxygen content. Moreover, no infant born to an anemic woman was anemic, demonstrating the ability of the fetus to adapt to maternal anemia even under conditions of high altitude.

The SaO$_2$ levels of infants born to anemic and non-anemic mothers were similar. Both the mother and fetus have several mechanisms for adapting to the oxygen demands of a fetus. Oxygen delivered to the fetus depends on utero-placental blood flow, maternal Hb, ventilation, and maternal oxygen saturation.

The inverse relationship between maternal and newborn hematocrit suggests that fetal hematopoiesis can successfully compensate for maternal anemia. The fetus may be protected from hypoxemia by increased blood flow and improved fetal oxygen extraction occurring as a response to maternal anemia at high altitudes. Data demonstrating these mechanisms are only available from studies in sheep.$^{9,10}$ One of the factors that may influence this adaptation may be a greater hemodilution during pregnancy at higher altitudes than that found
during pregnancy at sea level, resulting in an enhanced placental perfusion.\textsuperscript{12}

On the fetal side, at high altitudes newborns have enhanced erythropoiesis and high levels of blood Hb F, and as a result have much less severe intrauterine hypoxia than do children born to women native to low altitudes.\textsuperscript{4,20} After birth, although the neonate has a high level of Hb F, its high affinity for oxygen may actually limit the release of oxygen from red blood cells. In contrast, a postnatal increase in the level of 2,3-diphosphoglycerate promotes the release of oxygen from Hb and thus lowers SaO\textsubscript{2} for a given partial pressure of arterial oxygen in the first week of life at sea level.\textsuperscript{21}

Infants in our study had SaO\textsubscript{2} curves very similar to infants born to both Tibetan women and to American women living at a high altitude in Leadville, Colorado.\textsuperscript{6,13} The decrease in SaO\textsubscript{2} during the first week of life and the increase thereafter was consistent with previous observations with similar experimental designs at 3,658 meters and 3,100 meters.\textsuperscript{6,13} Our study also demonstrated that throughout the four-months of the study period, infants born to anemic mothers did not show any difference in their SaO\textsubscript{2} levels compared with those born to non-anemic mothers. This would be expected due to their higher Hb levels.

Infants had higher oxygenation levels while awake compared with when feeding or sleeping. This was also reported in previous studies in Colorado, Tibet, Bolivia, and Peru.\textsuperscript{6,13,22,23} As such, studies on infants at high altitudes need to standardize values based on the activity of the baby.\textsuperscript{14}

Maternal anemia at high altitudes does not adversely affect hematocrit or newborn oxygen content among normal weight infants. There is a need for studies in neonates that examine the mechanism for this successful adaptation at high altitudes.

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REFERENCES


![FIGURE 3. Mean respiratory rate in infants at 3,750 meters while awake and asleep. Left panel: 10 minutes to 24 hours; right panel: 10 minutes to 4 months. The data of infants born to both anemic women and non-anemic women are pooled since there was no difference in respiratory rate between the two groups.](image-url)


