Glucose Metabolism in Pregnancy at High Altitude

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OBJECTIVE — To assess insulin sensitivity and β-cell function associated with lower maternal fasting plasma glucose levels at high altitude compared with sea level.

RESEARCH DESIGN AND METHODS — We studied 215 pregnant women at 8–42 weeks of gestation in Peru. The women were recruited from Cerro de Pasco, which is situated 4,370 m (14,340 feet) above sea level, and Lima, which is at sea level. We also examined 53 nonpregnant control subjects (22 in Cerro de Pasco and 31 in Lima). Fasting plasma glucose, insulin, C-peptide, and proinsulin concentrations were measured in samples obtained from the antecubital vein between 8:00 A.M. and 10:00 A.M. after an overnight period of fasting for 10–14 h. Insulin resistance and β-cell function were calculated using homeostasis model assessment.

RESULTS — Fasting C-peptide levels and β-cell function were similar, fasting concentrations of insulin and proinsulin were lower, and insulin sensitivity was higher at high altitude compared with sea level.

CONCLUSIONS — Maternal fasting plasma glucose that is lower at high altitude than at sea level in the presence of similar insulin secretion is associated with higher peripheral insulin sensitivity. This may partly explain the lower birth weights at high altitudes.

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Pregnancy is a state of increased insulin resistance and insulin secretion and of reduced hepatic insulin extraction (1). Fasting glucose concentrations are lower in pregnant women than in nonpregnant women, but the postprandial increase in glucose and insulin is substantially higher in the third trimester of pregnancy than in nonpregnant control subjects (2). Because transplacental transfer of glucose is directly proportional to maternal blood glucose (3), these higher maternal postprandial glucose levels would render more of the ingested glucose available to the fetus.

In male subjects acclimatized to high altitude over a period of 3 weeks, fasting insulin does not change, although plasma glucose is lower than at sea level because of increased glucose utilization (4). In women studied under similar conditions at high altitude, fasting glucose levels were also lower, although carbohydrate utilization was decreased compared with sea level (5). We have shown that in women native at high altitude, fasting plasma glucose is lower than at sea level, and in pregnancy the levels decrease further (6).

This study aimed to compare the insulin sensitivity and β-cell function of pregnant women and nonpregnant control subjects living at high altitude with those of women living at sea level. This was done by measuring fasting insulin, proinsulin, and C-peptide concentrations in peripheral venous blood and by subsequent homeostasis model assessment (HOMA) (7).

RESEARCH DESIGN AND METHODS — Samples of venous blood were obtained from 215 pregnant women in Peru. The subjects were attending for routine antenatal care at 8–42 weeks of gestation at the District Hospital in Cerro de Pasco (14,340 feet above sea level) and the Instituto Materno-Perinatal in Lima (sea level). Venous blood samples were also obtained from 53 nonpregnant control subjects (22 in Cerro de Pasco and 31 in Lima). All women gave written consent to participate in the study, which was approved by the ethics committee of the Peruvian Ministry of Health. Only Mestizos who had both native Quechuas and Spanish ancestry, who were permanent residents, and whose parents and grandparents were born and had lived at the same altitude were included. None of the participants had a family history of diabetes. Gestation was calculated from the maternal last menstrual period and ultrasound biometry. Maternal age, BMI, level of education, and gestational age are compared in Table 1.

Maternal PO2 and pH were measured in all patients with a portable blood gas analyzer (OPTI 1; AVL, Graz, Austria) using solid-state single-use optical fluorescence cassettes. Full 1-point gas calibration for PO2 was performed automatically after insertion of each cassette. Stable standard reference cassettes were used for verification of low, medium, and high levels. Arterialized capillary samples were taken from the ear lobe. Samples obtained by this method have been shown to have blood gas contents similar to arterial samples.

Maternal hematocrit was determined by the microcapillary method.

Plasma glucose concentrations were determined immediately by the glucose oxidase/peroxidase method (Gluco Touch; LifeScan, Milpitas, CA) in samples obtained from the antecubital vein between 8:00 A.M. and 10:00 A.M. after an overnight period of fasting for 10–14 h. This glu-
Glucose metabolism at high altitude

Table 1—Maternal characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sea level</th>
<th>High altitude</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregnant</td>
<td>Nonpregnant</td>
</tr>
<tr>
<td>n</td>
<td>123</td>
<td>31</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>25.3 (8.3)</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25.5 (7.0)**†</td>
<td>29.4 (6.2)†</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3 (+1.1)</td>
<td>23.0 (3.7)*</td>
</tr>
<tr>
<td>Secondary school</td>
<td>72.3</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are n, mean (1 SD), or %. *P < 0.05 for the difference between sea level and high altitude; †P < 0.05 for the difference between pregnant and nonpregnant groups.

Table 2—Measured and derived variables

<table>
<thead>
<tr>
<th></th>
<th>Sea level</th>
<th>High altitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>123</td>
<td>31</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.66*** (0.44)</td>
<td>5.33*** (0.61)</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>43.8*** (34.80)</td>
<td>53.4*** (29.4)</td>
</tr>
<tr>
<td>Proinsulin (pmol/l)</td>
<td>6.60* (5.30)</td>
<td>6.00 (7.60)</td>
</tr>
<tr>
<td>C-peptide (pmol/l)</td>
<td>0.43 (0.25)</td>
<td>0.40 (0.20)</td>
</tr>
<tr>
<td>Insulin sensitivity (%)</td>
<td>121.0*** (96.9)</td>
<td>97.4*** (56.1)</td>
</tr>
<tr>
<td>β-cell function (%)</td>
<td>97.3 (53.5)</td>
<td>84.5* (23.0)</td>
</tr>
<tr>
<td>C-peptide-to–insulin ratio</td>
<td>9.11*** (4.27)</td>
<td>7.98*** (1.70)</td>
</tr>
</tbody>
</table>

Statistical analysis

In this cross-sectional study, the Kolmogorov Smirnov test was used to assess the normality of the data. Glucose, maternal age, and BMI values were normally distributed. Insulin, C-peptide, insulin sensitivity, and β-cell function values and the C-peptide–to–insulin ratio were not normally distributed and were thus log-transformed for regression analysis.

Pregnant and nonpregnant groups were compared separately at sea level and high altitude by multiple regression analysis, adjusting for maternal age, BMI, and gestational age. Significant interaction in our data indicated that the difference was small in early pregnancy and increased with gestation.

RESULTS

Fasting plasma glucose, insulin, proinsulin, and C-peptide concentrations and insulin sensitivity, β-cell function, and the C-peptide–to–insulin ratio at sea level and high altitude in pregnant women and nonpregnant control subjects are compared in Table 2.

Fasting plasma glucose

Fasting plasma glucose has been described previously (6). In brief, levels were lower at high altitude than at sea level. In the pregnant groups, there was significant interaction between group and gestation (P = 0.028), i.e., the difference between high altitude and sea level was small in early pregnancy and increased with gestation.

Insulin

Fasting insulin concentration in nonpregnant control subjects was lower at high altitude than at sea level (ratio 0.57; P = 0.001). At sea level, the fasting insulin concentration of the pregnant group at 10

Data are median (interquartile range). *P < 0.05 for the difference between sea level and high altitude; †P < 0.05 for the difference between pregnant and nonpregnant groups.
weeks was ~45% lower than it was in nonpregnant control subjects and increased with gestation \(y = \exp[3.2 + 0.024 \times \text{gestation}]\); \(R^2 = 0.208; P < 0.001\), so the concentration at 40 weeks was similar to nonpregnant values. At high altitude, there was no significant difference between pregnant women and nonpregnant control subjects (ratio 1.07; \(P = 0.56\)), and there was no significant change with gestation (\(R^2 = 0.013; P = 0.28\)). In the pregnant groups, there was significant interaction between group and gestation (\(P = 0.028\)) (Fig. 1).

**Insulin sensitivity**

Insulin sensitivity in nonpregnant control subjects was higher at high altitude than at sea level (ratio 1.18; \(P = 0.001\)). At sea level, insulin sensitivity decreased with gestation \(y = \exp[5.388 - 0.0235 \times \text{gestation}]\); \(R^2 = 0.122; P < 0.001\) after an initial increase of ~50%. At high altitude, there was no significant difference between pregnant and nonpregnant levels (ratio 0.94; \(P = 0.62\)), nor was there a significant change with gestation. In the pregnant groups, there was significant interaction between group and gestation (\(P = 0.044\)) (Fig. 1).

**β-cell function**

β-cell function in nonpregnant control subjects was lower at high altitude than at sea level (ratio 0.77; \(P = 0.039\)) but not significantly different in the pregnant groups (0.98; \(P = 0.77\)). There was a significant increase with gestation \(y = \exp[4.189 + 0.01562 \times \text{gestation}]\); \(R^2 = 0.205; P < 0.001\). At sea level, after an initial drop of ~10%, the β-cell function increased to levels ~30% higher than those of the control subjects. At high altitude, β-cell function of the pregnant groups at 10 weeks of gestation was similar to that of nonpregnant control subjects but increased with gestation, so at 40 weeks it was ~40% higher than that of nonpregnant control subjects (Fig. 2).

**C-peptide**

Plasma C-peptide concentration was not significantly different between high altitude and sea level in both the nonpregnant control subjects (ratio 1.10; \(P = 0.48\)) and in the pregnant groups (ratio 0.96; \(P = 0.525\)). There was a significant increase with gestation \(y = \exp[-1.355 + 0.01786 \times \text{gestation}]\); \(R^2 = 0.244; P < 0.001\). Fasting C-peptide values in pregnant women at 10 weeks were similar to nonpregnant control subjects but increased with gestation, thus at 40 weeks the levels were ~30% higher (Fig. 2). There was a high correlation between C-peptide and β-cell function (\(R = 0.582; P < 0.001\)).

**C-peptide–to–insulin ratio**

The C-peptide–to–insulin ratio was significantly higher at high altitude than at sea level, both in pregnant women (ratio 1.26; \(P < 0.001\)) and in nonpregnant control subjects (ratio 1.93; \(P < 0.001\)). At sea level, the C-peptide–to–insulin ra-
The data of this study demonstrate that compared with those at sea level, pregnant women native at high altitude have similar levels of C-peptide and \( \beta \)-cell function; lower fasting concentrations of glucose, insulin, and proinsulin; higher insulin sensitivity; and a higher C-peptide–to–insulin ratio. The BMI or socioeconomic status, as assessed by the level of education, could not explain these differences. They are thus unlikely to reflect differences in nutrition or levels of activity between the two groups. At high altitude, there is a potential interference of changes in hematocrit, pH, and \( \text{PO}_2 \) with the measurement of plasma glucose. However, the glucose monitoring device was used within manufacturers specifications, and we have specifically studied the effects of change in pH (up to \( \sim 8 \)) and hematocrit (increase from 41 to 48%) and have found them to be negligible (6). Thus, we believe that our findings regarding glucose values at high altitude are real and do not represent a methodological artifact.

At sea level, there was an initial decrease in glucose in the first trimester, as previously described (6). This confirms other reports (2) and is possibly due to a \( \sim 15\% \) increase in plasma volume (11) and higher insulin sensitivity, as suggested by lower insulin concentrations. Thereafter, insulin sensitivity decreased, and insulin secretion and C-peptide levels increased with gestation. It is well known that in normal pregnancy, insulin secretion in response to glucose is increased and hormones of placental origin augment the secretory responsiveness of the pancreatic islet cells. For example, the administration of progesterone to nonpregnant rats enhances insulin secretion and stimulates cell proliferation within the islets of Langerhans. Resistance to insulin action is increased by progesterone and other placental products, such as human placental lactogen, prolactin, and cortisol (12,13).

At high altitude, fasting plasma glu-
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Krampl and Associates

References


13. Freinkel N: Banting Lecture 1980: Of...


