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 P_{O_2} 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 P_{O_2} 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-

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Abbreviations: HOMA, homeostasis model assessment

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Maternal characteristics*

	Sea level		High altitude	
	Pregnant	Nonpregnant	Pregnant	Nonpregnant
n	123	31	92	22
Gestation (weeks)	25.3 (8.3)	—	24.4 (7.5)	—
Age (years)	25.5 (7.0)*†	29.4 (6.2)†	27.7 (5.8)*	30.1 (6.0)
BMI (kg/m^2)	24.3 (4.1)	23.0 (3.7)*	24.4 (3.0)†	26.7 (3.3)*†
Secondary school	72.3	—	73	—

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.

cose reflectance meter has been shown to be independent of changes in the following variables: pH within a range of 6.94 to 7.84 (8), hematocrit between 25 and 60%, and P_{O_2} within a range of 47 to 467 mmHg (9). Hematocrit, P_{O_2}, and pH values of the patients in this study were all within these limits. The mean hematocrit in our populations at sea level and at high altitude was 37% (range 29–42) and 45% (range 38–59), respectively; the mean pH was 7.45 (7.44–7.50) and 7.50 (7.44–7.57), respectively; and the mean P_{O_2} was 99.8 mmHg (80–115) and 52.8 mmHg (47–63), respectively. Plasma glucose was measured immediately because storage is associated with a decrease in glucose concentration (10).

Blood for measurement of insulin and C-peptide concentrations was collected into tubes containing EDTA and placed on ice. Within 2 h, samples were centrifuged at 3,000 rpm for 10 min, and plasma was frozen at –20°C until analysis at sea level (Vienna, Austria). Insulin, C-peptide, and proinsulin levels were measured by radioimmunoassays from Pharmacia-Upjohn (Uppsala, Sweden), CIS (Gif-Sur-Yvette, France), and Linco (St. Charles, MO), with intra- and interassay variations of ≤8, ≤9, and ≤8%, respectively. Insulin sensitivity and β-cell function were calculated by HOMA (7) using the nonlinear version incorporated in a computer program. This model is based on the fact that fasting plasma glucose and insulin concentrations are set at a level that is characteristic for the individual and that is determined by the interaction of glucose and insulin in a feedback loop. Comparison of fasting values with the HOMA model allows quantitative assessment of insulin sensitivity and β-cell function.

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 group (pregnant = 1, nonpregnant = 0). For comparisons between sea level and high altitude, the pregnant and nonpregnant groups were analyzed separately; the coefficient of altitude (sea level = 0, high altitude = 1) estimated the difference between high altitude and sea level, and regression analyses were also adjusted for maternal age, BMI, and gestation. Anti-log transformation of the group and altitude coefficients yielded the pregnant-to-nonpregnant ratio and the high altitude–to–sea level ratio, respectively. Interaction between the population and gestational age was calculated by adding a "gestational age* group" term to the regression model to assess whether the difference between the groups changes with gestational age. Significant interaction in our data indicated that the difference was small in early pregnancy and increased with gestation.

Plasma proinsulin concentrations were below the lower limit of detection of 2 pmol/l in 26 pregnant subjects (28.0%) and in 3 subjects (2.4%) at sea level. The χ^2 test was thus used to compare proinsulin levels. The *t* test and χ^2 test were used to compare maternal characteristics as appropriate. Analyses were performed using SPSS 8.0.0 for Windows (SPSS, Chicago, IL).

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

Table 2—*Measured and derived variables*

	Sea level		High altitude	
	Pregnant	Nonpregnant	Pregnant	Nonpregnant
n	123	31	92	22
Glucose (mmol/l)	4.66*† (0.44)	5.33*† (0.61)	4.39*† (0.56)	4.97*† (0.56)
Insulin (pmol/l)	43.8*† (34.80)	53.4*† (29.4)	31.5* (16.35)	35.1* (28.8)
Proinsulin (pmol/l)	6.60* (5.30)	6.00 (7.60)	3.55*† (4.88)	6.55† (7.28)
C-peptide (nmol/l)	0.43 (0.25)	0.40 (0.20)	0.40† (0.18)	0.46† (0.26)
Insulin sensitivity (%)	121.0*† (96.9)	97.4*† (56.1)	166.9* (80.0)	148.5* (129.3)
β-cell function (%)	97.3 (53.5)	84.5* (23.0)	90.2† (38.7)	73.3*† (39.4)
C-peptide–to–insulin ratio	9.11*† (4.27)	7.98*† (1.70)	11.95*† (5.45)	13.72*† (6.76)

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 ($y = \exp[-1.355 + 0.01786 \times \text{gestation}]$; $R^2 = 0.241$; $P < 0.001$). 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 ($R = 0.582$; $P < 0.001$).

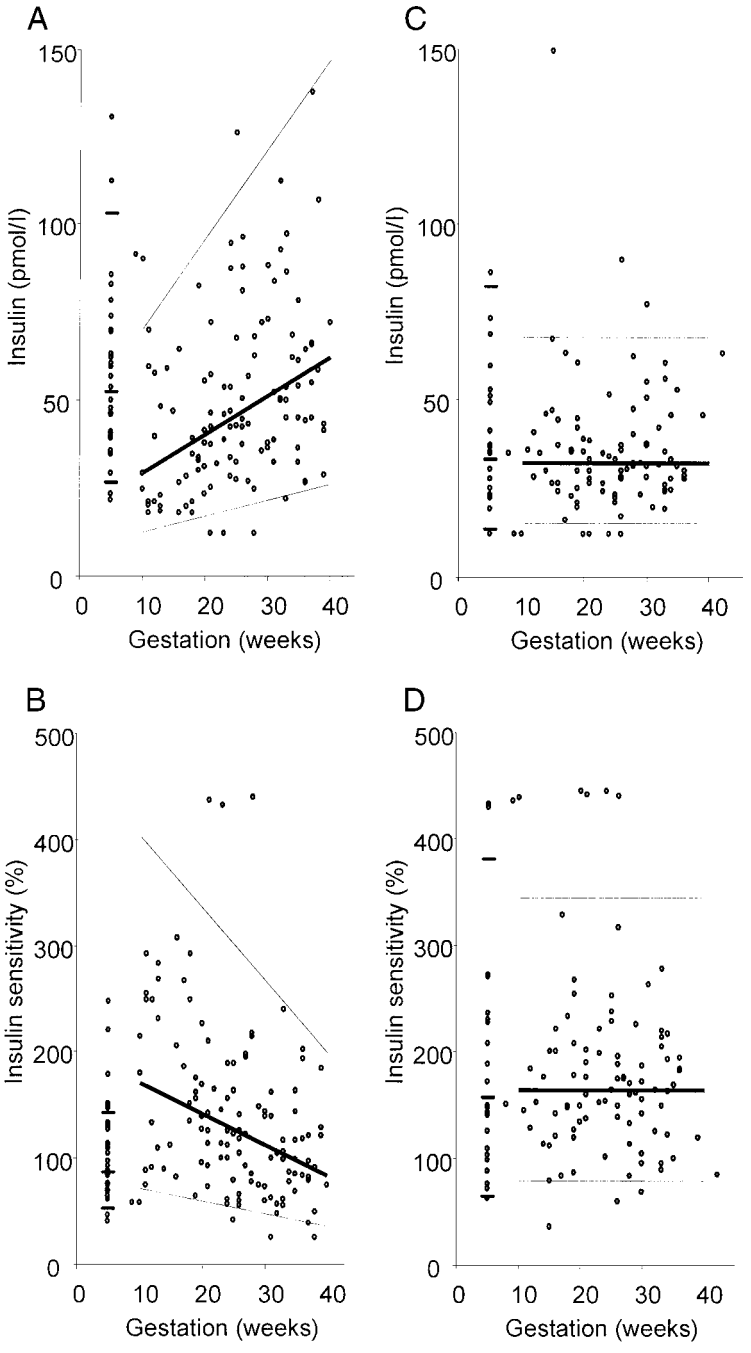

Figure 1—*Individual values of fasting plasma insulin concentration and insulin sensitivity at sea level (A and B) and high altitude (C and D). The long horizontal and diagonal lines are the 5th, 50th, and 95th centiles for values in pregnant women. The circles plotted at 5 weeks of gestation are the values from the nonpregnant control subjects, and the short horizontal lines are the 5th, 50th, and 95th centiles.*

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-

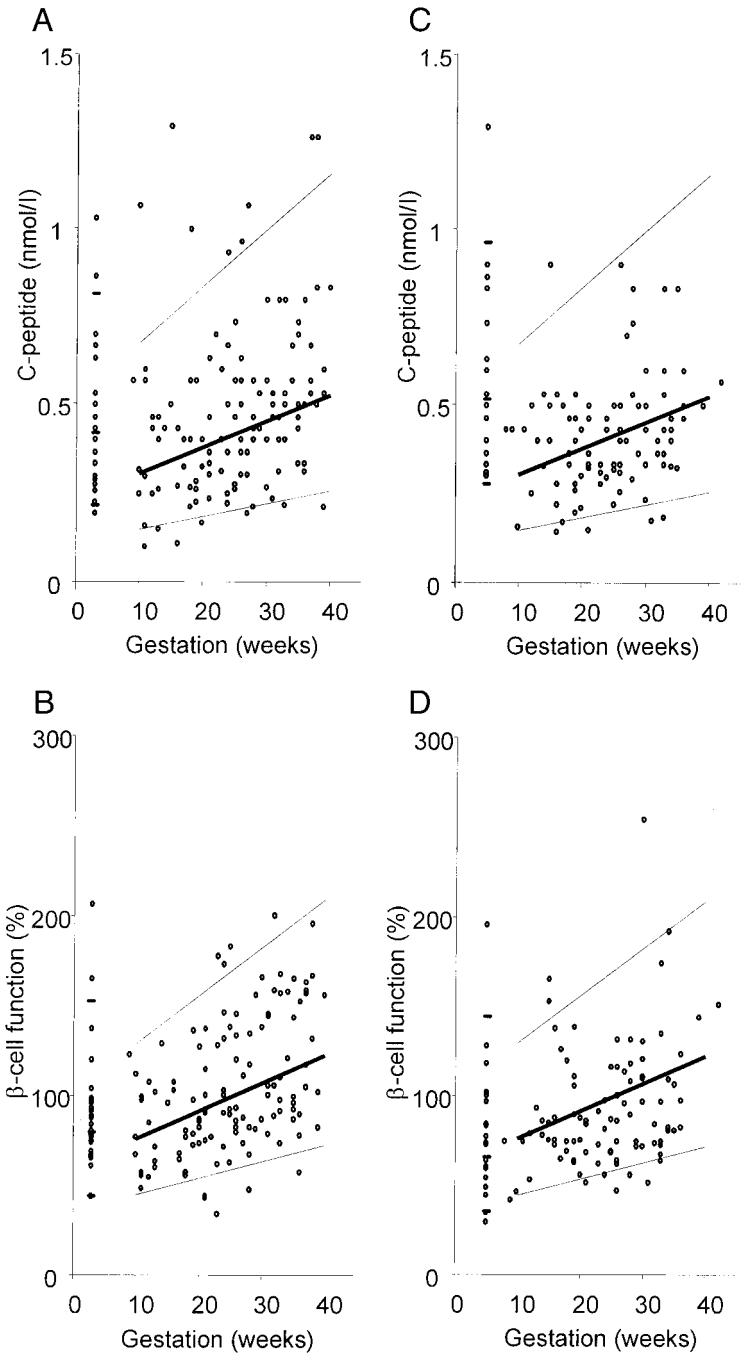

Figure 2— *Individual values of fasting plasma C-peptide concentration and β-cell function at sea level (*A *and* B*) and high altitude (*C *and* D*). The diagonal lines are the 5th, 50th, and 95th centiles for values in pregnant women. The circles plotted at 5 weeks of gestation are the values from the nonpregnant control subjects, and the short horizontal lines are the 5th, 50th, and 95th centiles.*

tio was higher in pregnant women than in nonpregnant control subjects (ratio 1.186; $P = 0.023$); however, at high altitude, the C-peptide–to–insulin ratio was lower in pregnant women than in nonpregnant control subjects (ratio 0.74; $P = 0.001$). There was no significant change with gestation at either sea level ($R^2 = 0.001$; $P = 0.691$) or high altitude ($R^2 = 0.008$; $P = 0.406$).

Proinsulin

Plasma proinsulin concentration was not significantly different between high altitude and sea level in the nonpregnant control subjects ($Z = -0.16$; $P = 0.87$). In the pregnant groups, fasting proinsulin levels were lower at high altitude than at sea level ($Z = -4.61$; $P < 0.001$). There was no significant difference between pregnant and nonpregnant groups at sea level ($Z = -0.48$; $P = 0.63$). At high altitude, proinsulin levels were lower in pregnant women than in nonpregnant control subjects ($Z = -2.76$; $P = 0.006$).

CONCLUSIONS — 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 β-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 P_{O_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 ~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 ~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-

cose, insulin, and proinsulin levels were lower and insulin sensitivity was higher than at sea level. Fasting glucose levels in nonpregnant control subjects were lower at high altitude than at sea level, but the drop in early pregnancy was far less pronounced than at sea level. This may reflect the smaller degree of hemodilution observed during pregnancy at high altitude (14). The further drop in fasting plasma glucose concentration in the absence of higher insulin levels may be attributable to an insulin-independent increase in glucose utilization. It is recognized that any given exercise task at altitude will be accomplished at a relatively greater effort than at sea level, and it is thus conceivable that pregnancy has greater energy requirements at high altitude than at sea level. Because of the lower maximum aerobic capacity at high altitude, the relative increase in metabolic rate during pregnancy may be greater at high altitude than at sea level. Therefore, carbohydrate oxidation would be the preferred metabolic pathway for aerobic exercise, because it provides the highest ATP yield per mole O_2 (15). At high altitude, the net glucose uptake into leg muscles in male subjects is increased compared with sea level (4). However, this effect could not be demonstrated in nonpregnant female subjects studied under similar conditions (5). Alternatively, hepatic glucose production, which increases with gestation at sea level (16), may fail to do so at high altitude.

Fasting insulin concentration was lower at high altitude than at sea level and did not increase with gestation. Our findings suggest that this is due to higher insulin sensitivity rather than impaired β-cell function. The HOMA model we used compares well with several tests of insulin sensitivity and β-cell function, including the insulin tolerance test and the hyperglycemic clamp (17,18). In addition, there was a highly significant correlation between C-peptide concentrations and β-cell function, and, like the derived β-cell function, C-peptide levels were not significantly different between high altitude and sea level. C-peptide and insulin are secreted in equimolar amounts from the β-cells, but because of the lack of hepatic extraction in peripheral blood, C-peptide measurements better reflect the secretory function of the β-cell (19).

Proinsulin concentrations were lower at high altitude compared with sea level. Normally, ~3% of the proinsulin escapes the cleavage into insulin, and C-peptide and can be detected in the portal circulation. In diabetes, plasma proinsulin levels increase, reflecting β-cell damage (20). We found the opposite in our population at high altitude, suggesting highly functional pancreatic β-cells.

Despite similar insulin secretion, fasting plasma insulin levels were lower at high altitude compared with sea level. This may be attributable to increased hepatic or placental insulin extraction. At high altitude, the C-peptide–to–insulin ratio was significantly higher than that at sea level, both in pregnant women and in nonpregnant control subjects. This may suggest that a higher proportion of newly secreted insulin is taken up by the liver. In acute exposure to high altitude, hepatic blood flow is increased (21), but no studies have investigated hepatic insulin clearance in pregnancy at high altitude. Alternatively, insulin extraction by the placenta may be increased at high altitude. The placenta at high altitude is larger, and the surface of the trophoblast villi, which contains the functional cells of the placenta, is greater than at sea level (22). In pregnancy at sea level, there is some evidence that this increased turnover may be the consequence of insulin degradation by the placenta (23), but several studies suggest that the extraction of insulin by the placenta in monotocous species (such as humans) may not be great enough to increase the fractional rate of maternal insulin turnover to a detectable degree (24).

Birth weight is dependent on the availability of both oxygen and glucose. The decrease of birth weight with altitude is generally attributed to hypoxemic hypoxia (25–27). At sea level, there is a well-described association between birth weight and maternal glucose metabolism, and there is a negative correlation between insulin sensitivity and birth weight (28). Therefore, our findings of low maternal fasting plasma glucose associated with high peripheral insulin sensitivity at high altitude may partly explain the lower birth weights at high altitude.

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