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Augmented uterine artery blood flow and oxygen delivery protect Andeans from altitude-associated reductions in fetal growth

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Julian CG, Wilson MJ, Lopez M, Yamashiro H, Tellez W, Rodriguez A, Bigham AW, Shriver MD, Rodriguez C, Vargas E, Moore LG. Augmented uterine artery blood flow and oxygen delivery protect Andeans from altitude-associated reductions in fetal growth. *Am J Physiol Regul Integr Comp Physiol* 296: R1564–R1575, 2009. First published February 25, 2009; doi:10.1152/ajpregu.90945.2008.—The effect of high altitude on reducing birth weight is markedly less in populations of high- (e.g., Andeans) relative to low-altitude origin (e.g., Europeans). Uterine artery (UA) blood flow is greater during pregnancy in Andeans than Europeans at high altitude; however, it is not clear whether such blood flow differences play a causal role in ancestry-associated variations in fetal growth. We tested the hypothesis that greater UA blood flow contributes to the protection of fetal growth afforded by Andean ancestry by comparing UA blood flow and fetal growth throughout pregnancy in 137 Andean or European residents of low (400 m; European $n = 28$, Andean $n = 23$) or high (3,100–4,100 m; European $n = 51$, Andean $n = 35$) altitude in Bolivia. Blood flow and fetal biometry were assessed by Doppler ultrasound, and maternal ancestry was confirmed, using a panel of 100 ancestry-informative genetic markers (AIMs). At low altitude, there were no ancestry-related differences in the pregnancy-associated rise in UA blood flow, fetal biometry, or birth weight. At high altitude, Andean infants weighed 253 g more than European infants after controlling for gestational age and other known influences. UA blood flow and O_2 delivery were twofold greater at 20 wk in Andean than European women at high altitude, and were paralleled by greater fetal size. Moreover, variation in the proportion of Indigenous American ancestry among individual women was positively associated with UA diameter, blood flow, O_2 delivery, and fetal head circumference. We concluded that greater UA blood flow protects against hypoxia-associated reductions in fetal growth, consistent with the hypothesis that genetic factors enabled Andeans to achieve a greater pregnancy-associated rise in UA blood flow and O_2 delivery than European women at high altitude.

genetic adaptation; hypoxia; intrauterine growth restriction; uteroplacental blood flow

HIGH-ALTITUDE RESIDENCE EXERTS a powerful influence on birth weight due to a diminution in fetal growth after 28 wk gestation (11, 15, 26). Of interest in understanding the mechanisms responsible is the observation first made by Jere Haas that Andean relative to European residents of South America were protected from this altitude-associated reduction in birth weight (9). We have confirmed this observation more recently, showing that Andean compared with European babies have a five-fold lower risk of being born small-for-gestational age (SGA) at high altitude (13). Our studies in Tibetans, another multigenerational high-altitude population, also demonstrate protection from altitude-associated reductions in birth weight when compared with Han ("Chinese"), a population that has more recently emigrated to high altitude (19).

Maternal physiological responses to pregnancy contribute importantly to altitude-associated reductions in fetal growth. Colorado women residing at 3,100 m demonstrate only half as much increase in uterine artery (UA) diameter with pregnancy as their low-altitude counterparts, with such differences being present well before the onset of altitude-associated reductions in fetal growth (12, 34). Moreover, maternal physiological responses to pregnancy distinguish multigenerational Andean or Tibetan high-altitude populations from shorter-resident groups. Specifically, Tibetans have greater UA blood flow velocity and redistribution of pelvic flow to favor the UA during the third trimester than Han (Chinese) at 3,600 m (20), and Andeans have 36% greater third-trimester UA blood flow than European women living at high altitude (31).

Such generational differences in the duration of high-altitude residence provide insight not only into the physiological processes involved but also the potential role of genetic mechanisms. Recently, two interpretations of Andean protection from altitude-associated reductions in fetal growth have been suggested. One is that the Andeans' greater uteroplacental blood flow plays a causal role in affording protection from altitude-associated reductions in fetal growth (31); this is supported by ancestry-group differences in UA blood flow that are present well before the onset of altitude-associated reductions in fetal growth. The other is that Andean-European differences in birth weight are likely placental rather than maternal in origin (i.e., fetoplacental glucose transport or utilization) as demonstrated by equivalent altitude-associated reductions in UA blood flow and O_2 delivery in Andean vs. European women at 38 wk of pregnancy (33, 35). Thus, whether maternal factors contribute to ancestry-group differences in birth weight at high altitude or whether such birth weight differences are due entirely to fetoplacental characteristics is unclear.

What is needed to distinguish between these two competing hypotheses are serial studies in Andean and European residents at both low and high altitude, as well as the inclusion of

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measurements made in the nonpregnant condition. Because reductions in fetal growth are present by *week 28*, comparisons before and after this time point afford the opportunity to determine whether alterations in blood flow are the cause or the consequence of smaller fetal size. Additionally, measurements in the nonpregnant state permit distinguishing maternal responses to pregnancy from constitutional differences in the women themselves. We, therefore, tested the hypothesis that greater UA blood flow and O_2 delivery contributed to the protection against altitude-associated fetal growth reduction afforded by Andean relative to European ancestry by asking whether high-altitude Andean women had a greater rise in UA blood flow and/or UA O_2 delivery by *week 20* than their European counterparts. Conversely, we considered that evidence against our hypothesis would consist of *1)* greater UA blood flow and O_2 delivery in Andeans than Europeans, irrespective of altitude, *2*) the presence of such differences *only* near term (i.e., after the point at which altitude begins to reduce fetal growth), and/or *3*) a finding that variation in UA blood flow or O_2 delivery was unrelated to birth weight directly, suggesting that factors other than maternal O_2 delivery (e.g., placental transport, substrate utilization) were important for protecting Andean women from altitude-associated reductions in fetal growth. In addition to serial measurements during pregnancy and the inclusion of measurements made in the nonpregnant condition, we used a larger number of AIMs and applied them to the determination of maternal ancestry, unlike the prior report that based ancestry-group classification on a smaller number of AIMs and fetal (newborn) DNA (35). Given the importance of fetal growth not only for neonatal well-being but also many later-in-life disorders, we considered it especially important to understand the role of maternal determinants of UA blood flow in defending against hypoxia-associated reductions in fetal growth.

MATERIALS AND METHODS

Ethical approval. All study participants gave their written informed consent to the study procedures, which conformed to the standards set by the latest revision of the Declaration of Helsinki. Such procedures were approved by the human subject review committees of the Colorado Multiple Institutional Review Board of the University of Colorado Denver and the Colegio Médico, its Bolivian equivalent.

Subjects. Subjects consisted of 212 women that had been recruited through their prenatal care providers. Inclusion criteria were that the woman was willing to participate, receiving prenatal care, being not more than 20 wk pregnant, having a singleton pregnancy, and facing no known risk for pregnancy complications. Exclusion criteria were incomplete delivery records or blood flow data ($n = 44$), or a high degree of European-Indigenous American genetic admixture as detailed below ($n = 31$). Of the 137 remaining women, 51 resided at low altitude (Santa Cruz, 400 m), and 86 lived at high altitude (La Paz, 3,600 m or El Alto, 4,100 m) in Bolivia. Approximately half of the women were of European or other low-altitude ancestry ($n = 28$ at 400 m and $n = 51$ at 3,600–4,100 m), with the remainder being of Andean ancestry ($n = 23$ at 400 m and $n = 35$ at 3,600–4,100 m). Data for 35 of the high-altitude women and 23 of the high-altitude European women were published previously (27, 31). Here, we include an additional 25 high-altitude European women, and the group of low-altitude European ($n = 28$) and Andean ($n = 23$) controls. At the time of study, the high-altitude Andean women were living 500 m higher than the high-altitude European subjects (3,993 ± 31 m vs. 3,489 ± 33 m, $P < 0.001$). The study was conducted over a period of ~7 years (La Paz, 2000–2007; Santa Cruz, 2005–2007). The longer time period required for data collection in La Paz was due to the fewer number of European subjects available for recruitment. The same operators conducted all studies at a given study location.

Women were studied serially at *weeks 20* and *36* of pregnancy, and again 4 mo postpartum for taking measurements in the nonpregnant state. Actual times of study were 21.1 ± 0.2 and 36.0 ± 0.2 wk of pregnancy and 3.6 ± 0.2 mo postpartum. Studies were conducted at the Instituto Boliviano de Biología de Altura (Bolivian High-Altitude Biology Institute) and the Clinica del Sur (Southern Clinic) in La Paz ($P_B = 495$ mmHg) and at Clinica Siraní (Siraní Clinic) in Santa Cruz ($P_B = 725$ mmHg).

Study protocol. On the first visit, each woman completed a questionnaire in the subject's spoken language to determine her self-identified ancestry; altitude of birth; childhood and current residence; medical history; parents' and grandparents' surnames; ancestry and altitude of birth; income, educational, and marital status; body weight before pregnancy; and medical and reproductive history. Each subsequent visit consisted of a general clinical exam, followed by a blood draw and the ultrasound study.

Self-identified ancestry was verified with reference to parental and grandparental surnames, as well as by a panel of 100 AIMs (22, 23). Traditional naming practices in Bolivia require retention of maternal and paternal surnames. Such surnames can be readily distinguished as to Andean (Aymara or Quechua) vs. other population origin. Each woman was asked for both of her parent's two surnames for a total of four surnames. As validated by comparison with gene markers (7), a woman was classified as Andean if she had three or more Andean surnames. European ancestry was assigned if three or more of her surnames were of non-Hispanic European origin, or she was of European nationality. This surname-based assessment was confirmed with reference to 100 AIMs that had been selected such that 51 had large frequency differences (>30%) between European and Indigenous American populations, 65 exhibited large differences between West African and Indigenous American populations, and 53 differed between West African and European populations using methodologies that are previously described (22, 23). Details, including allele frequencies in all parental populations, DNA sequences, exact positions of single-nucleotide polymorphisms (SNPs), PCR primers, and the amplification conditions used are available from the dbSNP database (www.ncbi.nlm.nih.gov/SNP) under the submitter handle PSU-ANTH (4, 5, 24). Final assignment of Andean ancestry required that a woman have at least three Aymara or Quechua surnames, no known non-Andean parentage, and >60% Indigenous American AIMs as classified using the maximum likelihood method. Women were classified as European if they self-identified as being of European ancestry and had <50% Indigenous American AIMs or if they had >50% Indigenous American AIMs they were clearly derived from other low-altitude Indigenous American populations (e.g., Guarani, Amazonian, or Central American groups). Women who did not fit these criteria were classified as "Mestiza" (mixed Andean-European ancestry) and were excluded from this report.

The clinical exam included measurements of maternal body weight, height, triceps, and subscapular skinfolds (Lange calipers; Beta Technology , Santa Cruz, CA) as an estimate of subcutaneous adiposity. Blood pressure was measured by arm cuff sphygmomanometer and heart rate by auscultation. Blood was withdrawn from an antecubital vein for measuring hematocrit in duplicate by the microcentrifuge technique and hemoglobin in triplicate using the cyanmethemoglobin method. Arterial oxygen saturation (Sa_{O_2}) was measured in a warmed finger using a transdermal pulse oximetry (Biox 3700, Ohmeda, Louisville, KY) and arterial O_2 content (Ca_{O_2}) calculated as [(1.36·hemoglobin) × Sa_{O_2}] for estimating UA O_2 delivery (Ca_{O_2}·UA blood flow), as previously described (27).

Vessel diameters, velocities, and fetal biometry were measured percutaneously using an ATL3000 ultrasound unit configured for obstetric use with color imaging and Doppler with a 4-MHz curved linear array probe. All ultrasound and Doppler measurements were

taken by the same operator at each altitude so as to minimize interinstrument and interoperator variability for a given location. Studies began by visualizing the common iliac (CI) artery 2–3 cm anterior to the bifurcation of the external iliac (EI) and the internal iliac arteries, and the EI artery 2–3 cm posterior to the bifurcation. The UA was then measured at its crossover with the EI and its diameter recorded in longitudinal view at a high angle of insonation using the cine-loop feature so as to obtain clear, parallel vessel margins. Because it was difficult to visualize the UA without color in all subjects, and color-imaging exaggerates the diameter obtained, we measured diameter with color-imaging and then removed the effect of color imaging by using the linear relationship between the with- and without-color values in the CI artery at a similar anatomical depth as described previously (31).

After measuring diameter and using anatomical landmarks to ensure that the same portion of the vessel was being insonated, the probe was rotated and the angle of insonation and size of the sampling frame were adjusted to obtain optimal velocity signals. A minimum of three and usually at least five consecutive beats were obtained from which peak systolic velocity (PSV) and end-diastolic velocity (EDV) values were recorded. The UA pulsatility index, PI = [peak systolic velocity − peak end-diastolic velocity]/mean flow velocity; resistance index, RI = [peak systolic velocity − peak end-diastolic velocity]/peak systolic velocity; and the systolic to diastolic ratio, S/D = peak systolic/peak end-diastolic velocity were also noted. The ATL3000 High Q-Automatic Doppler Measurement mode was then selected, and the time-averaged mean flow velocity (TAM) was calculated for the same consecutive beats. The mean vessel diameter was entered, and volumetric flow calculated as ($\pi r^2 \times$ TAM $\times$ 60), where r is the vessel radius, TAM expressed as centimeters per second, and flow in milliliters per minute. Because high angels of insonation introduce considerable error into the measurement of velocity, the angle was required to be $\leq 45°$ for all flow variables. Following completion of the UA and other vessel measurements on one side, procedures were repeated for the contralateral side, and all values were averaged from the woman's right and left sides. Resistance in the vascular beds supplied by the UA was estimated as mean arterial blood pressure/average unilateral UA blood flow. The UA O_2 delivery data estimate the amount of O_2 carried by the blood through the UA and does not necessarily reflect changes in the O_2 availability to the fetus, given that the placenta also extracts O_2.

Fetal abdominal and head circumference, biparietal diameter, femur length, and the peak systolic/end-diastolic (S/D) resistance indices in the middle cerebral arteries were obtained following the maternal vessel diameter and velocity measurements as previously described (27). Birth weight, gestational age, sex, length, and head circumference were obtained from newborn medical records completed by hospital personnel at the time of birth. All of the low-altitude and 95% of the high-altitude babies were born in hospitals, with the remainder (3 Andean and 1 European) being born at home but coming to the hospital for the baby to be weighed shortly after birth. Gestational age was calculated from that estimated at the *week 20* ultrasound exam, which was within 2 wk of that calculated using the elapsed weeks from the last menstrual period in all cases. Infants were considered to be SGA births when the birth weight for gestational age and sex were less than the 10th percentile of published sea-level values (30).

Statistics. Data are expressed as the means ± SE or the 95% confidence intervals (CI) for proportions in the text, tables, and figures. Variables were tested for normality using the Kolmogorov-Smirnov test. The Mann-Whitney *U*-test was used to compare Apgar scores as they were not normally distributed. Comparisons between groups at single time points were conducted using Student's *t*-test for continuous variables and χ^2-test for nominal variables. The effects of pregnancy, ancestry, and altitude on maternal and fetal characteristics, as well as the between-group differences in these effects were determined using one-, two- or three-way analysis of variance or covariance with repeated measures. The Tukey method was used to reduce the likelihood of false positives resulting from multiple comparisons. Multiple linear regression models were used to identify the relative contribution of variables known to be related to birth weight. Actual gestational age at the time of study was used as a covariate for all comparisons involving the effects of altitude or ancestry on fetal growth. All analyses were conducted using SPSS (Chicago, IL). Differences between groups or study times and relationships between variables were considered significant when the two-tailed $P < 0.05$ unless specified otherwise, and trends were reported when $0.05 < P < 0.10$.

RESULTS

Maternal characteristics. The Andean women's genetic background was overwhelmingly Indigenous American with more than 90% and 70% of AIMs being of Indigenous American origin in the high- and low-altitude groups, respectively. The proportion of European and West African AIMs was greater in the low- than high-altitude Andean women but relatively low in both groups (Table 1). On average 66% of the European women's AIMs were of European origin, with 26% being Indigenous American and 8% African. High-altitude European women had somewhat less Indigenous American or West African admixture than the low-altitude European group. To ensure that the relative proportion of women who mothered a child within her own ancestry group was similar between altitudes, we compared mother-father pairings and found no differences between low and high altitude. Specifically, the frequencies of mother-father pairings were as follows for low and high altitude, respectively: Andean-Andean/Mestizo, 32.7% and 39.1%; Andean-European, 5.8% and 1.1%; European-European/Mestizo, 53.8% and 55.2%; European-Andean, 7.7% and 1.1%; European-Unknown, 0% and 3.4% (all, P = NS).

Among the high-altitude residents, nearly all (97%) of the Andean women had been born at high altitude (≥2,500 m), whereas this was true for only 17% of the European women ($P < 0.01$); thus, individual Andean subjects had lived at high altitude longer than the European women (Table 1). At low altitude, a smaller number of European than Andean women had ever lived at high altitude (7% vs. 33% respectively, $P < 0.05$). European high-altitude women were slightly older and fewer low-altitude Andean women had more than a secondary school education, but otherwise maternal age education levels were similar. Europeans were taller, and *week 36* body weights were greater than Andean values at both altitudes. Low-altitude Europeans also had greater sums of skinfolds and body mass index when nonpregnant than their high-altitude counterparts (Table 1). Monthly household income was greater at low than high altitude among Andean women, but just the reverse was true for the European women. No Andean or low-altitude subjects smoked, and only 5% of the 41 high-altitude European subject who reported smoking behavior during pregnancy smoked. Parity was similar among European women at both altitudes, but it was higher in the high- than low-altitude Andeans (Table 1). More women were primigravid at low than high altitude: Andean = 58% [39, 76] vs. 26% [14, 42] and European = 54% [36, 70] vs. 33% [22, 47], respectively, both $P < 0.05$). Europeans living at high altitude began their prenatal care earlier, but otherwise, onset of care was similar among groups.

Table 1. *Maternal characteristics*

Variable	Altitude	Ancestry Group: European	Ancestry Group: Andean	*P* value
AIMs, % European	Low	49.7±2.4 (28)	15.2±1.9 (23)	<0.001
	High	75.0±3.0 (51)	4.0±1.4 (35)	<0.001
	p-altitude	<0.001	<0.001	
% Indian American	Low	40.6±1.9 (28)	74.3±1.8 (23)	<0.001
	High	18.3±2.6 (51)	93.8±1.7 (35)	<0.001
	p-altitude	<0.001	<0.001	
% West African	Low	9.7±1.0 (28)	10.5±0.7 (23)	NS
	High	6.7±0.86 (51)	2.2±0.75 (35)	<0.001
	p-altitude	<0.05	<0.001	
High-altitude residence, yr	Low			NS
	High	8.9±1.5 (48)	21.3±1.6 (35)	<0.001
	p-altitude			
Age, yr	Low	26.3±1.0 (28)	26.2±1.2 (23)	NS
	High	32.3±0.6 (49)	27.0±1.1 (35)	<0.001
	p-altitude	NS	NS	
≥ Secondary education, %	Low	100 [88, 100] (28)	92 [74, 98] (24)	NS
	High	100 [93, 100] (48)	86 [71, 94] (35)	<0.05
	p-altitude	NS	NS	
Height, cm	Low	160±1 (28)	155±1 (23)	<0.01
	High	162±1.0 (51)	150±1 (35)	<0.001
	p-altitude	NS*	NS	
Skinfolds (nonpreg), mm	Low	61.5±2.6 (26)	58.4±4.0 (20)	NS
	High	42.4±3.2 (33)	43.7±2.2 (26)	NS
	p-altitude	<0.001	<0.01	
BMI (nonpreg), kg/m	Low	26.5±0.9 (26)	25.1±0.6 (20)	NS
	High	24.2±0.5 (38)	26.9±0.7 (34)	<0.01
	p-altitude	<0.05	NS	
Weight at *week 36*, kg	Low	77.2±2.5 (24)	68.6±2.8 (19)	<0.05
	High	71.7±1.3 (44)	67.0±1.5 (35)	<0.05
	p-altitude	<0.05	NS	
Household income, $/mo	Low	281±38 (20)	211±36 (16)	NS
	High	1899±321 (32)	111±12 (35)	<0.001
	p-altitude	<0.001	<0.01	
Parity, no. live births	Low	1.6±0.6 (28)	1.7±0.2 (23)	NS
	High	1.9±0.1 (49)	2.7±0.3 (35)	<0.05
	p-altitude	NS	<0.01	
Week of 1st prenatal visit	Low	20.5±0.4 (28)	20.4±1.5 (23)	NS
	High	10.3±1.0 (23)	18.7±1.3 (33)	<0.001
	p-altitude	<0.001	NS	

Values are expressed as means ± SE for continuous variables or percentages and 95% CIs for categorical variables. Sample sizes are in parentheses. AIMs, ancestry informative markers; BMI, body mass index; nonpreg, nonpregnant; NS, nonsignificant. *$0.05 < P < 0.10$.

Uterine artery (UA) blood flow. At low altitude, UA diameter doubled by *week 20* (Table 2). Time-averaged blood flow velocity (TAM) rose progressively, with no differences occurring between ancestry groups. The rise in TAM was due to increases in PSV and EDV, which, in turn, resulted from a pronounced fall in UA vascular resistance. The fall in UA resistance was likely due entirely to higher flow since mean arterial pressure was similar across the time points studied (Table 2). Unilateral UA flow rose to nearly 400 ml/min by *week 36*, with much of this rise present at *week 20* (Fig. 1*A*). European nonpregnant UA blood flows were marginally greater than the Andeans, but there were no ancestry group differences during pregnancy (Fig. 1*A*) or in the pregnancy-associated changes (Fig. 2*A*).

At high altitude, pregnancy lowered UA vascular resistance and raised UA diameter and TAM in both groups. Andean compared with European women had similar values in the nonpregnant state, but UA blood flow was markedly greater at both *weeks 20* and *36* of pregnancy (68% and 56%, respectively, both $P < 0.001$; Fig. 1*B*). Such differences were due to greater UA diameters, not flow velocity (Table 2). Of note, ancestry group differences in the increase in UA diameter and blood flow were apparent by *week 20*, after which time, the changes were equivalent between groups (Fig. 2*B*). UA vascular resistance was lower at *week 36* in the Andean than European women, but there were no ancestry-group differences in the Doppler-derived UA resistance indices (Table 2). UA O_2 delivery was nearly twofold greater in the Andean than European women at *week 36* as the result of greater UA blood flow, not Sa_{O_2} or hemoglobin concentration (Table 2).

Comparing altitudes, the Andeans had similar pregnancy-associated changes in UA blood flow and UA O_2 delivery, but these changes were much smaller in the high- than low-altitude European women (Fig. 2). Pregnancy reduced hemoglobin concentration similarly in all groups (Table 2).

Fetal biometry and newborn characteristics. At low altitude, fetal biometry measurements were similar between ancestry groups at all times (Table 3). Andean and European newborns were of similar gestational age, birth weight, length, ponderal index, head circumference, and Apgar scores (1 min). Andean newborns had lower Apgar scores at 5 min than Europeans at low altitude (Table 4).

At high altitude, Andean babies had greater biparietal diameter, head circumference, abdominal circumference, and femur length at 20 wk gestation and lower middle cerebral artery S/D ratios than their European counterparts (Table 3). Gestational age and other newborn characteristics were similar between ancestry groups, with the exception of 1 min Apgar scores being lower in Andean than European newborns and the frequency of cesarean-sections being greater in the European women. Apgar scores in each ancestry group at low or high altitude were within the normal range at both 1 and 5 min, as defined by the American Academy of Pediatrics (1).

Comparing altitudes, high-altitude Europeans had smaller biparietal diameters and femur lengths at *week 20* and smaller head circumferences at *week 36* than those living at low altitude. There were no altitude differences in Andean fetal biometry measures. Middle cerebral artery resistance S/D ratio was lower in the high- than low-altitude babies at *week 36* in both ancestry groups, with European values also tending to be lower at 20 wk (Table 3). Birth weight was similar, but gestational age was 1.4 wk earlier, and preterm deliveries were more common in the European women at low than at high altitude. Inspection of the medical records revealed that this variation in gestational age was due to the low-altitude practice of scheduling cesarean sections ~1 wk before the estimated due date to avoid the encumbrance of labor. Although more Andeans had cesarean sections at low than high altitude, Andean compared with European deliveries more often occurred at public hospitals, where cesarean sections occurred closer to the due date. Andean birth weight and gestational age were similar at the two altitudes. European babies were more often male at high than low altitude, but birth weight did not differ between the sexes. Andean sex ratios were similar at the two altitudes. There were no differences between ancestry or altitude groups in the frequency of small-for-gestational-age infants.

Given the altitude- as well as ancestry-group differences in gestational age and other variables, we used multiple regression analysis first to identify those variables whose variation was related to birth weight and then to take such influences into account. Among all subjects, as well as within the ancestry or altitude groups, birth weight was correlated positively with gestational age, income, parity, male sex, and maternal height. After adjusting for variation in these variables, birth weights remained similar in the two ancestry groups at low altitude, but Andean babies weighed 273 g more than European babies at high altitude (Table 4). Across altitudes, Andean birth weights were also similar but high-altitude European babies weighed 375 g less than their low-altitude counterparts and had lower ponderal indices as well (Table 4).

Relationship between AIMs, UA blood flow and O_2 delivery, and fetal growth. At low as well as high altitudes, higher *week 20* UA blood flow or UA O_2 delivery was associated with greater fetal head and abdominal circumference (r value = 0.22 or 0.24 and 0.25 or 0.25, respectively, all $P < 0.05$), with the correlation between UA blood flow and fetal head circumference being particularly pronounced at high altitude (r value = 0.32, $P < 0.05$). Among all subjects, women with a greater pregnancy rise in UA blood flow at *week 36* tended to deliver heavier infants (r value = 0.23, $P = 0.10$).

Among Andeans at high altitude, a higher percentage of Indigenous American AIMs was associated with larger UA diameters at 20 wk of pregnancy (Fig. 3). There was also a trend for women with a higher proportion of Indigenous American AIMs to have greater pregnancy-associated increases in UA blood flow or O_2 delivery (r values = 0.39 or 0.42, both $0.05 < P < 0.10$). A higher percentage of Indigenous American AIMs was also associated with greater fetal head circumference at 20 and 36 wk (both r values = 0.28, $P < 0.05$) and birth weight at high altitude, whether or not the other factors influencing birth weight were taken into account (Table 5).

DISCUSSION

This isthe first study to examine the effects of altitude and ancestry on maternal vascular adjustment across pregnancy and their relationship to fetal growth. Our findings are novel in three respects. First they demonstrate that both altitude and ancestry influence the magnitude by which UA blood flow and O_2 delivery increase with pregnancy. Specifically, the effects of ancestry interact with that of altitude such that women of Andean origin have a greater rise in UA blood flow and O_2 delivery with pregnancy than European women at high altitude, with no such differences present at low altitude. Second, given that at high altitude, the Andeans' UA blood flow, UA O_2 delivery, and fetal biometry were greater than European values at *week 20*, well before the onset altitude-associated reductions in fetal growth (15), our results support the hypothesis that this ancestry-related variation in UA blood flow may contribute to the protection against altitude-associated reductions in fetal growth afforded by Andean ancestry. Third, our data showing the dose-dependent relationship between the percent Indigenous American ancestry and the pregnancy rise in UA blood flow or UA O_2 delivery and birth weight at high altitude support the hypothesis that a larger pregnancy-associated rise in UA blood flow and/or UA O_2 delivery may contribute to the greater birth weights apparent in Andeans relative to Europeans at high altitude.

The conduct of these studies faced several practical constraints stemming from the nature of health care resources present in Bolivia and the necessarily long duration of these serial studies. Uneven access to health care, especially for the poorer Andean high-altitude women, meant that it was most impractical to recruit women before becoming pregnant. We, therefore, used data obtained 3–4 mo postpartum as an index of the nonpregnant state. It is possible that UA diameter or other maternal characteristics had not returned to the prepregnant condition by this time (6) but, if so, the effects of pregnancy would have been even greater than those reported here. We know of no reason to think that such residual effects of pregnancy would differ between European and Andean women, and hence are unlikely to account for the ancestry-group differences observed. The high frequency of elective cesarean sections in Latin America (28) required that we adjust birth weights by variation of gestational age, as well as for other factors known to influence birth weight to isolate the effects of ancestry and altitude. The interpretation of our data should also take into account the fact that the proportion of Indigenous American ancestry was less in the low- relative to high-altitude Andean women, whereas the opposite was true for European women. The primary reason for the higher proportion of Indigenous American ancestry in low- relative to

high-altitude European women is due to greater admixture with lowland Indigenous American groups (e.g., Guarani). However, it is possible that the lesser Indigenous American admixture in low- than high-altitude Andean women may have expanded altitude-related differences among Andean subjects; it is for this reason that we also examined the relationship between the percentage of Indigenous American ancestry within individuals, UA blood flow parameters, and fetal growth. Another issue of importance for the interpretation of our data is that since a multiyear period was required to conduct these longitudinal studies concurrently at the two altitude sites, we were unable to have the same operator make all of the ultrasound measurements. We were careful to have the same operators at a given altitude, and we attempted to guard against systematic differences between altitudes by having a member of our research team observe studies at both locations and standardize measurement procedures. However, we cannot discount the possibility that operator effects contributed to differences between altitudes. For example, slight variation in cursor location can greatly influence the diameter and flow measurements obtained, given that vessel radius is amplified by a power of two in the flow calculations. We, therefore, consider that the greatest importance should be placed on comparisons of measurements conducted by the same operator (i.e., within-altitude comparisons). Using this approach, we demonstrated that Andean women have greater UA blood flow and O_2 delivery than European women exclusively at high altitude; these data do not suggest that Andean women's unique vascular response to pregnancy is irrespective of altitude. Correspondingly, our focus here has been on ancestry-group comparisons at a given altitude and, when making comparisons across altitudes, to use the changes from the nonpregnant to the pregnant state or from *weeks 20* to *36* of pregnancy, so as to effectively remove any operator effect.

Our UA diameter values agreed with previous reports both in terms of the magnitude of pregnancy-associated changes (13, 21). Our data also agreed with prior reports of smaller values in European than Andean women at high altitude (31, 35). However, unlike prior reports, Andean women did not have larger UA diameters near term than European women at low altitude (35), nor were values smaller in the high-altitude European women than those living at low-altitude (12, 34). While study times were similar, several differences characterized the high-altitude European women in the present study from our previous Colorado studies, including the higher altitudes at which they lived, their longer individual duration of high-altitude residence, and relatively greater Indigenous American admixture. Compared with the Zamudio et al. (35) report, our measurements were made earlier in pregnancy, but it is unclear why this would affect the values obtained since there was little change in UA diameter from *weeks 20* to *36*. As remarked above, we consider the most informative comparisons to be ones conducted by the same operator; such pregnancy-associated changes agreed with prior reports, insofar as both the Colorado and the Bolivian women of European ancestry had less pregnancy-associated increases in UA diameter at high than low altitude.

Also consistent with prior reports were the similarity in Andean and European UA O_2 delivery values at low altitude and the higher levels in UA O_2 delivery observed in the high-altitude Andean than European subjects (31, 35). However, although we found equivalent UA blood flow, Sa_{O_2} and hemoglobin levels in Andean and European women at low altitude, the similarity in UA O_2 delivery values in the prior report was due to greater hemoglobin concentrations in the European subjects. Whereas our hemoglobin levels were within the normal range (16, 25), the values at high altitude reported by Zamudio et al. (35) were in the 13.0–15 g/dl range associated with increased risk for preeclampsia, preterm birth, and/or intrauterine growth restriction (29). Perhaps the higher hemoglobin values reflected the later time point studied or indicated less plasma volume expansion in the European subjects. However, there is no evidence to suggest that ancestry influences plasma volume expansion during pregnancy, as we have reported previously at high altitude in Bolivia (27), or that altitude alters the increase in blood volume with pregnancy (unpublished observations). In any event, the similarities in UA diameter, hemoglobin, as well as other factors affecting UA O_2 delivery at low altitude refuted the concept that Andeans have intrinsically greater UA diameters than Europeans during pregnancy and supported the likelihood that the larger UA diameters in the Andean than European women during pregnancy at high altitude were due to different responses to the combined stress of pregnancy and residence at high altitude.

Given that the Andean women had higher levels of UA blood flow and O_2 delivery by midgestation relative to European women at high altitude, our data suggest that one physiological mechanism by which Andean ancestry protects fetal growth at high altitude is enhanced UA O_2 delivery. This disagrees with the conclusion of Zamudio et al. (35), who concluded that maternal oxygen delivery did not contribute to altitude- or ancestry-associated differences in fetal growth. In addition to the differences already cited, their study employed a cross-sectional study design in which data were obtained at a single time point just prior to delivery, whereas our studies were conducted longitudinally. A cross-sectional design was well suited to address their primary research questions regarding the relationship between placental characteristics and birth weight, but longitudinal studies have the advantage of being able to examine the relationship between UA O_2 delivery, blood flow, and fetal growth serially during pregnancy. Our study demonstrated that UA blood flow and O_2 delivery were positively associated with fetal growth by *week 20* of pregnancy at high altitude, prior to the point at which decrements in fetal growth are thought to begin. However, despite the large differences in UA blood flow and/or O_2 delivery between Andean women and European women at high altitude, fetal biometry was relatively similar at all times. Although the absence of group differences in fetal biometry may indicate that some factor(s) other than UA blood flow or O_2 delivery were influencing fetal growth, it is also possible that limited accuracy of biometry-based measurements were not able to detect variations in fetal growth that were present at delivery and/or that differences in UA blood flow preceded measurable differences in fetal growth. Thus, overall, we considered that our data were consistent with the hypothesis that UA blood flow played an important, etiological role in reduced birth weight at high altitude. Data from the Zamudio et al. (35) study were also consistent with this hypothesis, insofar as the birth weights of European infants at high altitude were more affected (i.e., diminished) by reductions in UA blood flow or O_2 delivery than European women at low altitude or Andean

Table 2. *Maternal uterine artery blood flow characteristics*

Variable	Altitude	Ancestry	Nonpregnant	*Week 20*	*Week 36*	Time	Interaction (Time × Altitude)	
							European	Andean
UA diameter, cm	Low	European	0.26±0.01 (26)§[b,c]	0.49±0.01 (28)§[a]	0.50±0.02 (24)*[a]	<0.001	<0.01	NS
		Andean	0.21±0.01 (18)§[b,c]	0.47±0.01 (23)§[a]	0.50±0.02 (19)§[a]	<0.001		
		p-ancestry	<0.01	NS	NS			
	High	European	0.41±0.03 (33)§[b,c]	0.54±0.01(32)§[a,c]	0.54±0.01 (43)*[a,b]	<0.001		
		Andean	0.39±0.01 (14)§[b,c]	0.63±0.01 (34)§[a]	0.65±0.01 (32)§[a]	<0.001		
		p-ancestry	NS	<0.01	<0.01			
TAM, cm/s	Low	European	7.5±0.7 (26)[b,c]	24.8±1.4 (28)[a,c]	31.3±2.0 (24)[a,b]	<0.001	NS	NS
		Andean	5.9±0.5 (18)*[b,c]	24.8.5±2.0 (23)[a]	30.8±2.5 (19)[a]	<0.001		
		p-ancestry	NS	NS	NS			
	High	European	10.3±1.7 (22)[b,c]	24.9±1.9 (31)[a]	29.8±1.9 (39)[a]	<0.001		
		Andean	9.8±2.6 (5)*[c]	28.0±2.8 (20)	35.7±3.5 (26)[a]	<0.01		
		p-ancestry	NS	NS	NS			
PSV, cm/s	Low	European	39.8±3.0 (26)[b,c]	77.0±4.1 (28)[a,c]	92.7±4.1 (24)[a,b]	<0.001	NS	<0.01
		Andean	31.2±2.2 (18)§[b,c]	78.6±5.9 (23)§[a]	81.3±4.1 (19)[a]	<0.001		
		p-ancestry	NS	NS	NS†			
	High	European	45.7±3.3 (25)[b,c]	69.5±4.3 (32)[a,c]	82.8±4.0 (43)[a]	<0.001		
		Andean	50.8±3.9 (11)§[c]	64.3±3.5 (34)§[c]	83.6±4.4 (31)[a,b]	<0.001		
		p-ancestry	NS	NS	NS			
EDV, cm/s	Low	European	7.1±0.6 (26)[b,c]	33.9±1.8 (28)[a,c]	45.5±2.4 (24)[a,b]	<0.001	NS	NS
		Andean	7.9±0.7 (18)[b,c]	37.8±3.1 (23)§[a]	42.9±2.9 (19)[a]	<0.001		
		p-ancestry	<0.05	NS	NS			
	High	European	6.2±2.0 (24)[b,c]	30.8±2.7 (27)[a]	38.7±2.9 (42)[a]	<0.001		
		Andean	5.3±2.2 (10)[b,c]	25.6±2.3 (29)§[a,c]	41.4±4.0 (24)[a,b]	<0.001		
		p-ancestry	NS	NS	NS			
UA vascular resistance, mmHg·ml^{-1}·min^{-1}	Low	European	5.1±0.9 (22)§[b,c]	0.3±0.0 (24)[a]	0.2±0.0 (24)§[a]	<0.001	<0.001	<0.001
		Andean	8.7±1.0 (14)§[b,c]	0.3±0.0 (18)[a]	0.2±0.0 (19)[a]	<0.001		
		p-ancestry	<0.05	NS	NS			
	High	European	1.7±0.2 (20)§[b,c]	0.3±0.0 (23)[a]	0.2±0.0 (26)[a]	<0.001		
		Andean	1.4±0.3 (5)§[b,c]	0.2±0.0 (16)[a]	0.1±0.0 (25)§[a]	<0.001		
		p-ancestry	NS	NS	<0.01			
MAP, mmHg	Low	European	77.1±1.2 (26)	78.8±1.3 (28)	76.9±0.9 (24)†	NS	NS	NS
		Andean	76.9±2.3 (20)*	75.2±1.4 (24)	77.4±2.1 (19)	NS		
		p-ancestry	NS	NS†	NS			
	High	European	78.3±1.3 (39)	78.6±1.5 (33)	79.8±1.2 (24)†	NS		
		Andean	71.5±1.2 (35)*	75.6±1.4 (35)	76.2±2.1 (35)	NS†		
		p-ancestry	<0.001	NS	NS			
UA RI	Low	European	0.9±0.02 (26)[b,c]	0.6±0.0 (28)[a]	0.6±0.0 (24)[a]	<0.001	NS	NS
		Andean	0.9±0.0 (18)[b,c]	0.6±0.0 (23)[a]	0.5±0.0 (19)[a]	<0.001		
		p-ancestry	NS	NS	NS			
	High	European	2.0±1.06 (33)	0.6±0.0 (32)	0.5±0.01 (45)	NS		
		Andean	1.0±0.05 (12)[b,c]	0.6±0.0 (34)[a]	0.5±0.0 (31)[a]	<0.001		
		p-ancestry	NS	NS	NS			
O_2 delivery, ml O_2/ml blood/min	Low	European	4.1±0.5 (26)§[b,c]	41.3±4.0 (25)§[a,c]	56.6±5.4 (24)[a,b]	<0.001	<0.01	<0.01
		Andean	2.1±0.4 (18)§[b,c]	40.8±5.3 (15)§[a]	49.0±4.6 (19)§[a]	<0.001		
		p-ancestry	NS	NS	NS			
	High	European	11.7±3.3 (16)§[b,c]	66.0±8.0 (24)§[a]	70.0±6.4 (31)[a]	<0.001		
		Andean	11.3±2.7 (5)§[c]	92.2±12.7 (16)§	130±17.9 (21)§[a]	<0.001		
		p-ancestry	NS	NS†	<0.01			
Sa_{O_2}, %	Low	European	98.8±0.3 (26)§	98.2±0.3 (25)§	98.5±0.3 (24)§	NS	<0.001	<0.001
		Andean	99.0±0.5 (20)§	98.1±0.6 (16)§	98.6±0.5 (19)§	NS		
		p-ancestry	NS	NS	NS			
	High	European	91.6±0.4 (36)§[b,c]	94.4±0.4 (28)§[a]	94.2±0.3 (42)§[a]	<0.001		
		Andean	92.3±0.3 (34)§[b,c]	94.5±0.3 (30)§[a]	94.0±0.3 (30)§[a]	<0.001		
		p-ancestry	NS	NS	NS			
Hemoglobin, g/dl	Low	European	11.9±0.2 (26)§[b,c]	10.4±0.2 (27)§[a]	10.7±0.2 (24)§[a]	<0.001	NS	NS
		Andean	11.3±0.2 (19)§[b,c]	10.3±0.2 (24)§[a]	10.3±0.2 (18)§[a]	<0.01		
		p-ancestry	NS†	NS	NS			
	High	European	14.5±0.2 (38)§[b,c]	13.3±0.2 (27)§[a]	13.5±0.2 (36)§[a]	<0.001		
		Andean	14.3±0.2 (32)§[b,c]	13.3±0.2 (33)§[a]	13.2±0.2 (35)§[a]	<0.001		
		p-ancestry	NS	NS	NS			
Hematocrit, %	Low	European	36.9±0.5 (26)§[b,c]	32.1±0.5 (27)§[a]	33.1±0.5 (24)§[a]	<0.001	NS	NS
		Andean	34.8±0.7 (19)§[b,c]	31.9±0.6 (24)§[a]	31.6±0.7 (18)§[a]	<0.01		
		p-ancestry	NS†	NS	NS†			

Continued

Table 2.—*Continued*

Variable	Altitude	Ancestry	Nonpregnant	*Week 20*	*Week 36*	Time	Interaction (Time × Altitude) European	Interaction (Time × Altitude) Andean
	High	European	44.7±0.5 (38)§[b,c]	40.2±0.6 (27)§[a]	41.0±0.5 (36)§[a]	<0.001		
		Andean	43.9±0.6 (32)§[b,c]	40.1±0.5 (33)§[a]	40.4±0.5 (35)§[a]	<0.001		
		p-ancestry	NS	NS	NS			

Effects of time, altitude, and ancestry were evaluated by 1- (time, altitude), 2- (interaction between time and altitude within ancestry group), or 3-way ANOVA (interaction between time, altitude, and ancestry). Values are shown as means ± SE with sample sizes shown in parentheses. TAM, time-averaged mean blood flow velocity; S/D, peak systolic velocity (PSV)/peak end-diastolic velocity (EDV); PI, pulsatility index ([peak systolic velocity − peak end-diastolic velocity]/mean flow velocity); RI, resistance index ([peak systolic velocity − peak end-diastolic velocity]/peak systolic velocity); MAP, mean artierial pressure; UA, uterine artery. Comparisons between altitude groups within each ancestry group and within pregnancy time point are designated as follows: †$0.05 < P < 0.10$, *$P < 0.05$, §$P < 0.01$. Significant differences between time points within ancestry and altitude groups are designated as follows: [a]Significantly different from nonpregnant (postpartum) value. [b]Significantly different from 20 wk. [c]Significantly different from 36 wk.

women at either altitude, and positive associations were seen between bilateral UA blood flow or O_2 delivery and birth weight exclusively in high-altitude European women (35). However, we should caution to add that we do not consider that our results exclude the involvement of other factors, such as variations in glucose availability, glucose transport, placental oxygen consumption or diffusing capacity, or fetal substrate utilization—in the protection of fetal growth at high altitude afforded by Andean ancestry (14, 34). In reality, any advantages incurred by increasing UA blood flow must be accompanied by adequate transport mechanisms within the fetoplacental unit. Although we consider it unlikely that a single variable can be used to explain such a complex physiological system as the regulation of fetal growth, we also think it is premature to conclude that the Andean women's higher levels of UA blood flow and O_2 delivery do not play an important role in protecting Andeans from altitude-associated reductions in fetal growth.

As in previous reports, we found that Andean babies weighed more than their European counterparts at high altitude once the influences of other known birth-weight determinants were taken into account (12, 17, 31). It should be noted that the 253- or 375-g birth weight differences between ancestry or altitude groups were not sufficient to increase the frequency of SGA infants in this report, but Andean ancestry's protection from such an altitude-associated increase is present in larger studies (13). However, our data contrast with those in the Zamudio et al. study (35), insofar as we did not find heavier birth weights in Andean women compared with European women at low altitude. This is most likely due to sampling variation given that similar Andean and European birth weights at low altitude have also been seen in several larger studies (8, 10, 13). A novel finding in the present study was that Andean fetal biometry was greater than European values at high altitude by 20 wk of gestation. Consistent with this, Andean mid-cerebral artery S/D ratios at *week 20* were unaffected by altitude, whereas the European values tended to be lower, suggesting that the brain-sparing thought to be a factor in asymmetric growth restriction may already be present. Because Andean UA blood flow was higher than European values by *week 20*, the demonstration that fetal biometry differences were also present supported the likelihood that the Andean women's greater UA blood flow and O_2 delivery contributed to their protection from altitude-associated reductions in fetal growth.

Given the differences between groups in several factors known to influence birth weight (gestational age, maternal height, infant sex, parity, and household income), it was particularly important to take such variation into account prior to isolating the effect of ancestry. After making such adjustments, our data demonstrated that the percentage of Indigenous American ancestry was positively associated with birth weight at high altitude. This agrees with our and Zamudio's previous studies at high altitude (31, 35) but differs from the latter report, which also found a relationship between AIMs and birth weight at low altitude. Several factors may be involved. We used a larger number of

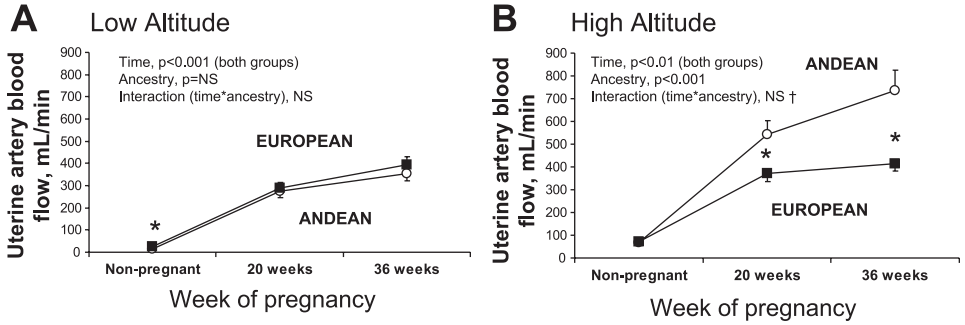

Fig. 1. Uterine artery (UA) blood flow increased with pregnancy in each ancestry group at low (*A*) or high (*B*) altitude. *A*: at low altitude, the pregnancy-associated rise in UA blood flow was equivalent between Andean and European women (interaction, ancestry × time = NS), and Europeans had slightly greater UA blood flow at 20 wk. *B*: at high altitude, the pregnancy-associated rise in UA blood flow tended to be greater in Andeans than Europeans, resulting in UA blood flows that were more than one-third larger at 20 or 36 wk in Andean women (both, $P < 0.05$). Comparing across altitudes, the Andean women had greater pregnancy-associated rise in UA blood flow, whereas the rise was unchanged in European subjects (time × ancestry × altitude, $P < 0.05$ and P = NS, respectively).

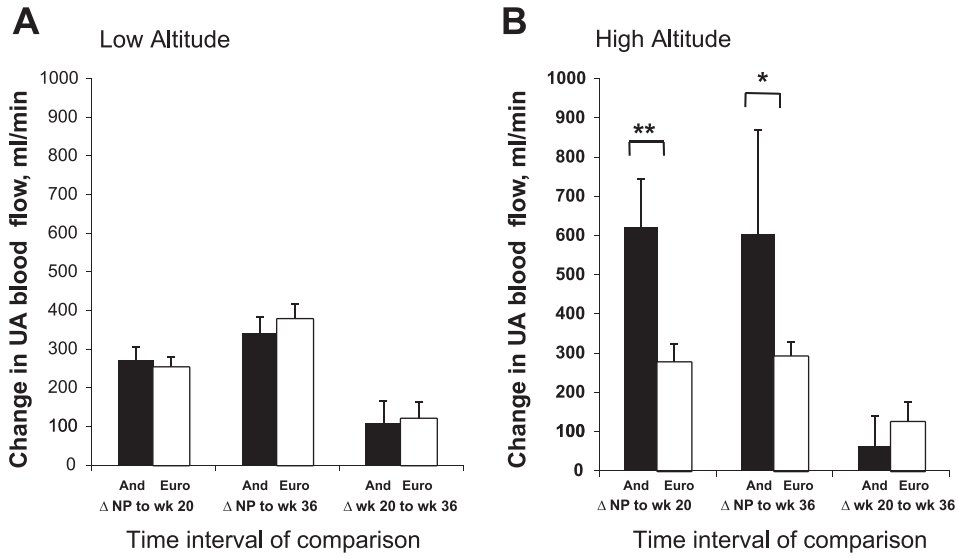

Fig. 2. The change in UA blood flow measurements across time at low (*A*) and high (*B*) altitude. *A*: at low altitude, there was no difference between ancestry groups in the magnitude with which pregnancy increased UA blood flow. *B*: at high altitude, Andean compared with European women had more than a two-fold larger increase in UA blood flow from the nonpregnant state to *week 20* or *week 36* (both $P < 0.05$). There was no ancestry-associated difference in the magnitude to which UA blood flow increased from *weeks 20* to *36* at either altitude.

AIMs, and hence could quantify individual Indigenous American ancestry with greater precision. Because we were primarily interested in ancestry-group differences in a maternal phenotype (UA blood flow), we applied AIMs to the determination of maternal ancestry, whereas the Zamudio study used fetal DNA, given that it was designed to collect placental materials. Fetal DNA is also influenced by paternal ancestry, which we have shown recently to have an effect on birth weight independently from maternal ancestry (3). Thus it is not clear in the Zamudio report whether the relationship present between AIMs and birth weight at low altitude was due to maternal, paternal, or fetal factors.

The dose-dependent nature of the relationship between percent Indigenous American ancestry and birth weight identified

Table 3. *Fetal biometry*

Variable	Ancestry	Altitude	*Week 20*	*Week 36*	Time
Biparietal dia, cm	Low	European	5.3±0.1(28)*	9.0±0.1 (24)	<0.001
		Andean	5.4±0.1 (24)	8.8±0.1 (19)	<0.001
	p-ancestry		NS	NS	
	High	European	5.1±0.1 (31)*	9.0±0.0 (43)	<0.001
		Andean	5.4±0.1 (33)	8.8±0.1 (30)	<0.001
	p-ancestry		NS†	<0.05	
Abd circ, cm	Low	European	17.0±0.2 (28)	31.7±0.4 (24)	<0.001
		Andean	17.3±0.5 (24)	31.1±0.3 (19)	<0.001
	p-ancestry		NS	NS	
	High	European	17.2±0.2 (30)	31.8±0.3 (43)	<0.001
		Andean	17.9±0.4 (33)	31.3±0.2 (30)	<0.001
	p-ancestry		NS	NS	
Head circ, cm	Low	European	18.9±0.2 (28)	30.2±0.6 (24)*	<0.001
		Andean	18.9±0.5(23)	31.3±0.3 (19)	<0.001
	p-ancestry		NS	NS	
	High	European	18.4±0.2 (31)	31.8±0.4 (43)*	<0.001
		Andean	19.5±0.4 (32)	30.8±0.7 (30)	<0.001
	p-ancestry		<0.05	NS	
Femur length, cm	Low	European	3.8±0.1 (28)§	7.0±01 (24)	<0.001
		Andean	3.8±0.1 (24)	6.9±0.9 (19)	<0.001
	p-ancestry		NS	NS	
	High	European	3.5±0.0 (31)§	7.0±0.0 (43)	<0.001
		Andean	3.9±0.1 (33)	7.9±0.8 (30)	<0.001
	p-ancestry		<0.01	NS	
MC artery S/D	Low	European	6.9±0.8 (27)†	5.0±0.4 (24)*	NS†
		Andean	6.5±1.1 (24)	5.0±0.4 (19)*	<0.001
	p-ancestry		NS	NS	
	High	European	4.8±0.7 (39)†	4.0±0.3 (43)*	NS
		Andean	6.2±1.0 (32)	3.5±0.4 (28)*	<0.05
	p-ancestry		NS	NS	

Values are expressed as means ± SE. †$0.05 < P < 0.10$. abd, abdominal; S/D, peak systolic velocity/peak end diastolic velocity; MC, middle cerebral; SGA, small for gestational age (<10th percentile for gestational age and sex (30) without adjustment for maternal body size or other characteristics). Values are adjusted for actual gestational age for altitude and ancestry comparisons and are displayed for adjustments made within ancestry groups. Comparisons between altitudes within ancestry ancestry groups are noted as follows: †$0.05 < P < 0.10$, *$P < 0.05$, §$P < 0.01$.

Table 4. *Delivery and newborn characteristics*

Variable	Altitude	European	Andean	Ancestry
Gestational age, wk	Low	37.8±0.3 (28)	38.8±0.6 (23)	NS
	High	39.2±0.2 (52)	39.2±0.2 (33)	NS
	p-altitude	<0.001	NS	
Cesarean section, %	Low	57 [39, 73] (28)	70 [49, 84] (23)	NS
	High	59 [44, 72] (46)	26 [14, 42] (35)	<0.01
	p-altitude	NS	<0.01	
Birth weight, g	Low	3272±110 (28)	3191±122 (22)	NS
	High	3148±54.2 (52)	3043±61.8 (35)	NS
	p-altitude	NS	NS	
Birth weight*, adjusted, g	Low	3353±126 (20)	3194±149 (15)	NS
	High	2978±81 (33)	3231±81 (33)	<0.05
	p-altitude	<0.05	NS	
Length, cm	Low	49.4±0.2 (27)	49.3±0.4 (22)	NS
	High	50.0±0.4 (47)	48.8±0.4 (32)	NS
	p-altitude	NS	NS	
Ponderal index, kg/m^3	Low	27.6±0.6 (27)	26.4±0.8 (22)	NS
	High	25.9±0.5 (47)	26.0±0.5 (32)	NS
	p-altitude	<0.05	NS	
Head circ, cm	Low	35.0±0.3 (27)	35.1±0.3 (22)	NS
	High	34.6±0.2 (40)	34.0±0.2 (30)	NS†
	p-altitude	NS	<0.01	
Apgar score, 1 min	Low	7.6±0.1 (28)	7.1±0.1 (22)	NS
	High	8.3±0.1 (51)	7.8±0.2 (30)	<0.01
	p-altitude	<0.001	NS	
Apgar score, 5 min	Low	8.6±0.1 (28)	8.3±0.2 (22)	<0.05
	High	9.1±0.1 (51)	9.0±0.1 (30)	NS
	p-altitude	<0.001	<0.001	
Preterm, %	Low	25 [13, 43] 28	17 [7, 37] 23	NS
	High	13 [7, 25] 52	6 [2, 20] 33	NS
	p-altitude	NS†	NS	
Male, %	Low	36 [21, 54] 28	45 [27, 65] 22	NS
	High	63 [49, 75] 49	46 [30, 62] 35	NS
	p-altitude	<0.05	NS	
SGA, %	Low	18 [8, 36] (28)	14 [5, 33] (22)	NS
	High	18 [10, 32] (44)	22 [11, 41] (27)	NS
	p-altitude	NS	NS	

Values shown are expressed as means ± SE or percentages and 95% CI for proportions. †$0.05 < P < 0.10$. SGA, small-for-gestational age (<10th percentile for gestational age and sex (30) without adjustment for maternal body size or other characteristics); circ, circumference. *Birth weight adjusted for gestational age, monthly income, parity, infant sex and maternal height within each altitude group, one-tailed *P* value.

in the present study was consistent with the hypothesis that genetic factors are involved in the protection of fetal growth at high altitude. A limitation of our (and others) data is the inability to distinguish Andean from other Indigenous American groups given the current lack of gene markers for determining ancestry on such a fine scale. The data that we obtained by questionnaire was particularly helpful in this regard as it provided information about the source of the Indigenous American parentage. Because the Indigenous American inhabitants of the Andean plateau have had a long history of residence at high altitude, which is not the case for any of the other South or Central American (or European) populations from which the women were descended, we concluded that it was Andean rather than Indigenous American ancestry that conferred protection from altitude-associated reductions in fetal growth. Because not only were AIMs related to birth weight but also to fetal biometry, UA diameter and blood flow, and O_2 delivery, and because such relationships were present by *week 20*, we

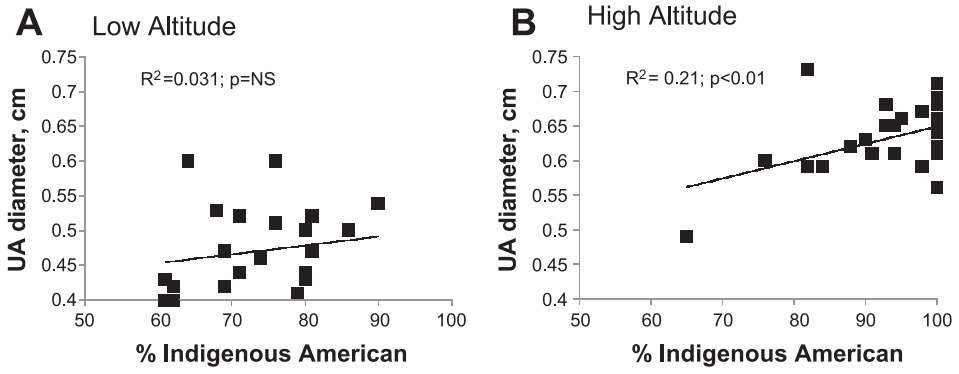

Fig. 3. The relationship between Indigenous American AIMs and UA diameter in Andean women at low (*A*) and high (*B*) altitude. *A*: at low altitude, UA diameter did not change with the percentage of Indigenous American AIMs among Andean women. *B*: at high altitude, Andean women with a higher proportion of Indigenous American AIMs had greater UA diameters.

Table 5. *Multiple regression analysis of the relationship between indigenous American ancestry and birth weight*

Independent Variables (*x*)	Low Altitude (β)	*P* Value	High Altitude (β)	*P* Value*
Gestational age, wk		NS	0.43	<0.001
Maternal height, cm		NS	0.38	<0.05
Infant sex, female		NS		NS
Parity, no. live births		NS	0.18	=0.10
Income, U.S. dollars		NS	0.26	NS†
% Indigenous American AIMs*		NS	0.30	<0.05
Adjusted R^2	−0.071	NS	0.299	<0.001

Dependent variable (*y*) = birth weight in grams. †$0.05 < P < 0.10$; *One-tailed *P* value.

concluded that *1*) the protective effect of Andean ancestry was present by midgestation and *2*) this effect may operate, at least in part, via increasing maternal UA blood flow and O_2 delivery. Furthermore, because this protective effect of Andean ancestry on fetal growth was only present at high altitude, our findings implicate the possibility for gene-by-environment interaction or the importance of the environmental conditions of pregnancy and high altitude for influencing the expression of Andean-specific genes. Gene-environment interaction is becoming increasingly recognized in a variety of conditions, including, for example, the effect of *CYP1A1 Mspl* or *EPHX1* genes to modify the effects of passive smoke exposure during pregnancy on birth weight (32).

Perspectives and Significance

Given the widespread importance of fetal growth not only for neonatal well-being but also for a growing range of disorders later in life (2, 18), the identification of parental, fetal, and environmental attributes that protect fetal growth and birth weight is increasingly appreciated. Studies at high altitude provide a unique natural laboratory to identify specific genes involved in the protection of fetal growth and the molecular signaling pathways through which they exert their effects. We consider likely candidates to be factors involved in maternal vascular response to pregnancy, including those influencing maternal vascular reactivity, growth, and remodeling, such as oxidative stress, angiogenic and/or immunological factors.

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