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Greater uterine artery blood flow during pregnancy in multigenerational (Andean) than shorter-term (European) high-altitude residents

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Wilson MJ, Lopez M, Vargas M, Julian C, Tellez W, Rodriguez A, Bigham A, Armaza JF, Niermeyer S, Shriver M, Vargas E, Moore LG. Greater uterine artery blood flow during pregnancy in multigenerational (Andean) than shorter-term (European) high-altitude residents. *Am J Physiol Regul Integr Comp Physiol* 293: R1313–R1324, 2007. First published June 20, 2007; doi:10.1152/ajpregu.00806.2006.—Multigenerational (Andean) compared with shorter-term (European) high-altitude residents exhibit less hypoxia-associated reductions in birth weight. Because differences in arterial O_2 content are not responsible, we asked whether greater pregnancy-associated increases in uterine artery (UA) blood flow and O_2 delivery were involved. Serial studies were conducted in 42 Andean and 26 European residents of La Paz, Bolivia (3600 m) at *weeks 20*, *30*, *36* of pregnancy and 4 mo postpartum using Doppler ultrasound. There were no differences postpartum but Andean vs. European women had greater UA diameter (0.65 ± 0.01 vs. 0.56 ± 0.01 cm), cross-sectional area (33.1 ± 0.97 vs. 24.7 ± 1.18 mm^2), and blood flow at *week 36* (743 ± 87 vs. 474 ± 36 ml/min) (all $P < 0.05$) and thus 1.6-fold greater uteroplacental O_2 delivery near term (126.82 ± 18.47 vs. 80.33 ± 8.69 ml $O_2 \cdot$ml blood$^{-1} \cdot$min^{-1}, $P < 0.05$). Andeans had greater common iliac (CI) flow and lower external iliac relative to CI flow (0.52 ± 0.11 vs. 0.95 ± 0.14, $P < 0.05$) than Europeans at *week 36*. After adjusting for gestational age, maternal height, and parity, Andean babies weighed 209 g more than the Europeans. Greater UA cross-sectional area at *week 30* related positively to birth weight in Andeans ($r = +0.39$) but negatively in Europeans ($r = -0.37$) (both $P < 0.01$). We concluded that a greater pregnancy-associated increase in UA diameter raised UA blood flow and uteroplacental O_2 delivery in the Andeans and contributed to their ability to maintain normal fetal growth under conditions of high-altitude hypoxia. These data implicate the involvement of genetic factors in protecting multigenerational populations from hypoxia-associated reductions in fetal growth, but future studies are required for confirmation and identification of the specific genes involved.

birth weight; genetic adaptation; hypoxia; small-for-gestational age; uteroplacental vascular resistance

CONSIDERABLE ATTENTION HAS focused on the factors influencing birth weight, given its substantial influences on mortality during the neonatal period (25), as well as later in life (1). Among its many determinants, residence at high altitude exerts one of the strongest effects, being greater than that of parity, maternal age, or moderate smoking (15, 23).

The lower birth weights seen at high altitude are due chiefly to the reduced O_2 availability (hypoxia) of the high-altitude environment, which serves, in turn, to slow fetal growth, not shorten gestation. However, the mechanisms by which chronic hypoxia slows fetal growth are unknown. Human and experimental animal data indicate that alterations in maternal circulatory responses to pregnancy are likely involved; in species experiencing a reduction in fetal growth at high altitude, chronic hypoxia decreases the normal pregnancy-associated rise in uterine artery (UA) nitric oxide production, halves the mid-gestation increase in UA DNA synthesis, and inhibits flow-induced UA vasodilation (19, 24, 43). Consistent with these findings, Colorado high-altitude residents have smaller UA diameters and lower blood flows near term than low-altitude controls (46). Thus, a possible explanation for the slowed fetal growth seen at high altitude is that chronic hypoxia opposes the normal enlargement in UA diameter and increase in blood flow so as to reduce the delivery of O_2 and other vital nutrients to the uteroplacental circulation.

While a reduction in birth weight has been seen in every high-altitude population studied to date, the magnitude of the reduction varies systematically (32). Across a 2,800–4,800 m altitude gradient, multigenerational Tibetan high-altitude residents have one-third the birth weight decline seen in newcomer Han ("Chinese") (29). Likewise, Andean newborns are small-for-gestational age (SGA) one-third as often as babies born to European women residing at high altitude (3,600 m) in Bolivia (17), regardless of whether or not the Europeans were themselves born and raised at high altitude (12).

We sought to use this naturally occurring variation in the magnitude of altitude-associated fetal growth reduction as a means for testing the hypothesis that lower birth weight at high altitude is due to decreased uteroplacental O_2 delivery. We measured arterial oxygenation and UA blood flow, their proximate determinants, and fetal biometry serially during pregnancy in 42 Andean and 26 European healthy residents of La Paz. Birth weight and other newborn information were obtained at delivery. In a companion paper (41), we showed that maternal arterial oxygenation did not differ in the Andean vs. European women, although the pregnancy-induced rise in ventilation more closely correlated with increased levels of arterial O_2 saturation, birth weight, and ponderal index in the

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Andean group. Here, we consider the alternate possibility, namely, that UA blood flow during pregnancy was greater in the Andean vs. European high-altitude residents. The study results were consistent with this latter possibility, suggesting that long-term, perhaps genetic changes over multiple generations of high-altitude residence have influenced maternal vascular responses to pregnancy so as to confer protection from hypoxia-associated reductions in fetal growth.

MATERIALS AND METHODS

Subjects

Subjects were the same 42 women of Andean and 26 women of European ancestry living in La Paz or El Alto, Bolivia, as those described in the accompanying article (41). The women were recruited through their prenatal care providers. Criteria for accepting women into this study included being in good health, being not more than 20 wk pregnant, having a singleton pregnancy, receiving prenatal care, willing to participate, and presenting no known risk for developing preeclampsia or other complications in this pregnancy. All gave written informed consent to study procedures that had been approved by the human subject review committees of the Colorado Multiple Institutional Review Board of the University of Colorado Health Sciences Center and the Colegio Médico, its Bolivian counterpart. Studies were conducted at the Instituto Boliviano de Biología de Altura (Bolivian High-Altitude Biology Institute) and the Clinica des Sur (Southern Clinic) in La Paz (barometric pressure = 495 mmHg). Because birth weight data were not available for 6 of the 42 Andeans, and 6 of the 26 European women left at *weeks 32–34* to give birth at low altitude, birth weights and other neonatal data were present for 36 Andeans and 20 Europeans. None of the women developed gestational diabetes, but two Andeans and one European woman were diagnosed with mild preeclampsia following *week 36* of the study. Their study results did not differ from those of the other subjects for any of the parameters measured, and hence, their data are included here.

Variables and Instrumentation

Each woman's self-identified ancestry, altitude of birth, and residential history, her parents' and grandparents' ancestry and altitude of birth, age, occupation, habitual activity level, body weight before pregnancy, and medical history were obtained by questionnaire administered in the subject's spoken language. Andeans were self-identified as being of Aymara or Quechua descent with no known foreign parentage. Among the 26 non-Andean women, 20 were of European ancestry, while the others were of mixed European and Central American (Mexican, Caribbean) or Southeast Asian (Korean) parentage. Because the overwhelming majority (77%) was European, the group is referred to as "European" in the text, tables, and figures.

Ancestry was confirmed using a panel of 81 Ancestry Informative Markers (AIMs) selected to provide information about ancestry proportions (4, 37). Of these, 51 had large (>30%) frequency differences between European and Native American populations, 65 exhibited large differences between West African and Native American populations, and 53 differed between West African and European populations. 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 (3, 4, 37). The maximum likelihood method (7) was used to estimate individual genomic ancestry.

La Paz and El Alto together span a 3,200–4,200 m range; hence, both the neighborhood and the altitude, measured by altimetry, were identified for each woman. Body weight was determined the morning of the study day using a balance scale, with subjects wearing a dressing gown. Height was obtained at the first visit by stadiometer. Triceps and subscapular skinfolds were measured using Lange calipers (Beta Technology, Santa Cruz, CA) and blood pressure was measured by arm cuff sphygmomanometer, with the average of right and left side values recorded. Maternal heart rate was measured by auscultation and fetal heart rate by Doppler monitor.

Blood was withdrawn from the antecubital vein via an indwelling catheter, with minimal use of a tourniquet. Samples were processed for measuring hematocrit in duplicate using the microcentrifuge technique and hemoglobin in triplicate using the cyanmethemoglobin technique. Arterial O_2 saturation (Sa_{O_2}) was measured in a warmed finger using transdermal pulse oximetry (Biox 3700, Ohmeda, Louisville, KY), as previously described (41). Arterial O_2 content (Ca_{O_2}) was calculated as [(1.36·hemoglobin) × Sa_{O_2}]. Total blood volume was determined using a carbon monoxide (CO) rebreathing technique using an OSM3 Oximeter (Radiometer, Copenhagen, Denmark), as described previously (41) and which has been shown previously to agree well with other methods (5, 10), and the Evans blue technique at high altitude (11).

Vessel diameters, velocities, and fetal biometry were measured pericutaneously using an ATL3000 ultrasound unit configured for obstetrical use with color imaging and Doppler. Maternal vessels were examined bilaterally, and results were reported as the average of the right- and left-side measurements. All measurements were taken with a 4-MHz curved linear array probe using the same machine, at the same location, and with the same operator so as to minimize interinstrument and interoperator variability. The common (CI) and external iliac (EI) arterial diameters were obtained bilaterally, with and then without color. The CI and EI arteries were visualized 2–3 cm anterior and posterior, respectively, to the bifurcation of the EI and internal iliac arteries. The uterine artery (UA) was measured at its crossover with the EI. Diameter was recorded in longitudinal view at a high angle of insonation using the cine loop feature so as to obtain clear, parallel vessel margins. A minimum of three, and usually at least five consecutive beats, were obtained from which peak systolic velocity, either minimum or end-diastolic velocity, and the time-averaged mean flow velocity (TAM) values were recorded.

Birth weight, gestational age, sex, length, and head circumference were obtained for babies born at high altitude using medical records completed by hospital personnel at the time of birth. Gestational age was calculated as that estimated at the *week 20* ultrasound exam and, in all cases, was equivalent to that calculated using weeks from the last menstrual period. Babies were classified as SGA when the birth weight for gestational age and sex was less than the 10th percentile of published sea-level values (44).

Protocol

Women were studied serially at *weeks 20*, *30*, and *36* of pregnancy and 4 mo postpartum for a measurement in the nonpregnant state. Actual weeks of gestation were 23.4 ± 0.6, 30.8 ± 0.2, 36.6 ± 0.6 wk of pregnancy, and 3.8 ± 0.3 mo postpartum. Background data were obtained by questionnaire on the initial visit. At each visit, the physical exam was done first, followed by the blood withdrawals, the blood volume measurements, and lastly the ultrasound exam.

For measurement of blood volume, subjects rested quietly in a seated position with a noseclip in place and breathed 100% O_2 through a rebreathing circuit from which CO_2 was removed and 100% O_2 periodically added. After 5 min, a baseline blood sample was withdrawn. A known volume of CO (60 ml ATP) was then added to the rebreathing circuit, and blood samples were taken after 10 and 15 min of rebreathing. Total blood volume was calculated from the equation [(CO added/ΔCO content) × [1/Hb] × 100] where CO was the volume of CO added to the rebreathing circuit, ΔCO content was the difference in CO content between the baseline and the average of the 10- and 15-min samples, and Hb the measured total hemoglobin concentration in grams per deciliter, as obtained using the cyanmet-

hemoglobin technique. In our subjects, the ΔCO-Hb was ~5%. Red blood cell mass was calculated as a total blood volume multiplied by hematocrit after using the correction factor of 0.98 to adjust for the effect of trapped plasma (5). The remainder was considered plasma volume.

For each study, vessel diameters were obtained first, and mean luminal diameter was calculated from the images obtained without color at midsystole and middiastole as [(2·diastolic + systolic diameter)/3]. Images without color were used since color imaging exaggerates luminal diameter. Because it was difficult to visualize the UA without color in all subjects, values were adjusted to remove the effect of color imaging by using the linear relationship between the with (x)- and without (y)-color values measured in the CI artery at a similar anatomical depth. Once the diameter measurement had been completed, the probe was rotated using anatomical landmarks to ensure that the same portion of the vessel was being insonated, and the angle of insonation and size of the sampling frame were adjusted to obtain optimal velocity signals. After selecting the ATL3000 High Q-Automatic Doppler Measurement mode, the TAM was calculated for the same consecutive beats. The mean vessel diameter was entered and volumetric flow was calculated as ($\pi r^2 \times$ TAM $\times$ 60) where r is the vessel radius in cm^2, TAM is expressed in cm/s, and volumetric flow is expressed in ml/min. Because high angles of insonation introduce considerable error into the measurement of velocity, the angle was required to be ≤45° for all velocity and volumetric flow calculations. Uteroplacental vascular resistance was calculated as (mean arterial blood pressure/UA volumetric flow). Uteroplacental resistance indices—namely, 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 velocity/peak end-diastolic velocity)—were noted as well. The ratios of EI to CI flow (EI/CI), UA artery to CI flow (UA/CI), and UA to EI artery flow (UA/EI) were calculated as indices of the distribution of CI flow to the leg (EI) vs. the uteroplacental (UA) circulation.

Fetal abdominal and head circumference, biparietal diameter, and femur length) were measured by biometry at each study time. Although effort was made to study each woman at the same gestational age, actual gestational age at the time of study varied somewhat within and between groups; therefore, the fetal biometry values reported were adjusted by ANCOVA using actual gestational age as the covariate. The S/D resistance indices for the fetal umbilical and middle cerebral arteries were also recorded.

Statistics

Data are expressed as the means ± SE or the 95% confidence intervals for proportions in the text, tables, and figures. All maternal blood flow and resistance measures were averaged from measurements obtained on the woman's right and left sides. Comparisons between groups at single times were conducted using Student's t-tests for continuous variables and χ^2-test for nominal or ordinal variables. The effects of pregnancy or ancestry were tested using one- or two-way ANCOVA with contrasts and Tukey's multiple comparisons. Actual gestational age at the time of study was used as a covariate when assessing the effect of ancestry on fetal biometry. Multiple linear regression was employed to identify those maternal and infant characteristics related to birth weight among our study subjects, with the criterion for inclusion and exclusion at $P \leq 0.10$. Significant covariates (gestational age, maternal height, and parity) were set to the average values for the two groups combined to isolate the effect of population ancestry on birth weight and ponderal index. All analyses were conducted using StatView (SAS, Santa Cruz, CA) or SPSS (Chicago, IL). Comparisons or relationships were considered significant when $P < 0.05$ and as trends when $0.05 < P < 0.10$. Two-tailed P values are reported unless the direction of the comparison was specified in advance, in which case one-tailed tests were used.

RESULTS

Maternal Demographic Characteristics

All the Andeans had been born at high altitude (≥ 2,500 m) and nearly all (94%) were raised there as well. The European women had lived at high altitude an average of 6 yr, with all but one being born and raised at low altitude (Table 1). The altitudes at which the women currently resided varied from 3,200 to 4,100 m, with the Andean women living ~700 m higher than the European subjects.

Nearly all (95%) the Andean women's genetic markers were of American Indian origin, confirming their self-identified ancestry (Table 1). There was comparatively little variation in American Indian ancestry; for 85% ($n = 35$) of the subjects, more than 90% of their AIMs were of American Indian origin, 3 of the women had 80–90% American Indian AIMS, and the remainder ($n = 4$) had >60% American Indian AIMs. The European women's AIMs were more variable; for half ($n = 13$), more than 90% of their AIMs were of European origin, with no American Indian and very little (~3%) West-African parentage. For the other half, 35% of the AIMs were of European origin, 58% of American Indian origin, and 7% of West-African origin. The women with greater American Indian admixture reported some Central American or Caribbean parentage (Mexico, Trinidad).

The Andeans were younger than the Europeans and of higher parity and gravidity, but with a similar frequency of primigravidae (Table 1). Although the Europeans were taller, and heavier at *week 36*, their reported prepregnant body mass index, body weight, skinfolds, and pregnancy weight gain were the same as in the Andean women. No women smoked cigarettes, by self-report or evaluation of CO-Hb levels. By study design, all women received prenatal care, but the European women began their care earlier and had a greater number of prenatal visits than did the Andeans. Monthly household incomes and education levels were markedly lower in the Andean than European women. Andeans also reported higher levels of habitual activity than the European women.

Maternal Blood Volume and Other Systemic Characteristics

Plasma and total blood volume rose during pregnancy with no change occurring in red blood cell mass adjusted for body weight (Fig. 1*A*, Table 2). As a result, hematocrit and hemoglobin fell in both groups (Table 2). Both groups exhibited a hyperventilation-induced rise in Sa_{O_2} that helped preserve arterial O_2 content (Ca_{O_2}). However, Ca_{O_2} fell nonetheless in the Andeans and tended to do so as well in the European women, with values being lower in the Andean than European groups at *week 20* and across all time points (Table 2).

European blood pressures were higher than Andean values when nonpregnant, at *week 36* and across all time points (Table 2). Pregnancy did not change blood pressure or heart rate in either group. Heart rates were also higher in the European than Andean subjects at *week 36* as well as across all time points (Table 2).

Table 1. *Maternal characteristics*

Variable	Andean	European	*P* Value
Altitude of current residence, m	4072±13 (36)	3375±34 (14)	<0.0001
Residence at high altitude, yr	21.3±1.2 (42)	4.4±1.5 (24)	<0.0001
Ancestry, %			
European	3.3±1.0 (41)	72.8±7.1 (19)	<0.0001
American Indian	95.6±1.1 (41)	22.8±6.7 (19)	<0.0001
West African	1.2±0.4 (41)	4.5±1.1 (19)	<0.0001
Age, yr	27.2±1.0 (42)	32.4±0.8 (25)	<0.0001
Parity, no. live births	3.0±0.3 (42)	2.1±0.2 (25)	<0.05
Gravidity, no. pregnancies	3.4±0.3 (42)	2.3±0.2 (25)	<0.05
Primigravid, %	23.8 [10, 42] (42)	23.1 [13, 38] (26)	NS
Prepregnant weight, kg	58.8±1.5 (42)	63.5±2.4 (17)	NS*
BMI, kg/m^2	26.1±0.6 (42)	24.6±1.2 (16)	NS
Skinfolds$_{triceps+subscapular}$, mm	39.7±1.8 (42)	42.7±3.0 (24)	NS
Height, cm	150.0±0.6 (42)	162.0±1.3 (26)	<0.0001
Weight at *week 36*, kg	64.9±1.6 (41)	70.7±1.9 (20)	<0.05
Weight gain *week 20–36*, kg	7.4±1.3 (38)	6.0±0.6 (14)	NS
Monthly household income, $	142±24 (42)	2338±445 (18)	<0.0001
Prenatal care, week of 1st visit	19±1 (36)	12±2 (16)	<0.01
Number of prenatal visits	5±0 (36)	8±1 (16)	<0.01
Education, %			
None	2.4 [0.3, 11] (42)	0.0 [0, 0] (24)	<0.0001
Primary school	19.0 [9, 33]	0.0 [0, 0]	
Secondary school	66.7 [52, 79]	20.8 [8, 40]	
Univ/technical school	11.9 [5, 24]	79.2 [60, 92]	
Habitual activity			
1 = low, 2 = medium, 3 = high	2.2±0.1 (41)	1.8±0.1 (18)	<0.05

Values are shown as means ± SE or 5% confidence intervals for proportions, with sample sizes in parentheses. *$0.05 < P < 0.10$. NS, not significant.

Maternal Blood Flow Characteristics

CI artery. CI blood flow was higher in the Andean than European women in both the nonpregnant and pregnant condition (Fig. 1*B*). Pregnancy increased CI diameter, but the increase was greater in the Andean compared with European subjects (35% vs. 20%, respectively, Table 3), which served, in turn, to double their levels of blood flow (Fig. 1*B*). The percent American Indian AIMs correlated positively with CI flow when nonpregnant or pregnant ($R^2 = 0.18$, 0.16, 0.27, 0.26 at pregnancy *weeks 20*, *30,* or *36* respectively, all $P < 0.05$) as the result of relationships between the AIMs and flow velocity as well as vessel diameter (data not shown).

EI artery. EI blood flow was also higher in the Andean than in European women, especially when nonpregnant (Fig. 1*C*). Diameter increased slightly more with pregnancy in the Andean than European groups (12 vs. 8%), but flow velocity fell in the Andeans (Table 3) such that there was no change in EI volumetric flow across time in either group (Fig. 1*C*). The Europeans' lower EI flows were not the result of the EI receiving less CI flow, since EI/CI values were greater in the European than the Andean group across all times (Fig. 2*C*). The percent American Indian AIMs was weakly correlated with EI flow when nonpregnant ($R^2 = 0.15$, $P < 0.05$) but not during pregnancy.

UA, resistance indices, and UA O_2 delivery. Pregnancy markedly increased UA diameter, blood flow velocity, and volumetric flow. The pregnancy-associated rise in flow velocity was the same in the two groups, but the Andean women had a 16% greater increase in UA diameter and 34% greater cross-sectional area than the European women, producing 1.6-fold higher volumetric flow near term (Fig. 1*D*, Table 3). The temporal pattern for the rise in UA flow differed as well; flow peaked at *week 30* in the Europeans but rose continuously in the Andeans (Fig. 1*D*). The percent American Indian AIMs correlated positively with UA diameter ($R^2 = 0.32$, 0.21, and 0.37 at *weeks 20*, *30,* and *36*; all $P < 0.001$) but no such relationships were present with flow velocity.

The S/D, PI, and RI fell with pregnancy, with the decline in PI and RI being greater in the Andean than the European group (Table 3). Even though marked differences in UA volumetric flow were present, the UA resistance indices were not lower in the Andean than European women at any time. When uterine vascular resistance was calculated directly from mean arterial pressure and UA blood flow, resistance values were lower in the Andean than European women subjects at all time points and especially at *week 36* (Table 3).

UA O_2 delivery increased during pregnancy, achieving 1.6-fold higher values in the Andean women near term (Table 3). Since arterial O_2 content was not greater in the Andean women (Table 2), the Andeans' higher near-term UA O_2 delivery was due entirely to greater UA blood flow.

Lower extremity blood flow distribution. Pregnancy did not affect the proportion of CI flow being directed to the UA in either group (Fig. 2*A*). The UA/CI flow ratios were higher in the European than the Andean group as the result of the Andeans' higher UA and the Europeans' lower CI flows. The pregnancy-associated rise in UA/EI flow indicated redistribution of lower extremity flow to favor the UA in both groups, with no differences between groups at any time (Fig. 2*B*). EI/CI flow declined with pregnancy in both groups, but was lower in the Andean than European women at all times and especially at *weeks 30* and *36* (Fig. 2*C*).

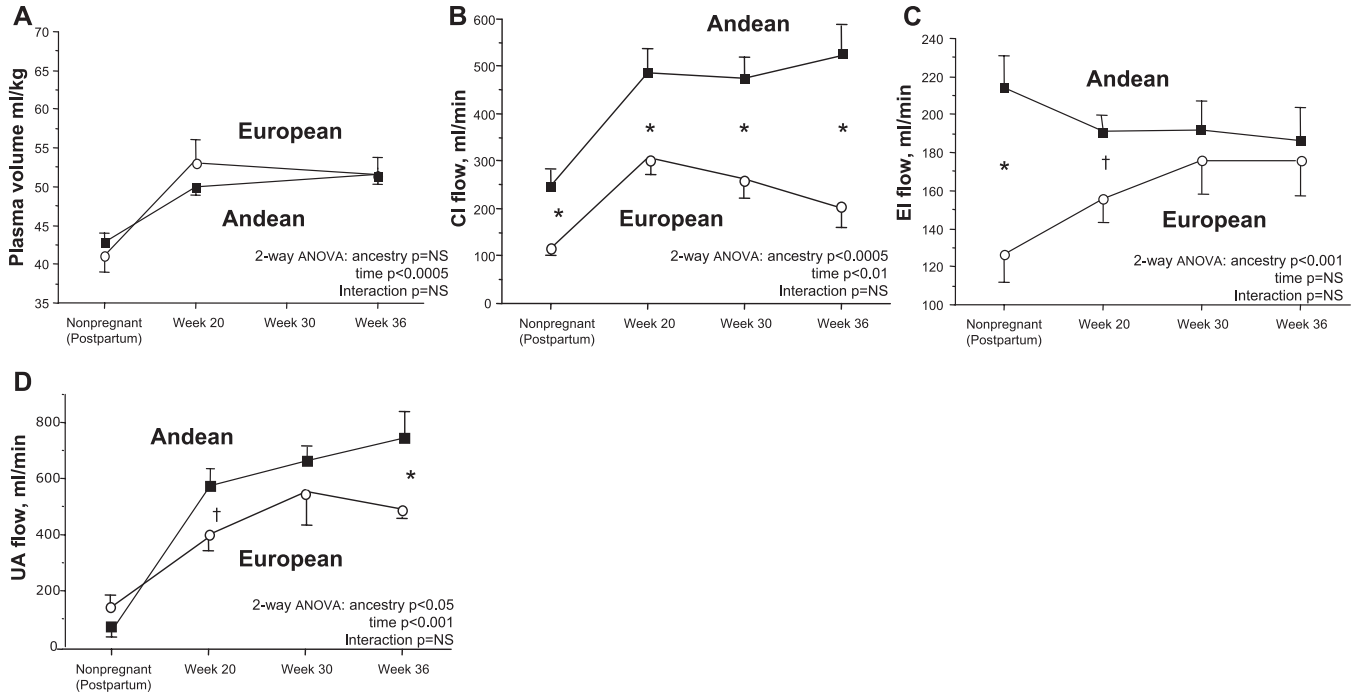

Fig. 1. *A*: plasma volume per kilogram body weight rose with pregnancy in both the European and Andean groups (one-way ANOVA, $P < 0.01$ and 0.0001, respectively) with nonpregnant time points showing differing values from *week 20* to *36* in each group. No significant differences existed between the two groups at any time. *B–D*: pregnancy increased common iliac (CI) and uterine artery (UA) (one- or two-way ANOVA, $P < 0.05$) blood flow, with nonpregnant values differing from *week 20*, *30*, and *36* values in each group. External iliac (EI) blood flow did not change with pregnancy (one-way ANOVA within each group or two-way ANOVA, P = NS). Andean compared with European subjects had higher CI, EI, and UA blood flow across all time points. Solid squares denote means ± SE values from 42 women of Andean ancestry studied serially during pregnancy and 3 mo postpartum. Open circles denote values obtained from 26 women of European ancestry. *Pairwise differences ($P < 0.05$) between ancestry groups at the time points designated. †Show trends $0.05 < P < 0.10$.

Relationship between changes in blood flow and blood volume. While plasma volume, CI, EI, and UA flow all increased during pregnancy, variation among subjects in the flow variables was unrelated to plasma volume at any time.

Fetal Biometry, Delivery, and Newborn Characteristics

During gestation, Andean babies had slightly greater head circumferences and tended to have greater biparietal diameters across all ultrasound measurement times, but differences between groups were slight and did not attain statistical significance at any single time (Table 4). Femur length was greater in the Andean babies at *week 20* and across all times. Umbilical artery S/D ratios fell progressively during gestation in both groups, with no differences occurring between groups. The middle cerebral artery S/D ratio was also similar between groups, although Andean values tended to fall and be lower than the European values at *week 36*.

Considering the 20 European and 36 Andean babies born at high altitude for whom birth weight data were available, there were no differences between groups in birth weight, gestational age, ponderal index, or sex distribution (Table 5). Baby length as well as head circumference were slightly greater in the European than Andean groups (Table 5). Because multiple factors influence birth weight and several known determinants differed between the two groups, we used multiple linear regression analysis to identify the variables that were related to birth weight in our study subjects. Among the characteristics listed in Tables 1 and 4, maternal height, parity, and infant gestational age were identified (partial correlation coefficients = 0.47, 0.26, and 0.41, P = 0.000, 0.002 and 0.06, respectively) and, together with ancestry, generated the following multiple regression model: $y = -209.4x_1 + 51.3x_2 + 103.9x_3 + 32.9x_4 - 5{,}992.0$ where y was birth weight in gm, x_1 represented European ancestry, x_2 parity, x_3 gestational age (wk), and x_4 maternal height (cm). Thus, after controlling for the influences of parity, gestational age, and maternal height, Andean babies weighed 209 g more than the European newborns (Table 4). Ponderal index tended to be greater as well in the Andean vs. European babies as well (one-tailed $P = 0.06$).

Greater UA cross-sectional area at *week 30* correlated positively with infant birth weight in the Andean subjects, but negatively in the European group (Fig. 3). The scatterplots and correlation coefficients (r values) shown in Fig. 3 are the raw values; after adjusting for variation in birth weight due to gestational age, maternal height and parity, the R^2 values increased markedly; the UA cross-sectional area-birth weight partial correlation coefficients were +0.39 ($P < 0.01$) in the Andeans and −0.37 ($P < 0.05$) in the Europeans. Similar but less significant relationships were seen when UA volumetric flow was considered as the independent variable, due chiefly to the smaller number of subjects in whom flow (vs. diameter) measurements were available.

DISCUSSION

This is the first study to measure uterine artery (UA) blood flow serially during pregnancy at high altitude in groups with differing prevalence of hypoxia-associated reductions in birth weight. Moreover, it is the first to examine whether differences

Table 2. *Maternal characteristics in the nonpregnant (4 mo postpartum) state at weeks 20 and 36 of pregnancy*

Variable	Group	Nonpregnant (Postpartum)	*Week 20*	*Week 36*	*P*-Time	*P*-Ancestry
Total blood volume, ml/kg	Andean	75.8±2.3 (41)†‡	83.0±1.6 (37)*	85.5±1.7 (39)*	<0.01	
	European	72.6±3.5 (13)†‡	87.5±3.2 (17)*	86.0±3.9 (14)*	<0.05	NS
	P-ancestry	NS	NS	NS		
Plasma volume, ml/kg	Andean	42.8±1.2 (41)†‡	50.0±1.0 (37)*	51.4±1.1 (39)*	<0.0001	
	European	41.1±2.1 (13)†‡	53.5±2.5 (17)*	51.4±2.5 (14)*	<0.01	NS
	P-ancestry	NS	NS	NS		
Red cell mass, ml/kg	Andean	32.8±0.8 (41)	32.9±0.7 (37)	34.2±0.8 (39)	NS	NS
	European	31.3±1.4 (13)	34.0±1.3 (17)	34.8±1.8 (14)	NS	
	P-ancestry	NS	NS	NS		
Hematocrit, %	Andean	44.4±0.5 (40)†‡	40.2±0.4 (38)*	40.6±0.5 (40)*	<0.0001	
	European	44.6±0.7 (15)†‡	40.1±1.1 (17)*	41.1±0.9 (16)*	<0.01	NS
	P-ancestry	NS	NS	NS		
Hemoglobin, g/dl	Andean	15.2±0.9 (39)†‡	13.3±0.2 (38)*	13.3±0.2 (40)*	<0.05	
	European	14.5±0.3 (15)‡	13.4±0.2 (17)	13.5±0.2 (17)*	<0.01	NS
	P-ancestry	NS	NS	NS		
Arterial O_2 saturation, room air, %	Andean	91.7±0.3 (41)†‡	94.6±0.3 (33)*	94.0±0.3 (38)*	<0.05	
	European	91.0±0.6 (16)†‡	94.3±0.6 (17)*	93.8±0.5 (18)*	<0.01	NS
	P-ancestry	NS	NS	NS		
Arterial O_2 content, ml/dl	Andean	17.9±0.2 (39)†‡	17.1±0.3 (33)*	17.1±0.2 (37)*	<0.05	
	European	18.0±0.4 (13)	17.3±0.4 (14)	17.4±0.4 (15)	NS	<0.01
	P-ancestry	NS	NS	NS		
Blood pressure, mmHg	Andean	72.5±1.0 (42)	76.1±1.5 (38)	75.1±1.5 (41)	NS	
	European	78.9±2.6 (18)	79.0±2.2 (19)	81.6±1.8 (20)	NS	<0.001
	P-ancestry	<0.01	NS	<0.05		
Heart rate, beats/min	Andean	75±1 (41)‡	79±2 (32)	81±2 (35)*	<0.05	
	European	78±3 (16)‡	79±5 (14)†	93±2 (18)*†	<0.01	<0.01
	P-ancestry	NS	NS	<0.01		

Values are shown as means ± SE or 95% confidence intervals for proportions, with sample sizes in parentheses. †$0.05 < P < 0.10$. *Significantly different from nonpregnant value. †Significantly different from *week 20* value, ‡Significantly different from *week 36* value using Tukey's post hoc tests. Interaction between the effects of time and ancestry were significant for heart rate ($P = 0.03$) but not for any other variable.

in UA blood flow and O_2 delivery contribute to the previously reported protection afforded by multigenerational high-altitude residence. Our data indicated that women of multigenerational (Andean) vs. shorter duration of high-altitude residence (European) had profoundly different uterine vascular adjustments to pregnancy. Specifically, UA blood flow and O_2 delivery were 1.6-fold greater in the Andean than European women as the result of greater lower body blood flow, in general, and a greater pregnancy-associated increase in UA diameter and UA blood flow, in particular. Andean babies were larger, both by biometry and by birth weight, once the known influences of gestational age, maternal height, and parity were taken into account. Thus we concluded that the previously recognized reduction in birth weight at high altitude is likely due, at least, in part, to lower UA blood flow and hence of delivery O_2 or other nutrient to the uteroplacental circulation.

Several kinds of difficulties needed to be overcome to conduct this study. One was to find a study site where both multigenerational and shorter-resident groups were present. La Paz, Bolivia was ideal in this regard, but the health care and other characteristics of its population meant that it was not practical to recruit subjects before they became pregnant. We therefore relied on determinations made 4 mo postpartum for an index of the nonpregnant state. Since not all cardiovascular parameters have returned to prepregnant values by this time (6), the actual effects of pregnancy may have been greater than those described here. However, such errors are likely to have been small, similar in the two ancestry groups, and hence unlikely to account for the group differences in UA blood flow and other flow characteristics reported. Another limitation pertains to the accuracy of the absolute flow estimates that can be achieved using Doppler ultrasound. While we and others have previously shown that pericutaneous Doppler ultrasound is reproducible and capable of accurately assessing changes within subjects and differences between groups within a given study (2, 33), the accuracy of the volumetric flow values in some vessels is limited. In particular, CI flows are probably underestimated, as judged by the fact that they are markedly less than the sum of the UA and EI flows. We think that this underestimation is due to the difficulty in obtaining the requisite, low angle of insonation in such a deep, horizontal vessel. There is also a difficulty in calculating TAM in vessels such as the CI or EI with high downstream vascular resistance and hence a period of reverse flow during diastole. The diameter measurements are not likely to be affected since its measurement is conducted at a high angle of insonation. Because the same calculation techniques were employed in all subjects, we consider that the relative differences between groups or changes across pregnancy are still valid, and hence, the values are reported here.

A strength of our study was that genetic markers were available from which population ancestry could be assessed. Test results confirmed the Andeans' overwhelmingly American Indian origin but also demonstrated considerable admixture among the European women, with approximately half showing some American Indian and West African ancestry. Because the American Indian and West African populations represented were also of low-altitude origin, and Andean populations are known to have resided at high altitude for much longer than the European-derived or other low-altitude groups (~10,000 vs. ~500 yr; see references in Ref. 32), we were assured that the two study groups differed in terms of

Table 3. *Maternal blood flow characteristics when nonpregnant (4 mo postpartum) and at weeks 20, 30, and 36 of pregnancy*

Variable	Group	Nonpregnant (Postpartum)	*Week 20*	*Week 30*	*Week 36*	*P*-Time	*P*-Ancestry	*P*-Interaction
Common iliac artery diameter, cm	Andean	0.66±0.02 (42)†‡§	0.89±0.02 (37)*	0.91±0.02 (39)*	0.88±0.02 (37)*	<0.0005		
	European	0.66±0.02 (20)†‡§	0.78±0.03 (19)*	0.81±0.03 (24)*	0.77±0.02 (21)*	<0.0005	<0.0005	NS††
	P-ancestry	NS	<0.01	<0.01	<0.001			
TAM, cm/s	Andean	11.3±1.0 (26)	12.4±1.0 (17)	12.7±0.9 (28)	13.2±1.1 (26)	NS		
	European	5.5±0.7 (16)†	9.4±1.0 (19)*	8.2±0.8 (21)	7.5±0.8 (18)	<0.05	<0.0005	NS
	P-ancestry	<0.0005	<0.05	<0.001	<0.0005			
External iliac artery diameter, cm	Andean	0.56±0.01 (42)†‡§	0.63±0.01 (37)*	0.62±0.01 (41)*	0.63±0.01 (39)*	<0.0005		
	European	0.60±0.02 (20)	0.65±0.01 (19)	0.65±0.01 (24)	0.64±0.01 (21)	<0.05	<0.01	NS
	P-ancestry	NS††	NS	NS††	NS			
TAM, cm/s	Andean	14.2±0.9 (28)†‡§	9.9±0.6 (18)*	10.2±0.6 (27)*	10.4±1.0 (28)*	<0.001		
	European	7.8±1.2 (17)	8.1±0.6 (19)	8.5±0.7 (21)	8.7±1.0 (17)	NS	<0.0005	<0.05
	P-ancestry	<0.0005	<0.05	NS††	NS			
Uterine artery diameter, cm	Andean	0.39±0.00 (19)†‡§	0.63±0.01 (37)*	0.65±0.01 (41)*	0.65±0.01 (38)*	<0.0005		
	European	0.39±0.01 (15)†‡§	0.56±0.02 (19)*	0.58±0.01 (24)*	0.56±0.01 (21)*	<0.0005	<0.0005	<0.01
	P-ancestry	NS	<0.0005	<0.0005	<0.0005			
Cross-sectional area, mm^2	Andean	12.2±0.3 (19) †‡§	32.0±0.8 (37)*	33.1±0.98 (41)*	33.1±0.97 (38)*	<0.0005		
	European	12.0±0.7 (15) †‡§	25.2±1.3 (19)*	26.8±1.23 (24)*	24.7±1.18 (21)*	<0.0005	<0.0005	<0.01
	P-ancestry	NS	<0.0005	<0.0005	<0.0005			
TAM, cm/s	Andean	9.1±3.0 (5)†‡§	31.0±3.2 (17)*	34.3±2.2 (28)*	34.9±2.7 (27)*	<0.001		
	European	12.4±3.3 (10)†‡§	26.7±2.3 (18)*	33.8±2.9 (21)*	32.7±3.0 (18)*	<0.0005	NS	NS
	P-ancestry	NS	NS	NS	NS			
PSV, cm/s	Andean	46.5±4.0 (15)†§	66.2±3.6 (37)§	76.7±4.9 (40)*	83.9±3.8 (38)*†	<0.0005		
	European	48.2±3.8 (13)†‡§	73.0±5.5 (19)*	80.2±4.6 (24)*	84.3±5.0 (21)*	<0.0005	NS	NS
	P-ancestry	NS	NS	NS	NS			
EDV, cm/s	Andean	5.6±1.7 (14)†‡§	26.2±2.1 (30)*†§	37.4±2.7 (30)*†	41.0±3.4 (28)*†	<0.0005		
	European	8.6±3.1 (13)†‡§	31.1±3.8 (15)*	39.8±2.7 (20)*	39.0±3.7 (20)*	<0.0005	NS	NS
	P-ancestry	NS	NS	NS	NS			
S/D	Andean	8.0±1.9 (14)†‡§	2.56±0.19 (37)*	2.18±0.07 (40)*	2.38±0.21 (38)*	<0.0005		
	European	6.6±2.0 (14)†‡§	2.16±0.10 (19)*	2.01±0.07 (24)*	2.13±0.12 (20)*	<0.0005	NS	NS
	P-ancestry	NS	NS	NS	NS			
PI	Andean	7.3±2.1 (14)†‡§	1.00±0.06 (37)*	0.87±0.04 (40)*	0.88±0.06 (38)*	<0.0005		
	European	2.4±0.5 (9)†‡§	1.03±0.21 (18)*	0.77±0.03 (23)*	0.81±0.06 (21)*	<0.0005	<0.0005	<0.0005
	P-ancestry	NS†	NS	NS††	NS			
RI	Andean	1.17±0.16 (16)†‡§	0.59±0.02 (37)*	0.55±0.02 (40)*	0.53±0.02 (38)*	<0.0005		
	European	0.87±0.06 (14)†‡§	0.57±0.05 (19)*	0.51±0.02 (24)*	0.53±0.03 (21)*	<0.0005	<0.01	<0.05
	P-ancestry	NS††	NS	NS	NS			
Vascular resistance, $mmHg \cdot ml^{-1} \cdot min^{-1}$	Andean	1.9±0.8 (5)†‡§	0.16±0.02 (17)*	0.13±0.02 (27)*	0.13±0.01 (25)*	<0.0005		
	European	1.2±0.2 (7)†‡§	0.24±0.03 (16)*	0.18±0.02 (20)*	0.21±0.03 (18)*	<0.0005	<0.05	<0.01
	P-ancestry	NS	NS††	NS	< 0.01			
O_2 delivery[2], ml $O_2 \cdot$ ml $blood^{-1} \cdot min^{-1}$	Andean	10.84±2.98 (5)§	94.48±13.61 (13)		126.82±18.47 (21)*	<0.01	NS	NS
	European	20.23±7.72 (6)†§	76.62±11.84 (13)*		80.33±8.69 (14)*	<0.01		
	P-ancestry	NS	NS		< 0.05			

Values are shown as means ± SE with sample sizes shown in parentheses. *Significantly different from nonpregnant (postpartum) value. †Significantly different from *week 20* value. ‡Significantly different from *week 30* value. §Significantly different from *week 36* value using Tukey's post hoc tests. ††$0.05 < P < 0.10$. TAM, time-averaged mean blood flow velocity; S/D, peak systolic velocity/peak end-diastolic velocity; 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).

multigenerational vs. shorter-duration residence at high altitude. Other differences existed between the Andean and European groups; namely, individual duration of high-altitude exposure, altitude of current residence, age, parity, body size, prenatal care, socioeconomic characteristics, and level of habitual activity. It was difficult to control for individual duration of high-altitude residence or the actual altitude of residence since there was virtually no overlap between the two groups. Such differences are unlikely to account for the Andeans' heavier birth weights given that the Andean women lived higher, not lower, than the Europeans. Additionally, previous studies do not indicate that lifelong high-altitude residence helps preserve fetal growth (12, 28); women born and raised at high altitude in Colorado have slightly lower birth-weight infants than do more recent migrants (42). The Andeans were younger, of greater parity, 12 cm (5 in) shorter, had lower body weights near term, began their prenatal care later, received fewer prenatal visits, had nearly 100-fold lower monthly household incomes, and reported slightly higher levels of habitual activity. Some of these maternal characteristics were

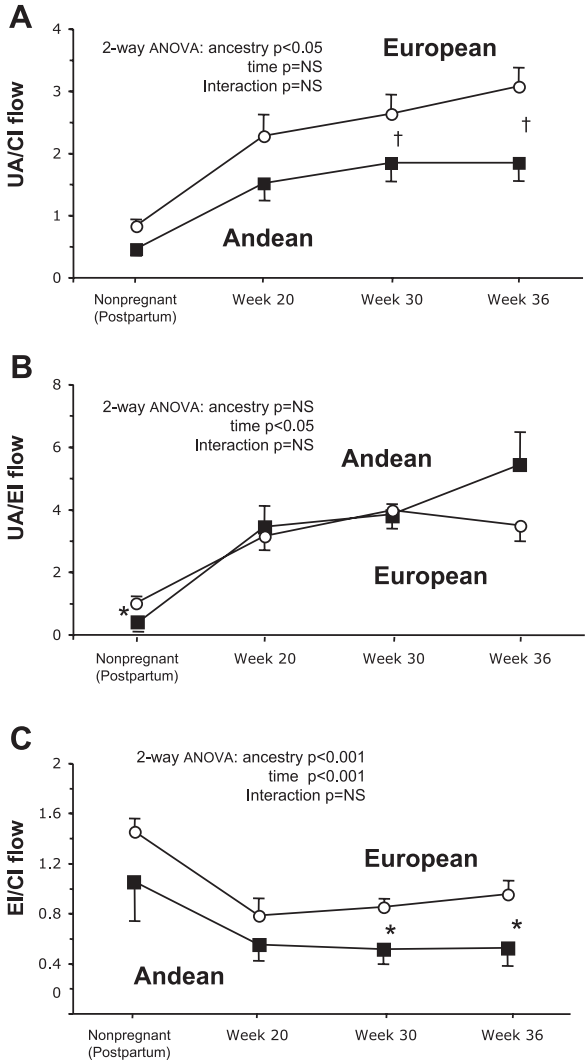

Fig. 2. *A*: European women had higher ratios of uterine artery to common iliac artery blood flow (UA/CI) than the Andean women, due to the Europeans' lower CI and the Andeans higher UA flows. Pregnancy did not change the UA/CI ratios, nor was there significant interaction between the effects of ancestry and pregnancy. *B*: UA relative to external iliac (EI) flow increased with pregnancy in the Andean and European groups, but there were no significant effects of ancestry or interaction between the effects of pregnancy and ancestry. *C*: Pregnancy lowered EI relative to CI flow (EI/CI) in both groups, with Andean ancestry lowering EI/CI relative to European values at all time points and especially *weeks 30* and *36* of pregnancy. Figure symbols are the same as in Fig. 1.

not related to birth weight or AC (maternal age, near-term body weight, week of 1st prenatal visit, number of prenatal visits, monthly household income, level of habitual activity) but others (maternal height, parity) demonstrated such associations. Because gestational age was also strongly related to birth weight, and there was a nonsignificant trend toward more preterm and fewer postterm Andean births, we used multiple linear regression to identify the other factors influencing birth weight and then covariance analysis to isolate the effect of population ancestry. We found that after adjusting for the variation among subjects and between groups in maternal height, parity, and gestational age, the Andean babies weighed 209 g more at birth than the Europeans and tended to have greater ponderal indices as well.

Other strengths of our study were its serial design and the completeness with which the determinants of uteroplacental O_2 delivery were assessed. By beginning our measurements at *week 20*, we were able to show that the Andeans' larger UA diameters were present well before *weeks 30–32*, which is when the slowing of fetal growth is thought to begin (22, 40). The early onset of these group differences and their persistence until term supported the likelihood that lower UA flows contributed to a reduction in fetal growth rather than being themselves a result of a lesser fetal demand. As shown in the companion paper (41), arterial oxygenation and its determinants (arterial O_2 saturation, hemoglobin concentration) did not differ between the Andean and European women. Although ethical and cultural constraints required noninvasive methods rather than arterial sampling for monitoring Sa_{O_2} and sampling venous blood for measuring hemoglobin concentration, the magnitude of error introduced is likely to be small, especially given the range of Sa_{O_2} values present (16). In addition, since the same methods were used in both groups, the magnitude and pattern of group differences were unlikely to be affected. Our use of pericutaneous Doppler ultrasound allowed us to characterize uterine (UA) as well as lower extremity (EI) flow. While the accuracy of the CI and EI flows was subject to the constraints mentioned above, comparisons of their changes with those occurring in the UA permitted assessing flow redistribution as a mechanism for raising uteroplacental O_2 delivery.

The present study was undertaken to test the study hypothesis that pregnancy affected UA blood flow differently in the two groups. There were clearly differences between the groups, as indicated by the significant effects of ancestry on UA flow, diameter, and cross-sectional area. There were also significant interaction effects, indicating that the effects of pregnancy on UA diameter and cross-sectional area differed in the two groups. These observations agreed with our hypothesis and also with our previous observations of higher UA flow velocities in Tibetan vs. Han ("Chinese") residents of Lhasa (3,600 m), Tibet Autonomous Region, as well as with the smaller diameters and hence lower flows seen at high vs. more moderate altitudes in Colorado (46). However, it is unclear whether the Andean or the European UA flows more closely resembled sea-level or lower-altitude values because both groups had higher UA flows than seen previously in healthy women residing at high altitude [3,100 m, 210 ml/min (46)], moderate altitude [1,600 m, 353 ml/min (33)] or sea level [342 ml/min (38)], supine (267 ml/min) and supine left lateral (410 ml/min) (14). The considerable variation in UA blood flows among these studies likely relates to postural effects, with supine as opposed to left lateral posture producing aortacaval compression and flow reductions (14). Color imaging in some (14, 38), but not other studies (33, 46), likely resulted in overestimating flow, since images are 5–10% larger with color imaging depending on depth of vessel location. Differences in instrumentation are also likely to be important. There is a trend for the estimated flow to increase with the passage of time, suggesting that advances in imaging that permit more accurate diameter measurement or better quantification of the time-averaged mean flow velocity may be involved. Therefore, we consider that it is only valid to compare flow between groups when the same instrumentation, operators, and analytical techniques are employed.

Table 4. *Fetal biometry characteristics*

Variable	Group	*Week 20*	*Week 30*	*Week 36*	*P*-Time	*P*-Ancestry	*P*-Interaction
Biparietal diameter, cm	Andean	5.7±0.1 (38)	7.9±0.1 (40)	8.8±0.1 (37)	<0.0005		
	European	5.3±0.2 (17)	7.5±0.2 (18)	9.0±0.1 (19)	<0.0005	NS	NS†
	P-ancestry	NS†	NS†	NS†			
Head circumference, cm	Andean	20.4±0.4 (37)	28.2±0.2 (40)	31.6±0.2 (36)	<0.0005		
	European	19.1±0.5 (17)	27.7±0.3 (22)	31.8±0.2 (19)	<0.0005	<0.05	NS
	P-ancestry	NS†	NS	NS			
Abdominal circumference, cm	Andean	18.9±0.4 (38)	26.8±0.3 (40)	31.2±0.3 (37)	<0.0005		
	European	17.8±0.6 (16)	26.3±0.4 (22)	31.7±0.4 (19)	<0.0005	NS	NS
	P-ancestry	NS	NS	NS			
Femur length, cm	Andean	4.1±0.1 (38)	6.0±0.1 (40)	7.0±0.1 (36)	<0.0005		
	European	3.8±0.1 (17)	5.8±0.1 (22)	7.0±0.1 (19)	<0.0005	<0.05	NS†
	P-ancestry	<0.05	NS†	NS			
Umbilical artery S/D, cm	Andean	4.2±0.4 (37)	3.1±0.1 (37)	2.9±0.2 (37)	<0.0005		
	European	4.7±0.6 (16)	3.1±0.1 (22)	2.8±0.4 (18)	<0.01	NS	NS
	P-ancestry	NS	NS	NS			
Middle cerebral artery S/D, cm	Andean	6.4±1.0 (36)	5.1±0.7 (38)	3.6±0.2 (35)	NS†		
	European	4.9±1.4 (16)	4.1±0.9 (21)	4.2±0.3 (18)	NS	NS	NS
	P-ancestry	NS	NS	NS†			

Values shown are means ± SE or 95% confidence intervals for proportions. †$0.05 < P < 0.10$. Fetal biometry values are adjusted for variation in actual gestational age at the time of study.

We considered the involvement of both systemic and uteroplacental factors to understand the physiological mechanisms that could account for the Andean and European group differences. Systemic effects of pregnancy begin early, with the maximal fall in vascular resistance and blood pressure and rise in cardiac output occurring by midgestation [*week 24*, (39)]. Because the Andeans had greater CI, EI, and UA blood flow, we considered it likely that their cardiac outputs were higher as well. Since blood volume (and hence preload) did not differ, differences in cardiac output could have been due to reduced systemic vascular resistance (afterload) or greater myocardial contractility. The Andean women's lower blood pressures and calculated uterine vascular resistances at *week 36* were consistent with a reduction in afterload. Lower blood pressures and greater flow-induced systemic vasodilation has been observed previously in long- compared with shorter-term high-altitude residents (18, 36), as well as in pregnant high- compared with low-altitude Andeans, perhaps due to greater nitric oxide production (13). Viewed conversely, the Europeans' CI flows may also have been limited by relative systemic vasoconstriction resulting from greater sympathetic activity, as suggested by their higher heart rates.

Table 5. *Delivery and newborn characteristics*

Variable	Andean	European	*P*-Ancestry
Hospital delivery, %	90.0 [78, 97] (40)	100 [88, 100] (20)	NS
Delivery type			
Spontaneous vaginal, %	80.6 [66, 91] (36)	40.0 [21, 62] (20)	
Cesarean section, %	16.6 [7, 31]	60.0 [38, 79]	<0.01
Other, %	2.8 [0.3, 12]	0.0 [0, 0]	
Birth weight, g	3,150±60 (36)	3,265±88 (20)	NS
Length, cm	48.8±0.4 (34)	50.4±0.5 (17)	<0.05
Ponderal index, kg/m^3	27.2±0.6 (34)	26.1±0.9 (17)	NS
Head circumference, cm	34.1±0.2 (31)	35.1±0.3 (16)	<0.01
Gestational age, wk	39.1±0.3 (35)	39.4±0.3 (20)	NS
Preterm, %	8.8 [2, 22]	0.0 [0, 0]	NS
Postterm, %	2.9 [0.3, 13]	5.0 [0.5, 21]	NS
Male, %	50.0 [34, 66] (36)	70.6 [47, 88] (17)	NS
SGA, %	14.7 [6, 29] (35)	15.0 [4, 35] (20)	NS
Adjusted birth weight, g	3,271±62 (34)	3,062±90 (19)	<0.05$^\delta$
Adjusted ponderal index, kg/m^3	27.4±0.7 (32)	25.1±1.1 (16)	NS†$^\delta$

Values shown are means ± SE or 95% confidence intervals for proportions. Adjusted birth weight or ponderal index values are those obtained using covariance analysis in which significant factors related to birth weight, gestational age, maternal height, and parity, are set to mean values for the two groups combined (39.2 wk gestational age, 153.9 cm maternal height, 2.6 parity). †$0.05 < P < 0.10$. δOne-tailed *P* value. SGA, small for gestational age (<10th percentile for gestational age and sex (38) without adjustment for maternal body size or other characteristics).

Uteroplacental changes are also important for raising UA blood flow, especially in humans for whom upright posture limits venous return and cardiac output during the 3rd trimester (39). Thus, raising UA flow during the 3rd trimester requires redistributing CI flow toward the UA and away from vascular beds supplied by other abdominal vessels or the EI artery (35). A key mechanism for doing so is a greater pregnancy-associated fall in uteroplacental than in nonuteroplacental vascular resistance. Lower uteroplacental resistance indices have been reported in a large, cross-sectional study of high- compared with low-altitude Andean residents of Peru, but newcomer groups such as Europeans were not examined (20). Our data show lower calculated uterine vascular resistances in the Andean than European subjects across all time points and at *week 36*, in particular. Surprisingly, there were no Andean-European differences in the S/D, PI, or RI during pregnancy. Such a discrepancy suggests that these resistance indices are of limited sensitivity and not able to detect a 1.6-fold differences in blood flow or vascular resistance. In this regard, it is important to note that the S/D, PI, or RI are not actual measures of vascular resistance but, simply, the ratios of flow velocity at various points in the cardiac cycle. One factor that likely contributed to the Andean women's lower uteroplacental vascular resistance was their larger UA diameters. Although the major resistance vessels in the human uteroplacental circulation are the arcuate, basilar (or spiral arteries in complicated pregnancies), the main

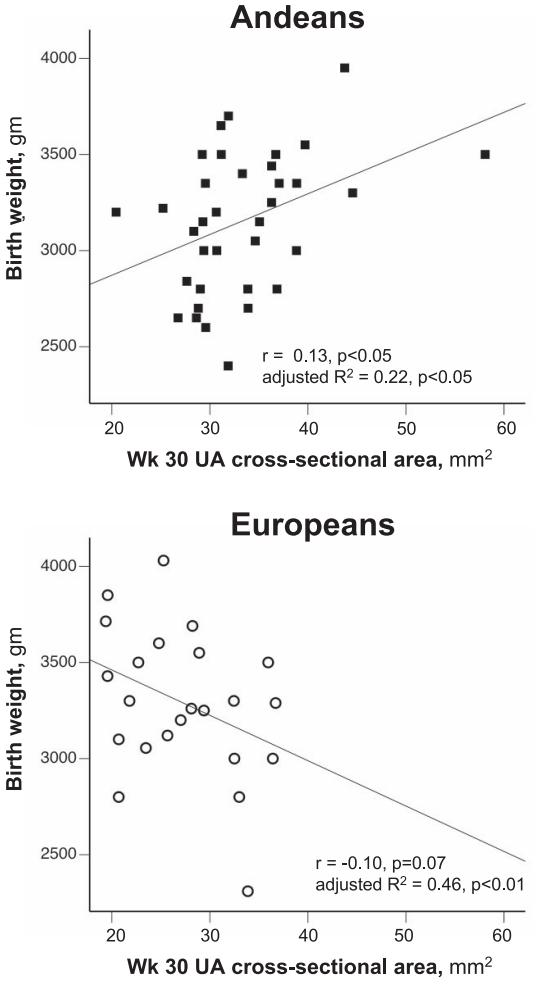

Fig. 3. In the Andean group (*top*), mothers with greater uterine artery (UA) cross-sectional area at *week 30* have infants with heavier birth weights. European women (*bottom*) show just the opposite relationship with greater UA cross-sectional area tending to be correlated with lower birth weights. The birth weight values plotted are the raw values. Shown also are the correlation coefficients and the adjusted R^2 values obtained when birth weight was normalized for variation in gestational age at delivery, maternal height, and parity. Inclusion of these covariates had substantial effects on the relationship between UA cross-sectional area and birth weight, especially in the European group.

UA also contributes, since in species with hemochorial placentation, two-thirds of uteroplacental vascular resistance resides upstream of the terminal, uteroplacental channels (26). The larger UA diameters in the Andean compared with the European women may have been due to greater vessel growth, differences in the levels of circulating or locally produced vasodilators and vasoconstrictors, and/or changes in sensitivity to such substances or to other physiological stimuli, such as blood flow itself (24, 34, 43). Such possibilities remain to be addressed in future studies.

As has been observed in previous studies, the birth weight seen at high altitude were ~200 g lower than sea-level norms but relatively greater in babies born to Andean compared with European women after adjusting values for the influences of other known determinants. Altitude-associated reductions in birth weight have been previously reported in Bolivia and neighboring countries, with the fall in birth weight being diminished in Andean vs. European groups (9, 12, 17, 31). Indicating that protection from altitude-associated reductions in fetal growth is not confined to Andeans are our data demonstrating that Tibetan babies born at high altitude also weigh more than Han ("Chinese") newborns (27, 29, 45), a group that has immigrated to high altitude even more recently than Europeans (32). Like the Andeans, the Tibetans' heavier birth weights cannot be attributed to differences in maternal body size, health care, or socioeconomic characteristics, suggesting that differences in maternal vascular adjustments to pregnancy were involved in the higher ratios of UA to CI or EI flow velocity seen in the Tibetan than Han pregnant women. However, the lack of imaging equipment prevented us from determining whether UA blood flow and O_2 delivery were greater in the Tibetan than Han groups (30).

The Andean women's higher UA blood flows and uteroplacental O_2 delivery in combination with their infant's higher (adjusted) birth weights suggested to us that differences in UA blood flow were responsible, at least in part, for the higher birth weights observed. Four observations supported this idea. First, reductions in UA flow seen in other conditions (e.g., preeclampsia) are associated with lower birth weights. Second, the European group's reduced UA blood flows and birth weights agreed with previous observations in shorter-term high-altitude residents in Colorado (46). Third, the Andean women's heavier birth weights were consistent with their babies' greater femur lengths, head circumference, and trend toward greater biparietal diameter across all gestational ages. It was surprising, however, was that abdominal circumference was not greater in the Andean group, perhaps due to the somewhat greater variation seen in this variable. It is tempting to speculate that the Andean women's greater fetal size was established early and that ancestry-group differences diminished near term, perhaps as a result of the European group relying on other mechanisms such as increased placental exchange or oxygen extraction at a time when their UA blood flows were diminishing. However, such comparisons are limited by the small sample sizes, differences between the Andean and European groups in their altitude of residence, as well as other factors affecting birth weight in the two groups. Fourth, within-group comparison showed that Andean women with greater UA cross-sectional area (or diameter) at *week 30* had heavier birth weight infants. These observations were consistent with our hypothesis that the Andean women's higher UA blood flows and greater uteroplacental O_2 delivery protected them from hypoxia-associated reductions in fetal growth. Although the Europeans' lower UA blood flows were consistent with their babies' lower birth weights, some other factor(s) also appeared to be influencing fetal growth in the European group. Specifically, unlike the positive association seen in the Andean group, the relationship between birth weight and UA cross-sectional area at *week 30* was negative in the European group. Similar, negative relationships were seen in the European group for other variables or other study times; lower UA blood flows at *week 30* or *36* were associated with heavier unadjusted and adjusted birth weights ($r = -0.20$ and -0.22, respectively, both $P < 0.05$) and a trend existed for higher uteroplacental vascular resistance to be associated with greater abdominal circumference at *week 36* ($r = 0.47$, $P = 0.06$). Such observations also support the idea that factors such as placental exchange or extraction, rather than UA blood flow, were the primary determinants of

3rd trimester fetal growth in the European group. Clearly, additional studies with larger sample sizes are required to document group differences in the temporal pattern of fetal growth.

Although the present study focused on the influence of population ancestry on UA blood flow and uteroplacental O_2 delivery in relation to fetal growth and birth weight, other factors may also have been involved. For example, lower UA blood flow would clearly affect the delivery of other nutrients. We were not able to measure glucose levels in the present study, but previous studies in Peru have shown that maternal plasma glucose levels are lower in high-altitude compared with low-altitude pregnant Andean women (21). In addition, lower expression of the glucose transporter-1 has been reported in the basal membrane placental fractions from high-altitude compared with lower-altitude Colorado pregnancies (46), suggesting that glucose uptake may be reduced as well. Thus decreases in aerobic, as well as anaerobic metabolism, may have contributed to the reductions in fetal growth and lower birth weights observed. Another factor that may have influenced birth weight were the group differences in maternal exercise levels since it has been previously shown that women who exercise regularly have ~250 g heavier birth-weight infants (8). However, unlike the Andean women, the exercise-related increase in birth weights is more likely due to improved placental exchange or O_2 extraction since both acute and chronic exercise reduce UA blood flow (8). Also arguing against the Andean women's higher levels of habitual activity being responsible for the birth-weight differences observed was the absence of an association between level of habitual activity and UA blood flow or birth weight in the present study. Future studies are required to better document the influences of diet and exercise on hypoxia-associated reductions in birth weight.

In summary, we found differences in uteroplacental vascular adjustments to pregnancy in multigenerational Andean compared with shorter-term European residents of high altitude. These ancestry-group differences in vascular adjustments to pregnancy could not be attributed to maternal body size, prenatal care, or other characteristics. Rather, higher lower-body blood flows and lower uteroplacental vascular resistance permitted the Andean compared with European women to achieve 1.6-fold greater levels of UA blood flow and O_2 delivery near term. Because UA blood flow but not arterial O_2 content was greater in the Andean than European group, it can be stated conclusively that the greater uteroplacental O_2 delivery was due to higher levels of UA blood flow. Consistent with our hypothesis, Andean babies were larger both by biometry and birth weight once the known influences of gestational age, maternal height, and parity were taken into account. Because UA blood flow and uteroplacental O_2 delivery were also markedly greater in the Andean than European women, we considered it likely that they contributed to the birth weight differences observed. These Andean-European blood flow differences were present in the absence of alterations in indices of uteroplacental vascular resistance (S/D, PI, RI), suggesting that volumetric flow rather than velocity-derived resistance indices is a more reliable guide for detecting uteroplacental ischemia under the kinds of chronic conditions studied here. Whether the Andean-European group differences observed here were due to genetic factors is unknown, but we speculate that multiple generations of high-altitude residence have altered the frequencies of hypoxia-inducible factor-regulated or regulatory genes to confer protection from hypoxia-associated fetal growth restriction.

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