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Do Anti-angiogenic or Angiogenic Factors Contribute to the Protection of Birth Weight at High Altitude Afforded by Andean Ancestry?

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Abstract

Objective—This prospective study was designed to determine whether variation in angiogenic (placental growth factor [PlGF]) and/or anti-angiogenic (soluble fms-like tyrosine kinase [sFlt-1]) factors contribute to the protective effect of highland ancestry (Andean) from altitude-associated reductions in fetal growth.

Study design—Plasma sFlt-1 and PlGF levels, uterine artery (UA) blood flow, and fetal biometry were determined in low-altitude (400 m; Andean n = 27, European n = 28) and high-altitude (3600 m; Andean n = 51, European n = 44) residents during pregnancy (20 and 36 weeks) and 4 months postpartum.

Results—High-altitude decreased sFlt-1 levels in both groups, Andeans had lower sFlt-1, comparable PlGF, lower sFlt-1/PlGF ratios, and higher UA blood flow throughout pregnancy relative to Europeans. Altitude decreased birth weight in Europeans but not Andeans. In high-altitude Europeans sFlt-1/PlGF and sFlt-1 levels were negatively associated with UA diameter and birth weight, respectively.

Conclusions—Lower sFlt-1 and sFlt-1/PLGF ratio may contribute to or result from variations in maternal vascular adaptation to pregnancy between Andean and Europeans at high altitude. Subsequently, these effects could potentially influence ancestry-associated differences in birth weight.

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Keywords

Fetal growth restriction; high-altitude adaptation; placenta growth factor; pregnancy; soluble fms-like tyrosine kinase 1

Introduction

The uterine artery (UA) undergoes profound dilation, growth, and remodeling during pregnancy that, collectively, permit a progressive rise in maternal UA blood flow and hence delivery of oxygen and other nutrients to the fetoplacental circulation.[1-4] The chronic hypoxia of residence at high altitude (≥2500 m) impairs maternal vascular adaptation to pregnancy, reducing the normal pregnancy-associated increase in UA diameter and rise in UA blood flow by about one third.[5,6] Such reduction in UA blood flow likely contributes to diminished fetal growth and the increased frequency of preeclampsia at high compared to low altitude.[7-11]

Notably, populations with many generations of residence at high altitude, such as Andeans or Tibetans, are relatively protected against this altitude-associated reduction in fetal growth.[9,11,12] Such protection in Andeans appears to be due, in part, to the preservation of a normal pregnancy-associated increase in UA diameter and blood flow; this is in contrast to Europeans, whose UA diameters and blood flow do not increase to the same extent.[13-15] The mechanisms responsible for these ancestry-associated differences in UA diameter, blood flow, and fetal growth are unclear.

Because angiogenesis (and angiogenic factors) are known to play an important role in the uterine vascular response to pregnancy,[3,16-19] we hypothesized that higher levels of angiogenic compared to anti-angiogenic factors in the maternal circulation may contribute to the higher UA blood flows and birth weights in Andeans relative to Europeans at high altitude. Placental growth factor (PlGF), and the anti-angiogenic factor soluble fms-like tyrosine kinase (sFlt-1) and their ratio are frequently used to describe angiogenic processes during pregnancy as levels of these factors are altered in both preeclampsia[20,21] and fetal growth restriction.[22,23] Chronic hypoxia downregulates PlGF and upregulates sFlt-1 expression via the hypoxia-inducible factor (HIF) pathway;[24,25] we, therefore, asked whether Andeans had higher PlGF, lower sFlt-1, and/or lower sFlt-1/PlGF ratio levels than Europeans and, if so, whether such differences were associated with UA blood flow or fetal growth at high altitude.

Material and Methods

Participants

Participants were 150 women, including 51 Andeans and 44 Europeans living at high altitude in La Paz or El Alto (3600-4100 m), as well as 27 Andean and 28 European low-altitude residents of Santa Cruz (400 m), Bolivia. Women were recruited through their prenatal care physician and were required to be of good health, no more than 20 weeks pregnant, receiving prenatal care, and at no known risk of developing pregnancy complications (eg, diabetes, chronic hypertension). Patients were excluded if they had lived at low altitude for more than 3 months, smoked, consumed more than 2 alcoholic beverages weekly before pregnancy, had any known risk factor for developing PE (ie, a current multiple-gestation pregnancy, chronic hypertension, gestational diabetes, or any cardiovascular or renal disease) or had evidence of infection; implementing these criteria minimized potentially confounding effects on fetal or gestational outcome. All women gave written informed consent to study procedures that had been approved by the human

participant review boards of the University of Colorado–Denver and its Bolivian counterpart, Colegio Médico. Patients were excluded if they had preeclampsia (>2 blood pressures ≥ 140/90 mm Hg at least 6 hours apart and >1 + proteinuria by dipstick or 300 mg/L in a 24-hour collection). Women who delivered babies with neonatal complications (eg, respiratory distress) or were missing birth or other essential data were also excluded.

Ancestry was determined by self-identification as being either Andean (ie, Aymara or Quechua) or European and confirmed by examining surnames (parental and grandparental) and genetic markers. We used a panel of 100 ancestry informative markers (AIMs) to quantify the proportion of each woman's genetic that could be ascribed to West African, European, or Indigenous American origin using the maximum likelihood method as described in our previous studies.[13,15,26] Data for the percentage AIMs in each ancestry group are reported in Table 1. Final classification as Andean required confirmation by having at least 3 of their 4 parental surnames being of Aymara or Quechua origin and >60% Indigenous American genetic ancestry. Women were classified as European if they self-identified as being of European or of other low-altitude origin and had <50% Indigenous American genetic ancestry. Women who did not fit these criteria were excluded from the analyses.

Protocol, Variables, and Instrumentation

Women were studied prospectively at 20 and 36 weeks of pregnancy and 4 months postpartum for a measurement in the nonpregnant state. Actual times of study were 21.7 ± 0.24 and 36.0 ± 0.17 weeks of pregnancy and 4.25 ± 0.43 months postpartum.

All samples were collected at or close to the participant's altitude of residence using the laboratory facilities at the Instituto Boliviano de Biología de Altura in La Paz or Clínica Siraní in Santa Cruz, Bolivia. At the first visit, each woman filled out a questionnaire to provide information regarding her ancestry, altitude of birth, age, body weight before pregnancy, education, and residential history. A general clinical examination including the measurement of height by stadiometer (at the first visit only), body weight by balance scale, and proteinuria by dipstick (Albustix, Bayer, Canada) was conducted at each visit. Venous blood was drawn by venipuncture into collection tubes containing EDTA; all samples were stored in 1-mL aliquots at –80°C and transported to our Denver-based laboratory for the measurement of sFlt-1 (specificity: 3.5 pg/mL, inter- and intra-assay precision of 5.5% and 3.2%, respectively) and PlGF (specificity: 7.0 pg/mL, inter- and intra-assay precision of 10.0% and 5.6%, respectively) by enzyme-linked immunosorbet assay ([ELISA]; R&D systems, Minneapolis, Minnesota). All nonpregnant PlGF levels were below the assay's lower limit of detection and zero values were assigned as previously described.[27]

Uterine artery diameter, blood flow velocity, and fetal biometry (cm) were measured percutaneously using an ATL3000 transabdominal ultrasound unit configured for obstetric use with color imaging and Doppler. Uterine artery diameter and blood flow velocity were used to calculate UA blood flow (mL/min). Briefly, measurements were taken with a 4-MHz curved linear array probe by the same operator using the same machine at the same location within each altitude study site to minimize inter-instrument and inter-operator variability. The angle of insonation was required to be ≤45° for all flow variables to avoid considerable error.[13] The UA was measured at its crossover with the external iliac as previously described.13 Fetal abdominal and head circumference and femur length were performed after the maternal blood flow velocity and diameter measurements. Gestational age was calculated using ultrasound at week 20, based on our previous observations that these values are within 2 weeks of that calculated from last menstrual period.13,15 Birth weight, length, gestational age, and infant sex were collected from medical records completed by hospital personnel at the time of delivery.

Statistics

Data are reported as the mean ± standard error of the mean (SEM) or as a percentage and 95% confidence interval (CI) for proportions. Comparisons between ancestry and altitude groups at single points were made using *t* tests for continuous variables or chi-square (χ^2) tests for nominal or ordinal variables. The effects of pregnancy, ancestry, or altitude were examined using 1-, 2-, or 3-way analysis of variance (ANOVA) and differences over time determined with Scheffé post hoc tests. Factors known to influence birth weight (income, gestational age, infant sex, maternal weight, and height) were included in the calculation of adjusted birth weight but were only retained in the model if they had significant effects thus, birth weight and ponderal index were corrected for maternal height and actual gestational age as a covariate as estimated from the 20-week ultrasound examination; these adjusted values are displayed in grams and gr/ht. Relationships between pro- or anti-angiogenic factors, UA blood flow and or diameter, fetal biometry, and birth weight were assessed in the pregnant group, using linear regression, with the actual gestational age of study included as a covariate. All analyses were conducted using SPSS (v. 12.0; Chicago, Illinois). Significance was reported when 2-tailed *P* values were <.05 unless otherwise specified. A trend was defined when $.05 < P < .10$.

Results

Maternal Characteristics

High-altitude Andeans were overwhelmingly of Indigenous American genetic ancestry (93.1% ± 1.3%) as assessed by AIMs. Andeans at low altitude had slightly higher European admixture (39.6% ± 2.3%) than those at high altitude (17.6% ± 2.7%), but all were largely of Indigenous American ancestry. High-altitude Europeans had somewhat larger European genetic ancestry proportions (76.2% ± 3.1%) than their low-altitude counterparts (50.9% ± 2.9%), due to greater Indigenous American admixture but questionnaire-derived data indicated that such admixture was of low-altitude, Central American or Caribbean origin (data not shown). All women had relatively low percentages of West African AIMs (Table 1A.).

Low-altitude Europeans were taller, weighed more at 36 weeks of pregnancy, and had higher educational levels than Andeans (Table 1A). At high altitude, the Andeans weighed less at week 36, were younger, of greater parity, shorter, had lower monthly incomes (Table 1A) and educational levels (Andeans: 11.76% [5.06, 22.65] vs Europeans: 73.17% [58.37, 84.83] $P < .001$), and had lived at high altitude longer than Europeans (20.4 vs 8.4 years, respectively, $P < .001$). Andeans at high versus low altitude were of greater parity, shorter, and had lower monthly incomes (Table 1A). Europeans at high versus low altitude were older, tended to be taller, weighed less at 36 weeks of pregnancy, and had higher incomes (Table 1A).

Newborn Characteristics

High altitude tended to reduce birth weight in Europeans but not Andeans (Table 1B). Gestational age varied between groups such that low-altitude Europeans delivered earlier (Table 1B), due largely to the high proportion of elective Cesarean sections and the practice of scheduling such deliveries 1 to 2 weeks before the due date. After correcting the birth weight for variation in gestational age and maternal height, high-altitude European babies weighed 275 g less than their low-altitude counterparts. No differences were observed when ancestry groups were compared at both altitudes.

Uterine Artery Characteristics

Pregnancy increased UA diameter and blood flow in all women but these pregnancy-associated changes were greater in Andean than European women at high altitude (Table 2). In both groups, maximal UA diameter was achieved by 20 weeks. High altitude reduced the pregnancy-associated rise in UA diameter in Europeans, but not in Andeans. Uterine artery blood flow was equivalent between ancestry groups at low altitude but was 22% and 26% greater in Andeans than Europeans at high altitude at 20 and 36 weeks, respectively. It should be noted that nonpregnant UA diameter and calculated UA blood flow were greater at high than low altitude in both ancestry groups.

Angiogenic and Anti-Angiogenic Factors

Pregnancy increased PlGF levels similarly in the Andeans and Europeans but the rise occurred earlier at high than low altitude (Figure 1, interaction between altitude and time, $P < .001$ for Andeans and $P < .05$ for Europeans). At low altitude, PlGF was positively associated with UA diameter or blood flow in all women at 20 weeks (partial R^2 for Europeans = .48 $P < .05$ and for Andeans = .63 $P < .01$). No associations were observed at high altitude.

Pregnancy increased sFlt-1 levels at both altitudes (Figure 2). The pregnancy-associated rise was similar between ancestry groups at low but not high altitude, where Andeans showed a smaller rise and therefore lower sFlt-1 levels than Europeans at 20 and 36 weeks. sFlt-1 levels were lower at high than low altitude in both groups, with the reduction being greater in Andeans than Europeans (interaction between the effects of altitude, time, and ancestry, $P < .05$).

At low altitude, the sFlt-1/PlGF ratio was similar at 20 and 36 weeks of pregnancy and between ancestry groups (Figure 3). In contrast, pregnancy increased the sFlt-1/PlGF ratio at high altitude, with the ratio being lower in Andeans than Europeans at both 20 and 36 weeks (Figure 3), principally as a result of lower sFlt-1 (Figure 2).

Among high-altitude Europeans, lower sFlt-1/PlGF ratios were associated with larger UA diameter at 36 weeks (Figure 4A). Heavier birth weights were associated with lower sFlt-1 levels at 36 weeks of pregnancy in high-altitude Europeans (Figure 4B), but no such association was present for Andeans or in either group at low altitude.

Fetal Growth Characteristics

There were no ancestry-related differences in fetal biometry at low altitude (Table 2). Among low-altitude Andeans, higher PlGF and lower sFlt-1/PlGF ratios at 20 weeks were associated with greater fetal abdominal circumference (R^2: .59; R^2: .37, respectively, both $P < .05$) and femur length (R^2: .62; R^2 .36, respectively, both $P < .05$). Among low-altitude Europeans, lower sFlt-1/PlGF ratios were also associated with greater head circumference (R^2: .28 $P < .05$) and femur length (R^2: .29 $P < .05$) at week 20. High-altitude Andeans had larger fetal head circumference and femur length relative to Europeans, and a trend toward greater abdominal circumference (Table 2). At high altitude, the PlGF levels at 20 weeks were positively associated with head circumference in Europeans (R^2:.91 $P < .001$) and abdominal circumference in Andeans (R^2: .53 $P < .001$).

Discussion

The current study presents novel evidence that high-altitude residence alters circulating levels of anti-angiogenic factors during pregnancy,[2] the extent of these alterations is ancestry dependent, and likely contributes to greater UA blood flow and protection of fetal

growth apparent in Andeans at high altitude. Specifically, in this study Andeans compared to Europeans at high altitude had lower sFlt-1 and sFlt-1/PlGF ratio levels at 20 and 36 weeks of pregnancy. Moreover, among high-altitude Europeans, lower anti-angiogenic factor sFlt-1 and sFlt-1/PlGF ratio levels were associated with heavier birth weights and greater UA diameters, respectively. Therefore, our data suggest that lower sFlt-1 and lower sFlt-1/PlGF ratio levels near term may contribute to greater UA blood flow and diameters seen in Andeans and thus the protection from altitude-associated reductions in fetal growth. To the best of our knowledge, this is the first study to demonstrate an association between circulating levels of angiogenic factors, fetal biometry, and UA blood flow during pregnancy.

Limitations of our study included smaller sample sizes at low compared to high altitude. Although we recruited an equal number of participants at both altitudes, greater admixture among the low-altitude Europeans (had >50% Indigenous American genetic ancestry) reduced our sample size slightly for that group. Another difficulty was that we had to rely on circulating levels of PlGF and sFlt-1 because only maternal blood samples could be obtained, and therefore could not distinguish between the contributions of a maternal versus fetal source of production for these substances. Second, contrary to our expectations, UA diameter and calculated UA blood flow values were greater at high than low altitude in the nonpregnant state in Europeans and Andeans. We were careful to have the same operators at a given altitude. However, we cannot disregard the possibility that operator- or equipment-related effects account, in part, for the variation between altitudes, given that even small differences in cursor placement can greatly influence the diameter and flow measurements, given that vessel radius is squared in flow calculations. Nonpregnant measurements were made postpartum, therefore we do not believe that menstrual cycle phase influenced our results. Furthermore, unlike our[9,13,15] and other previous findings,[14] adjusted birth weights were similar in Andean and European infants at high altitude, and we consider this result likely to be due to the smaller sample sizes in this versus previous report.

Our low-altitude data agree with previous studies of normal pregnancy in terms of the gradual nature of the rise in PlGF and the absolute values achieved.[21,28] At high altitude, however, PlGF increased earlier than at low altitude in both ancestry groups. We consider that the more abrupt increase in PlGF at 20 weeks may reflect a longer vasculogenic phase of placental growth; this idea is in accordance with the hypothesized 2-stage model which postulates that high altitude exerts a greater stimulatory effect on angiogenic factors early in pregnancy as a compensatory response.[29] Existing data suggest that PlGF levels are lower and sFlt-1 greater, in preeclampsia and/or fetal growth restriction, both of which are often marked by reduced uteroplacental blood flow resulting in reduced oxygen and available nutrients.[30-33] We believe that the greater PlGF levels seen at 20 weeks at high altitude may be due to lower levels of sFlt-1, suggesting that the normal binding that occurs between such factors[34,35] may not be happening by the middle of pregnancy at high altitude (ie, 20 weeks). The fact that greater PlGF levels at high compared to low altitude were evident by 20 weeks is important given that this is prior to the time when fetal growth is thought to decline in altitude-associated fetal growth restriction.[7]

Studies conducted in human placental villous explants,[36] primary cytotrophoblast cell cultures,[20] and intact animals[27] demonstrate that hypoxia upregulates sFlt-1 expression. Such upregulation would be anticipated to antagonize the normal pregnancy-associated rise in vascular endothelial growth factor (VEGF) and/or PlGF required for vascular remodeling and angiogenesis.[20,24,27,36-38] We, therefore, expected to find higher sFlt-1 in the maternal circulation at high than low altitude but, in contrast, we found lower sFlt-1 levels in both ancestry groups. One explanation for this may be that the production of sFlt-1 by peripheral blood mononuclear cells (PBMCs) is altered under conditions of hypoxia and

preeclampsia and may be cell-type specific.38 Rajakumur and colleagues38 report that hypoxia increases sFlt-1 production by PBMCs, however because they did not report cell differentials it is unknown what kind of PBMCs was producing sFlt-1. This is an important consideration for interpreting our results, given that acute and chronic hypoxia decrease the number as well as the proportion of T-lymphocytes (CD3+ and CD4+) among total PBMCs, whereas the opposite is true for natural killer (NK) lymphocytes (CD16 and CD56).39 Thus, we consider that the lower sFlt-1 values at high versus low altitude reported in this study, may reflect differences in the composition of PBMCs at high relative to low altitude. Our data also demonstrate that sFlt-1 levels in European women were elevated relative to Andean values. Such higher sFlt-1 levels were seen in combination with reduced UA blood flow, similar to what has been observed in preeclampsia and Small for Gestational Age (SGA) compared with normal pregnancies31،40; this literature, in combination with our data, support the likelihood that higher sFlt-1 levels and sFlt-1/PlGF ratios contributed to the lower UA blood flow and birth weights observed in previous studies of European versus Andean women at high altitude.9،13،14

Alterations in PlGF as well as sFlt-1 characterize pregnancies complicated by preeclampsia and fetal growth restriction, both conditions with marked reductions in uteroplacental blood flow. Consistent with this, we found that European women with greater sFlt-1 levels at 36 weeks delivered infants of lower birth weight at high altitude. Because previous studies show that the ratio of sFlt-1-to-PlGF levels are altered in pregnancies where there is reduced uteroplacental blood flow and fetal growth,[41-43] we also asked whether their ratio was influenced by effects of altitude or ancestry. Consistent with our hypothesis, Andean sFlt-1/PlGF ratios did not rise to as great an extent from 20 to 36 weeks as they did in the European participants. As a result, Andean sFlt-1 relative to PlGF levels were only half of those seen in Europeans near term (Figure 3). Given the association between higher sFlt-1/PlGF values and smaller UA diameter in the European women, we considered that these group differences in the sFlt-1/PlGF ratio were likely important contributors to the one-third smaller UA diameters and markedly lower UA blood flow values reported previously[13,15] and seen here in the Europeans compared to Andeans near term at high altitude.

In summary, Andean relative to European women have lower sFlt-1 and sFlt-1/PlGF ratios at high altitude, supporting the idea that these factors are related to Andean protection from altitude-associated reductions in fetal growth. Further study is needed to determine the mechanisms by which ancestry and altitude influence the pregnancy-related changes in these factors. The contribution of other factors also influencing maternal vascular response to pregnancy is also of interest. In particular, given the important role of soluble-endoglin, an antiangiogenic molecule of importance to preeclampsia,[43] and cytokines as local mediators of placental development and maternal immune response during normal and complicated pregnancies,[18,19,44-46] future studies are needed for determining their role in accounting for the effects of altitude and ancestry on UA blood flow and fetal growth.

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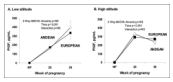

Figure 1.

At both altitudes and ancestry groups PlGF levels were greater during pregnancy than in the non-pregnant state. The pattern of increase across time differed such that PlGF increased early at high altitude (B) whereas levels rose throughout pregnancy at low altitude (A). This temporal difference resulted in greater PlGF levels at high than low altitude at 20 weeks in both ancestry groups (Andean: $p<0.001$, European: $p<0.05$).

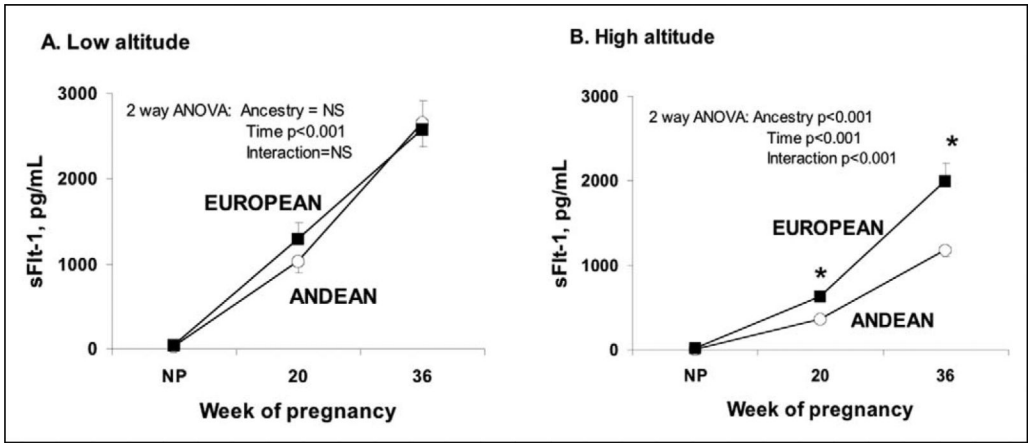

Figure 2.

At both altitudes and ancestry groups sFlt-1 levels increased across time. No differences were found between ancestry groups at low altitude (A). Pregnancy raised sFlt-1 at high altitude (B) to a greater extent in European than Andean women, with differences between groups being present at both weeks 20 and 36 ($p<0.05$).

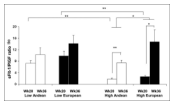

Figure 3.

High altitude Andeans and Europeans had higher sFlt-1/PlGF levels at 36 than at 20 weeks of pregnancy ($p<0.05$; $p<0.001$ respectively). High altitude Europeans had higher sFlt-1/PlGF ratio than high altitude Andeans ($p<0.05$). Women living at high altitude had lower sFlt-1/PlGF ratio than their counterparts at low altitude ($p<0.05$).

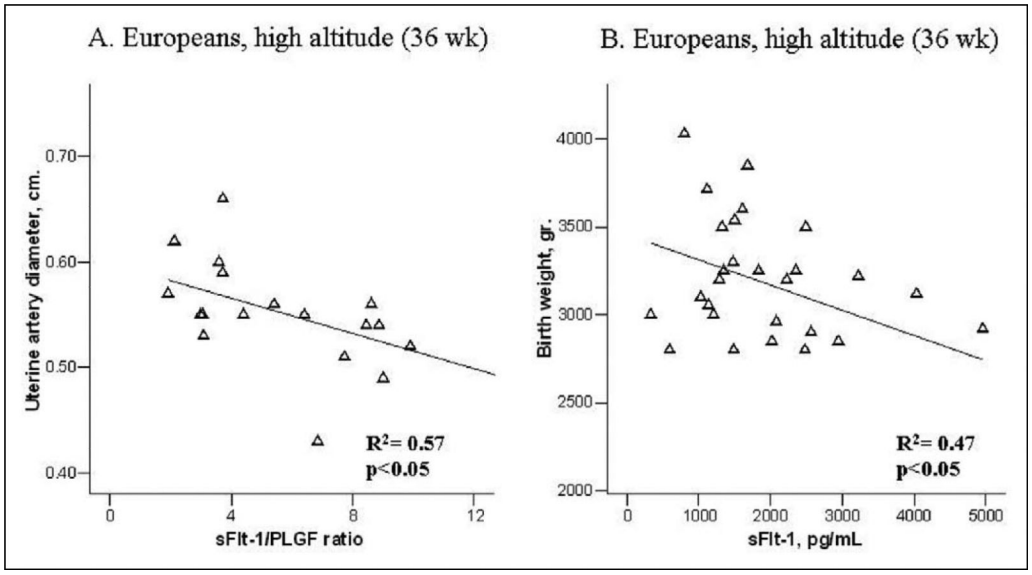

Figure 4.

High altitude Europeans with higher levels of sFlt1-PlGF ratio at 36 weeks of pregnancy had smaller UA diameters (A) and gave birth to smaller babies (B).

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Table 1

Maternal and Newborn Characteristics[a]

Variables		Ancestry	Altitude		
			Low	High	*P* Altitude
A. Maternal characteristics					
Ancestry, %	European	European	50.9 ± 2.9 (28)	76.2 ± 3.1 (44)	*P* < .001
		Andean	15.2 ± 1.7 (27)	4.6 ± 1.1 (51)	*P* < .001
		P ancestry	*P* < .001	*P* < .001	
	Amer-indian	European	39.6 ± 2.3 (28)	17.6 ± 2.7 (44)	*P* < .001
		Andean	75.3 ± 1.7 (27)	93.1 ± 1.3 (51)	*P* < .001
		P ancestry	*P* < .001	*P* < .001	
	West African	European	9.4 ± 1.1 (28)	6.2 ± 0.9 (44)	*P* < .05
		Andean	9.6 ± 0.7 (27)	2.2 ± 0.5 (51)	*P* < .001
		P ancestry	NS	*P* < .001	
Age	years	European	27.1 ± 1.1 (28)	31.8 ± 0.7 (43)	*P* < .001
		Andean	24.7 ± 1.1 (27)	26.9 ± 0.9 (49)	NS
		P ancestry	NS	*P* < .001	
Parity	no. live births	European	2 ± 0 (28)	2 ± 0 (43)	NS
		Andean	2 ± 0 (27)	3 ± 0 (49)	*P* < .001
		P ancestry	NS	*P* < .01	
Height	cm	European	159.5 ± 1.1 (28)	162.4 ± 1.1 (44)	NS[c]
		Andean	155.2 ± 0.8 (25)	150.0 ± 0.7 (49)	*P* < .001
		P ancestry	P < 0.01	P < 0.001	
Weight at 36 wks	kg	European	77.0 ± 2.5 (24)	71.8 ± 1.5 (38)	NS[c]
		Andean	67.4 ± 2.3 (19)	66.0 ± 1.3 (45)	NS
		P ancestry	*P* <.01	*P* < .01	
Monthly income	US dollars	European	320 ± 56 (22)	1793 ± 322 (28)	*P* < .001
		Andean	204 ± 32 (18)	131 ± 20 (51)	*P* < .01
		P ancestry	NS[c]	*P* < .001	
B. Newborn Characteristics					
Birth weight	g	European	3365 ± 91 (26)	3172 ± 57 (43)	NS[c]

Variables		Ancestry	Altitude		*P* Altitude
			Low	High	
		Andean	3267 ± 100 (21)	3119 ± 64 (38)	NS
		P ancestry	NS	NS	
Birth weight, adjusted[b]	g	European	3369 ± 89 (25)	3094 ± 69 (36)	$P < .05$
		Andean	3278 ± 123 (19)	3247 ± 83 (27)	NS
		P ancestry	NS	NS	
Infant length	cm	European	49 ± 0.2 (26)	50 ± 0.4 (39)	NS
		Andean	50 ± 0.3 (21)	49 ± 0.3 (34)	NS
		P ancestry	NS	NS	
Ponderal index	kg/m^3	European	28 ± 0.6 (26)	26 ± 0.6 (39)	NS[c]
		Andean	27 ± 0.7 (21)	27 ± 0.6 (34)	NS
		P ancestry	NS	NS	
Ponderal index adjusted[b]	kg/m^3	European	28 ± 0.6 (26)	26 ± 0.6 (39)	NS[c]
		Andean	27 ± 0.7 (21)	27 ± 0.7 (32)	NS
		P ancestry	NS	NS	
Gestational age	wks	European	38 ± 0.3 (26)	39 ± 0.2 (43)	$P < .01$
		Andean	39 ± 0.5 (21)	39 ± 0.3 (36)	NS
		P ancestry	$P < .05$	NS	

[a] Values are shown as mean ± SEM or 95% confidence intervals for proportions with sample sizes parentheses.

[b] Values are corrected for gestational age and maternal height, and displayed for comparisons made between the ancestry groups within altitude.

[c] $05 < P < 0.10$ and NS = not significant.

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Table 2

Fetal Biometry and Uterine Artery Characteristics[a]

				Week of Pregnancy			
Variable		**Altitude**	**Ancestry Group**	**Nonpregnant**	**Week 20**	**Week 36**	***P* Time**
UA diameter	cm	Low	European	0.26 ± 0.01 (25)[d]	0.49 ± 0.01 (28)[c]	0.51 ± 0.02 (24)	*P* < .001
			Andean	0.20 ± 0.01 (16)[e]	0.47 ± 0.01 (26)[e]	0.48 ± 0.02 (19)[d]	*P* < .001
			P ancestry	*P* < .05	NS	NS	
		High	European	0.41 ± 0.04 (30)[d]	0.54 + 0.01 (26)[c]	0.55 ± 0.01 (37)	*P* < .001
			Andean	0.39 ± 0.01 (l8)[e]	0.63 ± 0.01 (45)[e]	0.64 ± 0.01 (43)[d]	*P* < .001
			P ancestry	NS	*P* < .001	*P* < .001	
UA blood flow	m L/min.	Low	European	25.59 ± 3.70 (25)[d]	295.09 ± 25.17 (28)	400.76 ± 35.87(24)	*P* < .001
			Andean	12.50 ± 2.78 (16)	262.87 ± 26.12 (26)[e]	349.01 ± 32.41 (19)[d]	*P* < .001
			P ancestry	*P* < .01	NS	NS	
		High	European	73.94 ± 14.01 (19)[d]	361.57 ± 39.07 (25)	418.90 ± 33.91(34)	*P* < .001
			Andean	55.28 ± 22.28 (4)	564.43 ± 47.40 (22)[e]	705.25 ± 75.92 (31)[d]	*P* < .01
			P ancestry	NS	*P* < .01	*P* < .01	
Head circum	cm	Low	European	–	17.63 ± 0.53 (27)[c]	30.04 ± 0.92 (17)[c]	*P* < .001
			Andean	–	18.78 ± 0.56 (25)[c]	31.59 ± 1.04 (13)	*P* < .001
			P ancestry	–	NS	NS	
		High	European	–	19.11 ± 0.41 (25)[c]	31.95 ± 0.42 (36)[c]	*P* < .001
			Andean	–	20.46 ± 0.31 (42)[c]	31.08 ± 0.39 (41)	*P* < .001
			P ancestry	–	*P* < .05	NS	
Abdominal circum	cm	Low	European	–	16.03 ± 0.49 (27)[c]	31.92 ± 0.30 (17)	*P* < .001
			Andean	–	16.87 ± 0.50 (26)[c]	31.81 ± 0.34 (13)	*P* < .001
			P ancestry	–	NS	NS	
		High	European	–	18.00 ± 0.42 (24)[c]	32.06 ± 0.28 (36)	*P* < .001
			Andean	–	18.91 ± 0.32 (43)[c]	31.42 ± 0.26 (41)	*P* < .001
			P ancestry	–	NS[b]	NS	

Variable		Altitude	Ancestry Group	Week of Pregnancy: Nonpregnant	Week 20	Week 36	*P* Time
Femur length	cm	Low	European	–	3.53 ± 0.12 (27)	6.97 ± 0.05 (17)	*P* < .001
			Andean	–	3.75 ± 0.12 (26)	7.01 ± 0.06 (13)	*P* < .001
			P ancestry	–	NS	NS	
		High	European	–	3.71 ± 0.10 (25)	7.07 ± 0.54 (36)	*P* < .001
			Andean	–	4.12 ± 0.08 (43)	7.66 ± 0.51 (41)	*P* < .001
			P ancestry	–	*P* < .01	NS	

Abbreviations: Circum, circumference; UA, uterine artery.

[a] Values are shown as mean ± SEM, with sample sizes in parentheses.

[b] 05 < *P* < .10. Corrected for actual gestational age. Values are displayed for correction within ancestry group.

[c] *P* < .05.

[d] *P* < .01.

[e] *P* < .001 for altitude comparisons within the ancestry group and week of pregnancy.