Original Research Article

Lowland Origin Women Raised at High Altitude are not Protected Against Lower Uteroplacental O_2 Delivery During Pregnancy or Reduced Birth Weight

COLLEEN G. JULIAN,[1]* JENNIFER L. HAGEMAN,[1] MEGAN J. WILSON,[1] ENRIQUE VARGAS,[2] AND LORNA G. MOORE[1,3]
[1]*Department of Emergency Medicine, Altitude Research Center, University of Colorado Denver, Aurora, Colorado*
[2]*Instituto Boliviano de Biología de Altura, La Paz, Bolivia*
[3]*Graduate School of Arts and Sciences, Wake Forest University, Winston-Salem, North Carolina*

Objective. Maternal physiologic responses to pregnancy promoting fetal oxygen and nutrient delivery are important determinants of reproductive success. Incomplete physiologic compensation for reduced oxygen availability at high altitude (≥2,500 m) compromises fetal growth. Populations of highland (e.g., Andeans, Tibetans) compared with lowland origin groups (e.g., Europeans, Han Chinese) are protected from this altitude-associated decrease in birth weight; here we sought to determine whether maternal development at high altitude—rather than highland ancestry—contributed to the protection of birth weight and uterine artery (UA) blood flow during pregnancy.

Methods. In women of lowland ancestry who were either raised at high altitude in La Paz, Bolivia (3,600–4,100 m) ("lifelong," $n = 18$) or who had migrated there as adults ("newcomers," $n = 40$) we compared maternal O_2 transport during pregnancy and their infant's birth weight.

Results. Pregnancy raised maternal ventilation and arterial O_2 saturation equally, with the result that arterial O_2 content was similarly maintained at nonpregnant levels despite a fall in hemoglobin. UA blood flow and uteroplacental O_2 delivery were lower in lifelong than newcomer residents (main effect). Birth weight was similar in lifelong residents versus newcomers (2,948 ± 93 vs. 3,090 ± 70 gm), with both having values below those of a subset of eight high-altitude residents who descended to deliver at low altitude (3,418 ± 133 gm, $P < 0.05$).

Conclusion. Lifelong compared with newcomer high-altitude residents have lower uteroplacental O_2 delivery and similar infant birth weights, suggesting that developmental factors are likely not responsible for the protective effect of highland ancestry. Am. J. Hum. Biol. 23:509–516, 2011.

High altitude is a valuable context for understanding the processes of human adaptation since maternal physiologic responses to pregnancy at high altitude constitute a major effect on reproductive fitness. It has been well established that high-altitude residence decreases birth weight and that populations of highland ancestry (Tibetans, Andeans) have less severe reductions in birth weight at high altitude than populations that migrated more recently from low to high altitude (Europeans, Han Chinese) (Moore, 2011). Considerable evidence also demonstrates that women of highland origin have higher levels of uterine artery (UA) blood flow and uteroplacental O_2 delivery than those of lowland origin (Chen et al., 2002; Julian et al., 2009; Moore et al., 2001; Wilson et al., 2007; Zamudio et al., 2007). Comparing across altitudes, women of highland ancestry achieve normal or perhaps even elevated UA blood flow during pregnancy whereas UA blood flow of European (or other lowland origin) is reduced at high compared with low altitude in studies conducted using the same equipment and operator (Julian et al., 2009; Zamudio et al., 1995). One possibility for explaining the protective effects of highland ancestry is that genetic variants enabling a normal, pregnancy-associated rise in UA blood flow under conditions of chronic hypoxia have been selected for in Andeans and/or Tibetans. Alternatively, since populations of highland origin not only have a longer generational history of high-altitude residence but also the individual women have had a longer duration of high-altitude exposure, developmental factors may also be responsible for the protective effect of highland ancestry. Developmental factors have been shown, for example, to play a role in deciding the increase in lung volume seen in residents of high altitude (Frisancho et al., 1973; Johnson et al., 1985). Against the possibility that developmental factors are involved, previous studies have shown birth weights not to differ in babies born to lifelong versus newcomer high-altitude residents in Colorado (Moore et al., 1982b; Weinstein and Haas, 1977) and lower birth weights in lifelong European versus Andean residents of high altitude (Haas et al., 1980); three unique features of this study expand upon these initial findings. First, we consider that if a difference in birth weight existed between "newcomers" and "lifelong" high-altitude residents, that it would more likely be revealed at the higher elevations of La Paz, Bolivia (3,600–4,100 m) than in the comparatively lower altitudes of Colorado (3,100 m). Second, recent technologic advances permit non-invasive measurements of UA blood flow to assess the potential role of development at high altitude on maternal vascular adaptation to pregnancy. Finally, using novel genetic methods it is now possible to assess genetic admixture and genetic ancestry with a much higher resolution than that obtained by surname analysis. We therefore undertook the present

Contract grant sponsor: NIH; Contract grant numbers: HL60131 and HL079647; Contract grant sponsor: NSF and American Heart Association; Contract grant number: 0610129Z.

*Correspondence to: Colleen G. Julian, Department of Emergency Medicine, Altitude Research Center, University of Colorado Anschutz Medical Campus, 12469 East 17th Place, Bldg. 400, Aurora, CO 80045-0508, USA. E-mail: colleen.julian@ucdenver.edu

Received 2 December 2010; Revision received 21 January 2011; Accepted 6 February 2011

DOI 10.1002/ajhb.21167

Published online 27 April 2011 in Wiley Online Library (wileyonlinelibrary.com).

investigation to ask whether women of lowland ancestry who were either newcomer versus lifelong residents of high altitude differed in terms of their maternal O_2 transport responses to pregnancy and/or infant's birth weight. Studies were conducted in La Paz, Bolivia where persons of European ancestry have resided at altitudes ≥3,600 m for relatively short periods of time (one to four generations). Maternal uteroplacental O_2 delivery and its proximal determinants were measured serially during pregnancy and again postpartum as an index of the nonpregnant state, and infant birth weight determined at delivery. We considered that such studies would be informative for determining whether the protective effects of highland ancestry on UA blood flow and infant birth weight are acquired during development.

MATERIALS AND METHODS

Subjects

Subjects were 58 healthy women currently residing at high altitude in La Paz, Bolivia (3,600–4,100 m) who were recruited through prenatal care clinics. Studies were conducted at the Instituto Boliviano de Biología de Altura (Bolivian High-Altitude Biology Institute) and the Clinica del Sur (Southern Clinic) in La Paz. Inclusion criteria were that the women be of European or other lowland ancestry, in good health, receiving prenatal care, and at no known risk for developing pregnancy complications (e.g., history of preeclampsia or diabetes). The women granted informed consent to study procedures that had been approved by the Colorado Multiple Institutional Review Board (COMIRB) and the Colegio Médico, the equivalent ethical review group in Bolivia. Subjects were defined as "lifelong" residents (n = 18) if they had been raised at high altitude (>2,500 m) and "newcomers" (n = 40) if they migrated to high altitude as adults. Subjects included in this report are a subset of the 137 subjects who took part in a larger study designed to identify the role of increased maternal UA blood flow in protecting Andeans from altitude-associated reductions in infant birth weight (Julian et al., 2009).

Variables and definitions

Maternal residential history, socioeconomic, health, and reproductive history were obtained by questionnaire. Three women (all lifelong high-altitude residents) smoked during pregnancy but since there were no differences between smokers and nonsmokers for the primary outcome variables for lifelong residents (e.g., smoking had no effect on birth weight) these women were retained in the analyses reported here. Ancestry was determined by self-identification, parental and grandparental surnames (Chakraborty et al., 1989), and a panel of 100 ancestry-informative genetic markers (AIMs) (Shriver et al., 2003). Nearly half the women (four lifelong and 23 newcomer residents) had ≥80% European AIMs. For those with <80% European AIMs it was evident that Indigenous American ancestry was derived from lowland sources (e.g., Guarani, Aztec) both by self-report and surname analysis and hence these women were included in the analyses reported here.

Blood pressure was measured by arm cuff sphygmomanometer, and averaged from measurements made on the right and left sides. Maternal heart rate was measured by auscultation. Maternal body weight and height were obtained while lightly clothed. For assessing proteinuria, a clean-catch urine specimen was obtained at each visit using Albustix (Bayer, Elkhart, IN) and scored as negative, trace, 1+, 2+, 3+, ≥4+. Triceps and subscapular skinfolds were averaged from the right and left sides and summed as an index of maternal body fat.

All ventilatory studies were performed between 9:00 am and noon after an at least 2 hour fast. While resting quietly in the seated position and breathing room air through a bidirectional respiratory valve with a mouthpiece and nose clip in place, ventilation (VE), end-tidal O_2 and CO_2 tensions ($PETo_2$ and $PETco_2$), arterial O_2 saturation (SaO_2), and heart rate were monitored for 5 to 8 min or until values became stable as previously described (Vargas et al., 2007). $PETco_2$ was used as an index of $Paco_2$ because it provides an accurate measure of alveolar ventilation per unit CO_2 production that is independent of body size. SaO_2 was measured in a warmed digit by pulse oximetry (Biox 3700, Ohmeda, Louisville).

Blood was withdrawn from the antecubital vein by routine venipuncture. Hematocrit and hemoglobin concentration were determined using the microcentrifuge technique and the cyanmethemoglobin technique or OSM3 oximeter, respectively. Arterial O_2 content (CaO_2) was calculated as SaO_2 × hemoglobin (hb) concentration (gm/dl) × 1.36 (i.e., ml of O_2 that can bind to each gram of Hb). Vessel diameters and flow velocities (peak systolic velocity [PSV], either minimum or end-diastolic velocity [MDV, EDV], and the time-averaged mean [TAM] velocity) were measured pericutaneously using an ATL3000 ultrasound unit and a 4 MHz curved linear array probe configured for obstetrical use with color imaging and Doppler as previously detailed (Wilson et al., 2007). Maternal vessels, blood flows, and resistance indices were examined bilaterally and results reported as the average of the right- and left-side measurements. Vessel blood flows were calculated as $\pi r\ 2 \times \mathrm{TAM} \times 60$ where r is the vessel radius estimated without color imaging (Palmer et al., 1992; Wilson et al., 2007). Uteroplacental O_2 delivery was calculated as the product of CaO_2 and UA blood flow, and is expressed as ml O_2 × ml blood^{-1} × min^{-1}. All measurements were made using the same machine, location, and operator.

Birth weight, gestational age, infant sex, length, head circumference, and Apgar scores were obtained from medical records completed by hospital personnel at the time of birth. Although newborn anthropometry was performed by different personnel, data suggest that trained personnel have a low technical error of measurement, and values obtained have an acceptably low level of biased (WHO, 2006). Gestational age was calculated as weeks from the last menstrual period, which was equivalent in all cases to that estimated by fetal ultrasound at week 20. Preterm was considered as <37 weeks and postterm as >42 weeks gestation. Infants were classified as small for gestational age (SGA) when the birth weight for gestational age and sex was less than the 10th percentile of sea-level values (Williams et al., 1982). Eight of the high-altitude residents (seven newcomers, and one lifelong resident) descended at or near the beginning of the third trimester to give birth at low altitude. Newborn information for infants born at low altitude was obtained by requesting newborn and delivery records from the hospital where the delivery took place.

TABLE 1. Maternal characteristics

Variable	Newcomer	Lifelong	*P*
Residence in La Paz (yr)	3.5 ± 0.4 (37)	23.1 ± 2.2 (18)*	*
Ancestry AIMS (%)			
European	76.8 ± 3.9 (39)	63.1 ± 4.7 (17)**	**
Amerindian	15.0 ± 3.1 (38)	29.7 ± 4.3 (17)*	*
West African	8.6 ± 2.4 (39)	7.2 ± 1.1 (17)	NS
Age (yr)	32.5 ± 0.8 (38)	30.3 ± 1.0 (18)	NS
Primigravid (%)	30 [17–46] (37)	50 [29–71] (18)	NS
Prepregnant BMI (kg/m^2)	24.5 ± 0.8 (26)	25.2 ± 0.9 (14)	NS
$Skinfolds_{triceps + subscapular}$ (mm)	39.9 ± 2.8 (24)	51.0 ± 8.1 (10)	NS
Height (cm)	163.0 ± 1.1 (39)	158.6 ± 1.9 (17)**	**
Weight at wk 36 (kg)	71.5 ± 1.7 (30)	72.3 ± 1.9 (17)	NS
Weight gain wk 20→36 (kg)	6.4 ± 0.6 (18)	7.6 ± 1.2 (8)	NS
Monthly household income ($)	2067 ± 366 (24)	1263 ± 420 (13)	NS
Prenatal care			
wk 1st visit	11.1 ± 1.1 (19)	9.5 ± 2.4 (6)	NS
No. prenatal visits	7.2 ± 0.5 (21)	8.1 ± 0.3 (7)	NS
Education (%)			
≥Secondary school	100 [91–100] (37)	100 [81–100] (16)	NS
Proteinuria (≥1+) (%)			
Week 36	35 [17–59] (17)	28 [15–46] (29)	NS
Generations at high altitude[a]	1.1 ± 0.1 (37)	3.2 ± 0.3 (16)*	*
Generations at high altitude (spouse)[a]	1.5 ± 0.2 (35)	3.5 ± 0.3 (14)*	*
Smoking (% yes)	0 [0–12] (29)	19 [7–43] (16)	**
Preeclampsia (% yes)	9 [3–24] (33)	8 [1–33] (13)	NS

Values are shown as mean ± SEM or 5% confidence intervals for proportions, with sample sizes in parentheses.
[a]Generations at high altitude includes the infant as one generation.
*$P < 0.01$; **$P < 0.05$.

Statistics

Data are expressed as the mean ± SEM or the 95% CI for proportions. Comparisons between lifelong versus newcomer residents at single times were conducted using student's *t*-tests for continuous variables and chi-square for nominal or ordinal variables. The effects of pregnancy or high-altitude residence were tested using one- or two-way analysis of variance or covariance with contrasts and Tukey's multiple comparisons as appropriate. Correlation was employed to identify those maternal and infant characteristics related to birth weight and ponderal index among our study subjects, with the criterion for inclusion and exclusion at $P \leq 0.10$. Significant covariates (birth weight: gestational age; ponderal index: maternal income and parity) were set to average values for the two groups combined in order to isolate the effect of group on birth weight or ponderal index, respectively. Power analyses were conducted to evaluate the sample sizes required for detecting significant birth-weight differences between the lifelong and newcomer high-altitude residents using an alpha of 0.05. All analyses were conducted using SPSS 18.0 (Chicago, IL). Significance was reported when $P < 0.05$ and trends were considered when $0.05 < P < 0.10$.

Protocol

Women were studied at weeks 20 (21.9 ± 0.4) and 36 (36.4 ± 0.2) of gestation and 4 (3.8 ± 0.3) months postpartum as an index of the nonpregnant state. Background information was obtained by questionnaire on the initial visit, and followed by a physical exam, ventilatory studies, blood sample collection and an ultrasound exam at each visit.

RESULTS

Maternal characteristics

Age, educational status, reproductive history, weight at 36 weeks of pregnancy, pregnancy weight gain, skinfolds, and household income were similar but lifelong residents were shorter than newcomer women (Table 1). By study design, lifelong residents spent their childhoods at higher altitudes (3,530 ± 112 m vs. 451 ± 117 m, $P < 0.0001$) and had lived longer at high altitude than newcomers. All but five of the lifelong residents were born at high altitude; the average age of upward migration for these women was 10.2 ± 1.7 years. The average age at upward migration was 28.9 ± 0.9 years for newcomer high altitude residents and averaged 7.2 ± 2.1 for lifelong residents (including the five lifelong residents born at altitudes lower than 2,500 m). The number of generations of high-altitude residence (including the infant as one generation) was likewise greater for infants born to lifelong women than for newcomers (Table 1). Examination of genetic markers indicated that while the lifelong residents had substantial European ancestry, lifelong residents had greater levels of Indigenous American admixture than in newcomer women. However, by self-report and surname analyses, the source of Indigenous American admixture was of low-altitude origin and therefore all women were judged to be of low-altitude origin. There was no difference between groups in the proportion of West African origin (Table 1). Both groups began their prenatal care early and had a similar number of prenatal visits (Table 1). There were no differences in the frequency of proteinuria, preeclampsia, or other pregnancy complications between groups (Table 1).

Ventilatory and hematological characteristics

Pregnancy increased alveolar ventilation (i.e., ventilation per unit CO_2 production) in both groups as indicated by the fall in end-tidal pCO_2 ($PETCO_2$, Table 1). Consistent with this was the increase in total ventilation (VE) seen in the lifelong residents and the increase in end- tidal pO_2 ($PETO_2$) seen in newcomers (Table 2). Lifelong residents had lower levels of total VE than newcomers when nonpregnant. Tidal volume did not differ whether or not the data were adjusted by maternal height. Pregnancy increased Sao_2 in both lifelong residents and newcomers, with values being similar in the two groups at all times (Table 2).

Arterial O_2 content (CaO_2) declined with pregnancy in lifelong residents, but remained at nonpregnant levels in newcomers (Table 2). Newcomers had higher CaO_2 at week 20 than lifelong residents as a result of higher hemoglobin (Hb) levels (Table 2).

Circulatory characteristics

Nonpregnant and week 20 blood pressures were similar between groups, but newcomers had higher values than lifelong residents at week 36 of pregnancy (Table 2). Heart rate was similar between groups at all times, although newcomer values rose with pregnancy whereas the lifelong residents' values were unchanged.

Pregnancy increased UA diameter, lowered uterine vascular resistance, and therefore increased UA volumetric flow (Table 3, Fig. 1A) and O_2 delivery (see Fig. 2). UA blood flow and uteroplacental O_2 delivery were lower in lifelong residents than newcomers across all times

TABLE 2. Oxygen transport characteristics in the nonpregnant (4 mo postpartum) state and at weeks 20 and 36 of pregnancy

Variable	Group	Nonpregnant	Week 20	Week 36	*P*-time	*P*-native/newcomer
P_{ETO_2} rm air (mm Hg)	Lifelong	66.0 ± 2.1 (9)	72.7 ± 1.8 (8)	71.5 ± 1.8 (12)	NS*	NS*
	Newcomer	67.3 ± 1.1 (25)	74.3 ± 0.8 (19)[a]	74.3 ± 1.0 (26)[a]	<0.001	
		NS	NS	NS		
P_{ETCO_2} rm air (mm Hg)	Lifelong	33.5 ± 0.9 (9)	28.6 ± 1.1 (7)[a]	29.1 ± 0.8 (13)[a]	<0.05	NS
	Newcomer	33.2 ± 0.6 (25)	28.9 ± 0.6 (19)[a]	28.5 ± 0.6 (26)[a]	<0.001	
		NS	NS	NS		
Ventilation (l btps/min)	Lifelong	5.7 ± 0.5 (9)	10.6 ±1.4 (8)[a]	8.9 ± 0.6 (13)[a]	<0.05	NS*
	Newcomer	8.7 ± 0.7 (24)	9.5 ± 0.5 (19)	10.8 ± 0.6 (25)	NS*	
		<0.05	NS	NS*		
Hemoglobin (g/dl)	Lifelong	14.1 ± 0.2 (11)	12.7 ± 0.1 (8)[a]	13.1 ± 0.3 (11)[a]	$P < 0.05$	<0.01
	Newcomer	14.5 ± 0.2 (22)	13.6 ± 0.2 (19)[a]	13.7 ± 0.1 (24)[a]	$P < 0.01$	
		NS	<0.01	NS*		
Arterial O_2 saturation, rm air (%)	Lifelong	92.2 ± 0.5 (13)	94.7 ± 0.8 (8)[a]	94.4 ± 0.4 (16)[a]	<0.01	NS
	Newcomer	91.3 ± 0.7 (25)	94.3 ± 0.3 (21)[a]	94.1 ± 0.2 (28)[a]	<0.001	
	NS	NS	NS	NS		
Arterial O_2 content (ml/dl)	Lifelong	17.6 ± 0.3 (11)	16.4 ± 0.2 (8)[a]	16.9 ± 0.4 (11)	<0.05	<0.05
	Newcomer	18.0 ± 0.3 (22)	17.5 ± 0.3 (19)	17.5 ± 0.3 (24)	NS	
		NS	<0.05	NS		
Mean arterial pressure (mm Hg)	Lifelong	80.2 ± 1.6 (15)	75.4 ± 2.5 (8)	78.3 ± 2.1 (17)	NS	NS
	Newcomer	78.9 ± 1.9 (27)	79.5 ± 1.7 (26)	81.4 ± 1.4 (30)	NS	
		NS	NS	NS		
Heart rate (beats/min)	Lifelong	79.7 ± 3.1 (13)	77.3 ± 3.9 (8)	87.1 ± 3.7 (16)	NS	NS*
	Newcomer	79.1 ± 2.0 (24)	84.8 ± 1.7 (18)	92.8 ± 2.2 (29)[a,b]	<0.001	
		NS	<0.05	NS		

Values are shown as mean ± SEM with sample sizes in parentheses.
[a]Significantly different from nonpregnant value.
[b]Significantly different from week 20 value using Tukey's post hoc tests.
*$0.05 < P < 0.10$.

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

Variable	Group	Nonpregnant	Week 20	Week 36	*P* time	*P* native/newcomer
Uterine a.(diameter cm)	Lifelong	0.4 ± 0.0 (13)	0.5 ± 0.0 (7)[a]	0.5 ± 0.0 (13)[a]	<0.0001	NS*
	Newcomer	0.4 ± 0.0 (23)	0.6 ± 0.0 (26)[a]	0.6 ± 0.0 (31)[a]	<0.0001	
	P-native/newcomer	NS	NS	NS		
TAM (cm/sec)	Lifelong	9.7 ± 1.7 (12)	22.2 ± 3.9 (7)[a]	24.4 ± 2.7 (13)[a]	<0.01	NS*
	Newcomer	10.8 ± 3.0 (14)	26.7 ± 2.3 (25)[a]	31.7 ± 2.4 (27)[a]	<0.0001	
	P-native/newcomer	NS	NS	NS		
Volumetric flow (ml/min)	Lifelong	61.8 ± 9.2 (12)	317.25 ± 70.4 (7)[a]	324.1 ± 46.9 (13)[a]	<0.001	<0.01
	Newcomer	80.5 ± 22.6 (11)	401.4 ± 43.8 (25)[a]	428.8 ± 36.7 (27)[a]	<0.0001	
	P-native/newcomer	NS	NS	NS*		
PSV (cm/sec)	Lifelong	49.4 ± 5.5 (11)	73.8 ± 7.6 (8)[a]	81.0 ± 7.2 (13)[a]	<0.01	NS
	Newcomer	43.9 ± 3.9 (15)	72.9 ± 6.9 (25)[a]	82.5 ± 4.9 (31)[a]	<0.001	
	P-native/newcomer	NS	NS	NS		
EDV (cm/sec)	Lifelong	4.3 ± 2.1 (10)	31.2 ± 5.8 (8)[a]	36.0 ± 5.8 (13)[a]	<0.001	NS
	Newcomer	7.3 ± 2.8 (15)	31.0 ± 3.0 (20)[a]	39.5 ± 3.2 (30)[a]	<0.0001	
	P-native/newcomer	NS	NS	NS		
Vascular resistance (mm Hg/ml/min)	Lifelong	0.9 ± 0.1 (13)	0.6 ± 0.0 (8)[a]	0.5 ± 0.0 (16)[a]	<0.001	NS
	Newcomer	1.7 ± 0.3 (12)	0.3 ± 0.0 (21)	0.2 ± 0.0 (23)	<0.001	
	P-native/newcomer	NS	NS	NS		
Common iliac a. (diameter, cm)	Lifelong	0.6 ± 0.0 (15)	0.6 ± 0.0 (8)	0.7 ± 0.0 (16)[a]	<0.05	<0.01
	Newcomer	0.6 ± 0.0 (27)	0.7 ± 0.0 (26)[a]	0.8 ± 0.0 (31)[a]	<0.001	
	P-native/newcomer	NS	<0.01	NS*		
TAM (cm/sec)	Lifelong	7.3 ± 1.5 (9)	4.6 ± 0.9 (8)	7.3 ± 0.9 (15)	NS	NS
	Newcomer	6.5 ± 0.8 (21)	8.6 ± 0.8 (26)	7.5 ± 0.7 (26)	NS	
	P-native/newcomer	NS	<0.05	NS		
Volumetric flow (ml/min)	Lifelong	125.0 ± 30.6 (9)	84.2 ± 16.6 (8)[b]	178.8 ± 24.7 (15)[c]	<0.05	<0.05
	Newcomer	133.8 ± 17.6 (21)	260.3 ± 36.0 (26)[a]	185.3 ± 21.7 (26)	<0.01	
	P-native/newcomer	NS	<0.01	NS		
External iliac a. (diameter, cm)	Lifelong	0.6 ± 0.0 (15)	0.6 ± 0.0 (8)	0.7 ± 0.0 (16)	NS	NS
	Newcomer	0.6 ± 0.0 (28)	0.6 ± 0.0 (26)	0.6 ± 0.0 (31)[a]	NS	
	P-native/newcomer	NS	NS	NS		
TAM (cm/sec)	Lifelong	8.1 ± 0.7 (12)	6.7 ± 0.8 (8)	7.9 ± 0.7 (15)	NS	NS
	Newcomer	8.6 ± 1.0 (23)	8.3 ± 0.6 (25)	7.8 ± 0.8 (26)	NS	
	P-native/newcomer	NS	NS*	NS		
Volumetric flow (ml/min)	Lifelong	117.6 ± 10.6 (12)	111.2 ± 17.4 (8)	185.1 ± 28.0 (15)	<0.05	NS
	Newcomer	146.7 ± 16.4 (23)	151.2 ± 12.7 (25)	143.8 ± 17.3 (26)	NS	
	P-native/newcomer	NS	NS	NS		

Values are shown as mean ± SEM with sample sizes shown in parentheses.
[a]Significantly different from nonpregnant (postpartum) value.
[b]Significantly different from week 36 value using Tukey's post hoc tests.
[c]Significantly different from week 20 value.
*$0.05 < P < 0.10$.
a = artery, TAM = time-averaged mean blood flow velocity, S/D = peak systolic velocity/peak end-diastolic velocity, RI = resistance index ([peak systolic velocity-peak end-diastolic velocity]/peak systolic velocity).

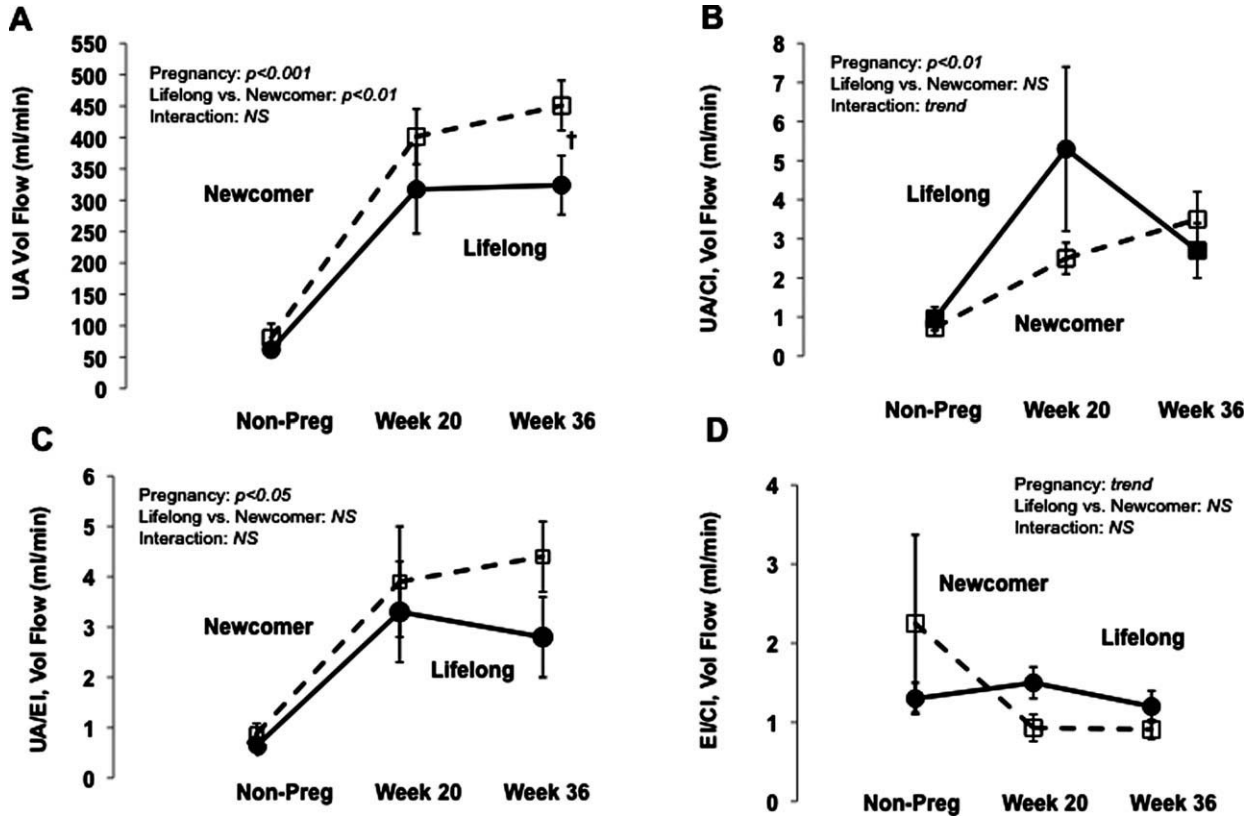

Fig. 1. A. Uterine artery (UA) volumetric flow rose with pregnancy in both lifelong and newcomer women ($P < 0.001$). Newcomers had greater volumetric flow than lifelong residents across all times ($P < 0.01$). B. The ratio of UA to CI volumetric flow increased with pregnancy in both groups but tended to do so more in lifelong than newcomer women. C. UA/EI volumetric flow rose with pregnancy, and there were no differences between groups at any time in the UA/EI ratio. D. EI/CI volumetric flow did not change with pregnancy in either group, and was similar between newcomers and lifelong residents at all times. Four month postpartum measurements are used as an index in the nonpregnant state to approximate prepregnant values. The interaction effect assesses whether the effect of pregnancy on each variable differs by high-altitude resident status.

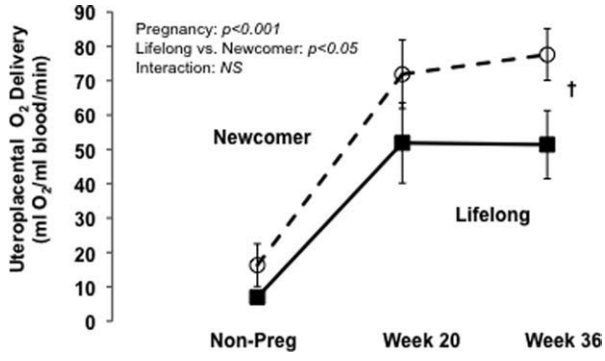

Fig. 2. Newcomers had greater uteroplacental O_2 delivery than lifelong residents across all times. O_2 delivery rose with pregnancy in both groups. Four-month postpartum measurements are used as an index in the nonpregnant state to approximate prepregnant values. The interaction effect assesses whether the effect of pregnancy on each variable differs by high-altitude resident status.

considered together (main effect) and tended to be so at week 36 considered separately as well (see Fig. 2), due to somewhat smaller UA diameters and lower flow velocity (Table 3).

Pelvic (common iliac, CI) and lower extremity (external iliac, EI) blood flow rose with pregnancy. There was less rise in CI flow in lifelong than newcomer high-altitude residents due to less pregnancy-associated increase in vessel diameter, but EI parameters were similar (Table 3). Pregnancy changed the distribution of pelvic blood flow in both groups such that a greater proportion of CI flow was directed to the UA and UA flow increased relative to EI flow (Fig. 1B,C).

Delivery and newborn characteristics

Birth weights were similar in the infants born at high altitude to lifelong versus newcomer high-altitude residents (Table 4). Gestational age, length, ponderal index, 1 and 5 min Apgar scores, proportion of male infants, and frequency of SGA or prematurity were similar in the lifelong and newcomer groups, as was the proportion delivering by elective cesarean section. Newborn head circumference was larger in the newcomer group (Table 4). Since birth weight was positively correlated with gestational age ($r = 0.54$, $P < 0.001$) and ponderal index positively correlated with maternal income and parity (r values = 0.38, and 0.31 respectively, both $P < 0.05$), we adjusted birth weight and ponderal index for these variables. However there was still no difference in birth weight or

TABLE 4. Delivery and newborn characteristics adjusted for gestational age

Variable	Newcomer	Lifelong	*P*
Hospital delivery (%)	96 [82–99] (28)	100 [81–100] (17)	NS
Delivery type			
Spontaneous vaginal (%)	39 [24–58] (28)	33 [15, 58] (15)	NS
Cesarean section (%)	61 [42–76] (28)	67 [42–85] (15)	
Birth weight (gm) (high-altitude births)	3,108 ± 76 (30)	2,916 ± 119 (17)	NS
Length (cm)	49.5 ± 0.5 (29)	48.3 ± 0.9 (16)	NS
Ponderal index (kg/m^3)	25.8 ± 0.7 (29)	26.0 ± 0.9 (16)	NS
Head circumference (cm)	34.9 ± 0.2 (27)	33.4 ± 0.5 (14)	<0.05
Gestational age (wks)	39.1 ± 0.3 (30)	38.8 ± 0.4 (17)	NS
Preterm (%)	13 [5–30] (30)	29 [13–53] (17)	NS
Post-term (%)	3 [1–17] (30)	0 [0–18] (17)	
Apgar score (1 min)	8.3 ± 0.2 (29)	7.9 ± 0.3 (17)	NS
Apgar score (5 min)	9.3 ± 0.2 (29)	8.7 ± 0.3 (17)	NS*
Male (%)	74 [55–87] (27)	47 [26–69] (17)	NS
SGA (%)	20 [10–37] (30)	24 [10–47] (17)	NS
Birth weight (gm) (adjusted)	3,090 ± 70	2,948 ± 93	NS
Ponderal index (kg/m^3) (adjusted)	25.6 ± 0.8	26.5 ± 1.1	NS

Values shown are mean ± SEM or 95% confidence intervals for proportions.
*$0.05 < P < 0.10$.
SGA = small for gestational age (<10th percentile for gestational age and sex without adjustment for maternal body size or other characteristics).

ponderal index between the lifelong and newcomer high-altitude residents (Table 4).

DISCUSSION

Our findings suggest that lifelong high-altitude residence is not sufficient to raise UA blood flow and uteroplacental O_2 delivery or to protect infants from the altitude-associated decrease in birth weight in populations of lowland origin. Specifically, women who were raised at high altitude compared to those who moved there as adults had an equivalent increase in arterial O_2 saturation during pregnancy and less, not more, rise in UA blood flow and uteroplacental O_2 delivery. Birth weights likewise were the same for infants born to lifelong and newcomer residents of high altitude but less than values for infants born to lowland origin women at low altitude reported in our previous publications (Julian et al., 2007, 2009).

Our study results are subject to certain limitations. The sample size for lifelong high-altitude residents was smaller than desired given the need to obtain a subject population without substantial admixture and, of course, for those women to be pregnant. Despite recruiting subjects over more than a 5-year period we were only able to enroll 18 women raised at high altitude who did not have substantial Indigenous American ancestry of probable Andean origin. We conducted power analyses to assess whether the magnitude of birth-weight differences seen previously between European and Andean high-altitude residents (Julian et al., 2009) could have been detected with the sample sizes obtained. With 18 subjects in each group, there is a 50% power or chance to detect such differences or 80% power with 42 subjects in each group. While thus we cannot definitively rule out protection from altitude-associated reductions in birth weight by lifelong high-altitude residence, the results obtained and presence of lower (not higher) levels of UA blood flow during pregnancy makes such an eventuality unlikely. While the departure of eight women at ~34 weeks to deliver at low altitude reduced the sample size available for study postpartum, this group provides information on the effect of normoxia on fetal growth during the last month of gestation. A final limitation was that technical difficulties prevented obtaining the requisite low angle of insonation necessary for measuring flow accurately in the deep, relatively horizontal CI, leading to probable underestimation of volumetric flow in this vessel. But since this limitation was present for all subjects, comparisons across time and between groups remain meaningful.

Our study design also benefited from certain strengths; namely the completeness of our assessment of uteroplacental O_2 delivery, the longitudinal nature of our study design, and our use of several means for determining population ancestry. The longitudinal study design not only afforded the opportunity to compare changes across pregnancy in the two groups, but also provided a nonpregnant measurement that allowed us to distinguish the effects of pregnancy from constitutional differences between lifelong and newcomer women unrelated to pregnancy. It should be noted that although recruiting women through their health care providers ensured that each woman was receiving prenatal care, it also meant that data obtained 4 months postpartum had to be used as an index of the nonpregnant state. We considered that any alterations in hematological variables due to blood loss, fluid shifts, or other factor at delivery would no longer be present, as supported by previous finding that there were no such differences in nulliparous versus 4 months postpartum women under similar conditions (Moore et al., 1986). Four independent methods were used for assessing ancestry—self-reported ancestry, parental and grandparental surnames, self and parental places of birth and residence, and AIMs. The AIMS allowed us to distinguish major geographic groups and the other sources of information enabled differentiating Andean Indigenous American ancestry from that of low-altitude Indigenous American groups. Using this strategy we were able to retain women with Indigenous American admixture of low-altitude origin for study.

A considerable anthropological literature stemming from Franz Boas' seminal work concerning changes in the head size and shape in the children of immigrants (Boas, 1912) supports the importance of developmental influences. At high altitude developmental factors are important in lung development, prompting an increase functional residual capacity which in turn reduces the alveolar-arterial O_2 gradient and may improve SaO_2 during exercise (Brutsaert et al., 2000; Frisancho et al., 1997; Zhuang et al., 1996). Current data, however, do not support an effect on birth weight, given that babies born to lifelong high-altitude residents in Colorado are not heavier than those of newcomers (Moore et al., 1982a,b; Weinstein and Haas, 1977). Consistent with this, Haas et al. also found lower birth weights in lifelong European than Andean high-altitude residents in Bolivia (Haas et al., 1980). Since the Colorado women lived at somewhat lower elevations (3,100 m) and the Bolivian studies did not include high-altitude newcomers or control for genetic ancestry, we felt reinvestigation of this question was warranted. Prior studies also did not seek to determine the physiological factors that might be influenced by developmental exposure. We therefore designed the present study to assess whether developmental factors influenced characteristics of maternal oxygen transport during pregnancy in ways that could confer

protection from altitude-associated reductions in fetal growth.

Our data agreed with prior reports insofar as we found no differences in birth weight or the frequency of SGA infants in lifelong versus newcomer women residing at high altitude.

Supporting the likelihood that birth weights in both groups were reduced, values were lower than those observed in subjects residing at low altitude in Bolivia and participating in the larger study of which this project was a part (Julian et al., 2009). Likewise the birth weights adjusted for gestational age for all high-altitude births in the present study averaged 3,066 ± 55 gm, which was lower than the 3,418 ± 133 g ($P < 0.05$) value observed in the eight subjects who elected to descend to low altitude at week ~34 and to remain there to give birth. Their descent was prompted by the policy of the US Government, for whom most of them worked, and derives from both concerns about the effect of altitude on birth weight as well as policies regarding malpractice insurance as opposed to descent out of medical necessity. Women who delivered at low altitude reported higher incomes, and weighed more at 20 weeks than those who delivered at high altitude, but other maternal characteristics with a known relationship to birth weight such as maternal education or adiposity were equivalent; this suggests that there is no apparent reason to believe that they would have delivered larger infants at high altitude as well. Notably, although there was a tendency for greater UA flow velocity and uteroplacental O_2 delivery at 36 weeks in the four women who delivered at low altitude for whom we were able to obtain third trimester ultrasound studies all other primary maternal determinants of oxygen delivery to the fetus (i.e., arterial oxygen saturation, hemoglobin, ventilation, end-tidal p_{O_2}, UA diameter and volume flow) at week 20 or week 36 of pregnancy were equivalent between women who delivered at low or high altitude. We consider this to suggest that physiologic or metabolic changes that encouraged greater fetal growth in the women who delivered at low altitude occurred after descent and was likely a direct or indirect product of increased ambient oxygen availability. While the number of subjects is small, this ~500 g birth-weight difference is about the same as that reported previously for babies born to the same mother whose entire pregnancy was spent at high vs. low altitude (Moore et al., 1982a). We include these values here insofar as they support the intriguing idea that restoration of normoxia late in pregnancy essentially reverses the effect of chronic hypoxia on infant birth weight.

The absence of heavier birth weights in lifelong than newcomer high-altitude residents was paralleled by the lack of higher levels of alveolar ventilation, SaO_2, or uteroplacental O_2 delivery. Lifelong high-altitude residents were expected to have lower VE than the newcomer women, given that prolonged residence at high altitude is known to blunt the hypoxic ventilatory drive and lower ventilation in Andeans and Europeans (Brutsaert et al., 2005; Severinghaus et al., 1966; Weil et al., 1971). The lower total VE seen in the lifelong than newcomer women in the nonpregnant state was consistent with this but pregnancy appeared to overcome the inhibitory effect of lifelong high-altitude residence such that VE rose normally, consistent with what we have reported previously (Moore et al., 1986). While pregnancy increased SaO_2 in both groups, CaO_2 was not higher because hemoglobin content fell due to a normal expansion in plasma volume in both groups (Moore, 2000; Vargas et al., 2007). Lifelong high-altitude residents had marginally but significantly lower CaO_2 at all times than the newcomers, and lower uteroplacental O_2 delivery as well due to smaller UA diameters and lower flow velocities. Interestingly CI flow was also lower in the lifelong high-altitude residents, suggesting that the lower UA flow may have been due to less pregnancy rise in cardiac output. In short, the European women who had resided at high altitude throughout their lives did not resemble women of highland ancestry (i.e., Andeans), a group characterized by markedly greater UA blood flow and uteroplacental O_2 delivery than seen in European high-altitude residents.

In summary, birth weights of babies born to lifelong versus newcomer residents of high altitude were lower than values seen in a subset of women descending late in pregnancy to give birth at low altitude or as reported previously for low-altitude control subjects participating in the larger study for which this present study was a part. Notably, lifelong high-altitude residents had lower, not higher, levels of uteroplacental O_2 delivery across all time points. We therefore concluded that lifelong high-altitude residence did not augment the pregnancy-associated increase in UA blood flow, or uteroplacental O_2 delivery nor did it protect against altitude-associated reductions in birth weight. We consider it possible that that for lowland natives the "adaptation" of exposure to chronic hypoxia during gestation and/or development may in fact inhibit rather than improve maternal oxygen transport under conditions of limited oxygen supply relative to demand (e.g., pregnancy). Such a speculation is similar to the observation that perinatal hypoxia decreases ventilatory response (Joseph et al., 2000; Okubo and Mortola, 1990) and increases pulmonary artery response to hypoxia in adulthood (Sartori et al., 1999). The absence of differences between newcomer and lifelong women suggests that greater than three generations of high-altitude residence is not sufficient to confer protection from altitude-associated reductions in fetal growth. Combined with recent evidence supporting the existence of genetic differences between Andean and Tibetan high-altitude populations and low-altitude controls (Beall et al., 2010; Bigham et al., 2009, 2010; Simonson et al., 2010; Yi et al., 2010) as well as relationships between genetic ancestry, UA blood flow, and birth weight in Andean high-altitude women (Julian et al., 2009), it appears likely that protection from altitude-associated fetal growth reduction is more likely due to genetic or other population-specific attributes than developmental effects.

ACKNOWLEDGMENTS

The authors express their appreciation to the research subjects for making this work possible, and to Marta Aguilar, Ana-Maria Alarcón, Dr. Fernando Armaza, Dra. Diva Bellido, Dr. José Carrasco, Dolly Condori, Cristina Gonzáles, Dr. Jhonny Gonzalez, Doña Hena de Hernandez, Freddy Lamachi, Miriam Lopez, Zaida Martinez, Caterina Romero, Tita Sanchez, Dr. Roberto Seguieros, Dra. Hilde Spielvogel, Dra. Wilma Tellez, Dra. Lilian Toledo, Dr. Marco Vargas, Dra. Mercedes Villena, Wilmar Velasquez, Dra. Elizabeth Zelada from Bolivia; Dr. Abby Bigham, Dr. Vaughn Browne, Darleen Cioffi-Regan, Damon Maes, Dr. Susan Niermeyer, Gene and Rosann McCullough, Dr. Mark Shriver, and Dr. Jack Reeves for their technical assistance and guidance.

LITERATURE CITED

Beall CM, Cavalleri GL, Deng L, Elston RC, Gao Y, Knight J, Li C, Li JC, Liang Y, McCormack M, Montgomery HE, Pan H, Robbins PA, Shianna KV, Tam SC, Tsering N, Veeramah KR, Wang W, Wangdui P, Weale ME, Xu Y, Xu Z, Yang L, Zaman MJ, Zeng C, Zhang L, Zhang X, Zhaxi P, Zheng YT. 2010. Natural selection on EPAS1 (HIF2alpha) associated with low hemoglobin concentration in Tibetan highlanders. Proc Natl Acad Sci USA 107:11459–11464.

Bigham A, Bauchet M, Pinto D, Mao X, Akey JM, Mei R, Scherer SW, Julian CG, Wilson MJ, Lopez Herraez D, Brutsaert T, Parra EJ, Moore LG, Shriver MD. 2010. Identifying signatures of natural selection in tibetan and andean populations using dense genome scan data. PLoS Genet 6:e1001116.

Bigham AW, Mao X, Mei R, Brutsaert T, Wilson MJ, Julian CG, Parra EJ, Akey JM, Moore LG, Shriver MD. 2009. Identifying positive selection candidate loci for high-altitude adaptation in Andean populations. Hum Genomics 4:79–90.

Boas F. 1912. Changes in bodily form of descendents of immigrants. Am Anthropol 14:530–562.

Brutsaert TD, Araoz M, Soria R, Spielvogel H, Haas JD. 2000. Higher arterial oxygen saturation during submaximal exercise in Bolivian Aymara compared to European sojourners and Europeans born and raised at high altitude. Am J Phys Anthropol 113:169–181.

Brutsaert TD, Parra EJ, Shriver MD, Gamboa A, Rivera-Ch M, Leon-Velarde F. 2005. Ancestry explains the blunted ventilatory response to sustained hypoxia and lower exercise ventilation of Quechua altitude natives. Am J Physiol Regul Integr Comp Physiol 289:R225–R234.

Chakraborty R, Barton SA, Ferrell RE, Schull WJ. 1989. Ethnicity determination by names among the Aymara of Chile and Bolivia. Hum Biol 61:159–177.

Chen D, Zhou X, Zhu Y, Zhu T, Wang J. 2002. Comparison study on uterine and umbilical artery blood flow during pregnancy at high altitude and at low altitude. Zhonghua Fu Chan Ke Za Zhi 37:69–71.

Frisancho AR, Frisancho HG, Albalak R, Villain M, Vargas E, Soria R. 1997. Developmental, genetic, and environmental components of lung volumes at high altitude. Am J Hum Biol 9:191–203.

Frisancho AR, Martinez C, Velasquez T, Sanchez J, Montoye H. 1973. Influence of developmental adaptation on aerobic capacity at high altitude. J Appl Physiol 34:176–180.

Haas JD, Frongillo EJ, Stepcik C, Beard J, Hurtado L. 1980. Altitude, ethnic and sex differences in birth weight and length in Bolivia. Hum Biol 52:459–477.

Johnson RL Jr, Cassidy SS, Grover RF, Schutte JE, Epstein RH. 1985. Functional capacities of lungs and thorax in beagles after prolonged residence at 3,100 m. J Appl Physiol 59:1773–1782.

Joseph V, Soliz J, Pequignot J, Sempore B, Cottet-Emard JM, Dalmaz Y, Favier R, Spielvogel H, Pequignot JM. 2000. Gender differentiation of the chemoreflex during growth at high altitude: functional and neurochemical studies. Am J Physiol Regul Integr Comp Physiol 278:R806–R816.

Julian CG, Vargas E, Armaza JF, Wilson MJ, Niermeyer S, Villena M, Moore LG. 2007. High-altitude ancestry protects against hypoxia-associated reductions in fetal growth. Arch Dis Child Fetal Neonatal Ed 92:F372–F377.

Julian CG, Wilson MJ, Lopez M, Yamashiro H, Tellez W, Rodriguez A, Bigham AW, Shriver MD, Rodriguez C, Vargas E, Moore LG. 2009. Augmented uterine artery blood flow and oxygen delivery protect Andeans from altitude-associated reductions in fetal growth. Am J Physiol Regul Integr Comp Physiol 296:R1564–1575.

Moore L. 2011. Uterine blood flow as a determinant of feto-placental development. In: Burton GJ, Barker D, editors. Placenta and fetal programming. Cambridge, UK: University of Cambridge Press.Moore LG. 2000. Comparative human ventilatory adaptation to high altitude. Respir Physiol 121:257–276.

Moore LG, Brodeur P, Chumbe O, D'Brot J, Hofmeister S, Monge C. 1986. Maternal hypoxic ventilatory response, ventilation, and infant birth weight at 4,300 m. J Appl Physiol 60:1401–1406.

Moore LG, Jahnigen D, Rounds SS, Reeves JT, Grover RF. 1982a. Maternal hyperventilation helps preserve arterial oxygenation during high-altitude pregnancy. J Appl Physiol 52:690–694.

Moore LG, Rounds SS, Jahnigen D, Grover RF, Reeves JT. 1982b. Infant birth weight is related to maternal arterial oxygenation at high altitude. J Appl Physiol 52:695–699.

Moore LG, Zamudio S, Zhuang J, Sun S, Droma T. 2001. Oxygen transport in Tibetan women during pregnancy at 3658 m. Am J Phys Anthropol 114:42–53.

Okubo S, Mortola JP. 1990. Control of ventilation in adult rats hypoxic in the neonatal period. J Appl Physiol 259:R836–R841.

Palmer SK, Zamudio S, Coffin C, Parker S, Stamm E, Moore LG. 1992. Quantitative estimation of human uterine artery blood flow and pelvic blood flow redistribution in pregnancy. Obstet Gynecol 80:1000–1006.

Sartori C, Allemann Y, Trueb L, Delabays A, Nicod P, Scherrer U. 1993. Augmented vasoreactivity in adult life associated with perinatal vascular insult. Lancet 353:2205–2207.

Severinghaus JW, Bainton CR, Carcelen A. 1966. Respiratory insensitivity to hypoxia in chronically hypoxic man. Respir Physiol 1:308–334.

Shriver MD, Parra EJ, Dios S, Bonilla C, Norton H, Jovel C, Pfaff C, Jones C, Massac A, Cameron N, Baron A, Jackson T, Argyropoulos G, Jin L, Hoggart CJ, McKeigue PM, Kittles RA. 2003. Skin pigmentation, biogeographical ancestry and admixture mapping. Hum Genet 112:387–399.

Simonson TS, Yang Y, Huff CD, Yun H, Qin G, Witherspoon DJ, Bai Z, Lorenzo FR, Xing J, Jorde LB, Prchal JT, Ge R. 2010. Genetic evidence for high-altitude adaptation in Tibet. Science 329:72–75.

Vargas M, Vargas E, Julian C, Armaza JF, Rodriguez A, Tellez W, Niermeyer S, Wilson M, Parra E, Shriver M, Moore LG. 2007. Determinants of blood oxygenation during pregnancy in Andean and European residents of high altitude. Am J Physiol Regul Integr Comp Physiol 293:R1303–1312.

Weil JV, Byrne-Quinn E, Sodal IE, Filley GF, Grover RF. 1971. Acquired attenuation of chemoreceptor function in chronically hypoxic man at high altitude. J Clin Invest 50:186–195.

Weinstein RS, Haas JD. 1977. Early stress and later reproductive performance under conditions of malutrition and high altitude hypoxia. Med Anthropol 1:25–54.

WHO. 2006. Reliability of anthropometric measurements in the WHO Multicentre Growth Reference Study. Acta Paediatr Suppl 450:38–46.

Williams RL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M. 1982. Fetal growth and perinatal viability in California. Obstet Gynecol 59:624–632.

Wilson MJ, Lopez M, Vargas M, Julian C, Tellez W, Rodriguez A, Bigham A, Armaza JF, Niermeyer S, Shriver M, Vargas E, Moore LG. 2007. 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:R1313–1324.

Yi X, Liang Y, Huerta-Sanchez E, Jin X, Cuo ZX, Pool JE, Xu X, Jiang H, Vinckenbosch N, Korneliussen TS, Zheng H, Liu T, He W, Li K, Luo R, Nie X, Wu H, Zhao M, Cao H, Zou J, Shan Y, Li S, Yang Q, Asan Ni P, Tian G, Xu J, Liu X, Jiang T, Wu R, Zhou G, Tang M, Qin J, Wang T, Feng S, Li G, Huasang, Luosang J, Wang W, Chen F, Wang Y, Zheng X, Li Z, Bianba Z, Yang G, Wang X, Tang S, Gao G, Chen Y, Luo Z, Gusang L, Cao Z, Zhang Q, Ouyang W, Ren X, Liang H, Zheng H, Huang Y, Li J, Bolund L, Kristiansen K, Li Y, Zhang Y, Zhang X, Li R, Li S, Yang H, Nielsen R, Wang J, Wang J. 2010. Sequencing of 50 human exomes reveals adaptation to high altitude. Science 329:75–78.

Zamudio S, Palmer SK, Stamm E, Coffin C, Moore LG. 1995. Uterine blood flow at high altitude. In: Sutton JR, and Houston CS, editors. Hypoxia and the brain. Burlington, VT: Queen City Press. p112–124.

Zamudio S, Postigo L, Illsley NP, Rodriguez C, Heredia G, Brimacombe M, Echalar L, Torricos T, Tellez W, Maldonado I, Balanza E, Alvarez T, Ameller J, Vargas E. 2007. Maternal oxygen delivery is not related to altitude- and ancestry-associated differences in human fetal growth. J Physiol 582:883–895.

Zhuang J, Droma T, Sutton JR, Groves BM, McCullough RE, McCullough RG, Sun S, Moore LG. 1996. Smaller alveolar-arterial O2 gradients in Tibetan than Han residents of Lhasa (3658 m). Respir Physiol 103:75–82.