AMERICAN JOURNAL OF HUMAN BIOLOGY 15:330–341 (2003)

Human Physiological Adaptation to Pregnancy: Inter- and Intraspecific Perspectives

L. CHRISTIE ROCKWELL,[1]* ENRIQUE VARGAS,[2] AND LORNA G. MOORE[3]
[1]*Department of Anthropology, Temple University, Philadelphia, Pennsylvania 19122, USA*
[2]*Instituto Boliviano de Biología de la Altura, La Paz, Bolivia*
[3]*Department of Anthropology, University of Colorado at Denver, Denver, Colorado 80217-3364, USA*

ABSTRACT Reproductive success requires successful maternal physiological adaptation to pregnancy. An interspecific perspective reveals that the human species has modified features of our haplorhine heritage affecting the uteroplacental circulation. We speculate that such modifications — including early implantation and deep, widespread invasion of fetal (trophoblast cells) into and resultant remodeling of maternal uterine vessels — are responses to or compensation for the biomechanical constraints imposed by bipedalism which, in turn, render our species susceptible to the pregnancy complication of preeclampsia. Preeclampsia is characterized by incomplete remodeling of maternal uterine vessels as the result of shallow trophoblast invasion, which in turn reduces uteroplacental blood flow and frequently leads to intrauterine growth restriction (IUGR). Using an intraspecific perspective, we consider the fitness-related consequences of variation in uteroplacental blood flow during high-altitude pregnancy. Although birth weights are reduced at high altitudes in Bolivia, multigenerational Andean residents are relatively protected from altitude-associated IUGR. Our preliminary data suggest that Andean women have greater uteroplacental oxygen delivery than European high-altitude residents due to more complete growth and remodeling of maternal uterine vessels. Identification of the physiological and genetic mechanisms involved in such inter- and intraspecific variations in pregnancy physiology will likely be useful for understanding human evolution and contemporary challenges to successful reproduction. Am. J. Hum. Biol. 15:330–341, 2003.

Maternal physiological responses during and prior to pregnancy directly influence fecundity, fertility, and intrauterine morbidity and mortality and hence the course of evolution. Considering the length of time involved (~10 months), the maternal physiological responses to pregnancy are as great or greater than those experienced at any other time of postnatal life. Some of these are shared with our primate cousins and others distinguish our taxon. Here we use first an interspecific and then an intraspecific perspective to highlight the unique features of the human physiological adaptation to pregnancy and their significance for reproductive success which, for the purposes of this article, we define as the production of a healthy newborn. Both the inter- and intraspecific perspectives suggest that natural selection has in the past and continues to operate in the present on maternal physiological responses to pregnancy. As such, we view physiological adaptation to pregnancy as an evolutionary gate, admitting attributes that contribute to reproductive success and turning away those that do not.

A hemochorial placenta is common to all haplorhines (tarsiers, monkeys, apes, and humans). Several features that affect the establishment of the uteroplacental blood supply appear to be unique to humans (although this remains uncertain in the absence of more complete documentation in our closest ape relatives). Those of interest include the depth and extent of invasion of fetal trophoblast cells[1] into maternal tissue and the timing of implantation. We consider the additional influence of bipedalism on uteroplacental blood flow in an effort to explain the uniquely human predilection

[1]The trophoblasts are the peripheral cells of the blastocyst, which attach the conceptus to the uterine wall.

Contract grant sponsor: NIH; Contract grant numbers: TW01188, HL60131; Contract grant sponsor: Temple University Presidential Summer Research Fellowship.

*Correspondence to: L. Christie Rockwell, Department of Anthropology, 1115 W. Berks St., Temple University, Philadelphia, PA 19122. E-mail: lrockwel@temple.edu

Received 16 August 2002; Accepted 15 December 2002

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajhb.10151

for the maternal pregnancy complication of preeclampsia.[2] To test the importance of sustaining high uteroplacental blood flow for ensuring fetal and maternal well-being, we draw on our current studies of the adaptive challenges posed by reproduction at high altitudes. The most pervasive environmental characteristic of high altitude, lowered O_2 availability, or hypoxia, interferes with implantation, compromises the pregnancy-associated development of blood supply to the fetus, and results in poor pregnancy outcome, including an increased incidence of preeclampsia (PE) and intrauterine growth restriction (IUGR) (Blackburn and Clegg, 1979; Moore et al., 2001a; Palmer et al., 1999; Rockwell et al., 2000; Zamudio et al., 1995). Further, a growing body of evidence demonstrates that the influence of IUGR does not end at delivery, but rather, acting through the mechanism of "fetal programming," increases the offspring's likelihood of developing cardiovascular disease later in life (Barker et al., 1992). Both the inter- and intraspecific perspective offer the opportunity to identify the physiological mechanisms tied directly to achieving reproductive success and thereby of direct relevance for the processes of natural selection and evolutionary adaptation.

INVASIVE IMPLANTATION, BIPEDALISM, AND SUSCEPTIBILITY TO PREECLAMPSIA

The placenta is an organ used by eutherian mammals that permits the fetal and maternal circulations to exchange nutrients and waste products. The structural and functional complexity of this organ is reflected by several distinct placental classification systems which, because the features vary independently of one another, alternatively group placentae on the basis of fetal villous structure, maternal–fetal blood flow geometry, shape of the placenta, or interhemal barrier structure. Grosser's 1927 classification, the most commonly referenced in the anthropological literature, is based on the number of cell layers that separate maternal and fetal blood (Morriss et al., 1994). Among primates, two types of placentae are most common. The majority of strepsirhine primates have an epitheliochorial placenta in which the maternal uterine epithelium remains structurally intact throughout the pregnancy, whereas the haplorhine primates have a hemochorial placenta. An intimate relationship between maternal blood and fetal trophoblast cells, the result of the invasive properties of the trophoblast cells, characterizes the hemochorial placenta (reviewed in Pijnenborg et al., 1981).

The process of implantation that results in the formation of a hemochorial placenta begins when the blastocyst[3] breeches the epithelium of the mother's uterus and then progresses inward, invading the deeper endometrial tissue (stroma) to anchor the conceptus (Fig. 1). The fetal trophoblast cells differentiate into villous or extravillous phenotypes[4] (reviewed in Irving et al., 1995; Morrish et al., 1998) which either fuse to form a multinucleated layer in contact with the endometrium (Athanassiades et al., 1998) or migrate even further into maternal tissue as extravillous cytotrophoblasts (EVC). Some EVC are embedded in the maternal stromal tissue (interstitial invasion) where they may give paracrine (intercellular) signals. Other EVC express cell surface antigens that mimic maternal endothelial cells and enables them to migrate up the spiral arteries (endovascular invasion). Additional systems are also involved in endovascular migration, including angiopoietin-2 (Ang-2) and its receptor Tie-2 (Goldman-Wohl et al., 2000; Wulff et al., 2002). EVC migration results in the erosion of the vascular smooth muscle layer of the maternal spiral arteries, loss of vasoactivity, subsequent dilation, and a fall in uteroplacental vascular resistance. Low placental vascular resistance facilitates high uteroplacental blood flow if blood pressure remains unchanged (Moll and Kunzel, 1973). As we have argued previously, another factor serving to increase uteroplacental perfusion might be a positive feedback system in which initial lowering of vascular resistance in the placental bed contributes to increased flow and shear stress in the upstream uterine artery, thus stimulating its growth and a further increase in blood flow to the placenta (Rockwell et al., 2000). The displacement of vasoactive vessels outside

[2]Preeclampsia is among the leading maternal complications of pregnancy. It is diagnosed on the basis of hypertension and significant proteinuria during pregnancy in an otherwise normotensive woman.

[3]The term blastocyst describes the developmental stage of the conceptus that has an inner cell mass and an external cell layer, the trophoblast shell.

[4]Villous trophoblasts make up the outermost layer of the fetal villae, finger-like projections within which fetal capillaries of the placenta grow. Extravillous trophoblasts further invade maternal tissue.

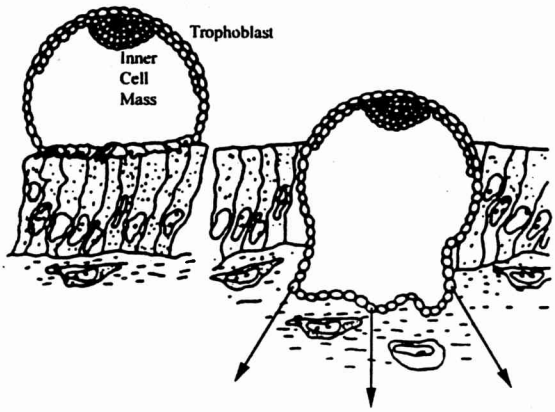

Fig. 1. The blastocyst is composed of two cell types, the inner cell mass and the outer layer of trophoblast cells. At implantation, the trophoblast adheres to the maternal epithelium (left). In mammals that develop an epitheliochorial placenta no further invasion of maternal tissue occurs, but in mammals that develop a hemochorial placenta the trophoblast cells breech the maternal uterine epithelium and invade to varying degrees (right). The differentiation and migration of the trophoblast cells is discussed in the text (modified from Guillomot et al., 1993).

the low resistance placental bed and their decreased vasoconstrictor as well as enhanced vasodilator responsiveness also play important roles in increasing uteroplacental blood flow (Stock and Metcalfe, 1994). Thus, EVC invasion in early pregnancy may have consequences for the continued increase in uteroplacental blood flow as pregnancy progresses. Species in which an epitheliochorial placenta forms do not establish the placenta as a site of low vascular resistance and the maternal vasculature remains intact (Moll and Kunzel, 1973).

Human deviations from our haplorhine heritage

Given the structural features that influence placental hemodynamics, it is of interest to consider some distinctions between humans and the nonhuman haplorhine primates. In advance, we note that the data for the nonhuman primates is scant at best. Some information is simply not available (e.g., for gorillas). Three points, however, are noteworthy. Humans, in comparison with tarsiers, ceboids, and cercopithecoids are characterized by invading trophoblast cells that are highly dispersed throughout the uterus, the placental area occupies a larger portion of the uterus, and a larger number of maternal arteries — some quite distant from the implantation site — are invaded by fetal cells and remodeled to supply the intervillous space[5] (Gruenwald, 1972; Pijnenborg et al., 1981). The evolutionary basis of and adaptive significance for the human morphology is largely unexplored but suggests to us an enhanced functional role for these features. Second, implantation in humans is particularly deep and interstitial;[6] the blastocyst is completely embedded in the uterine stroma. This condition contrasts with monkeys, the tarsier, and possibly the orangutan and chimpanzee (Benirschke, 1983: 388), in which the blastocyst remains more superficially positioned relative to the uterine tissue. Third, although comparative data are scarce for many primate

[5]The intervillous space is a potential space between the projecting fetal villa. It is filled with blood because of the erosion of the maternal tissue and opening of maternal blood vessels.

[6]Interstitial is a term used to refer to the positioning of the human blastocyst. It comes to lie completely within the subepithelial tissue of the endometrium, the stroma, and the maternal epithelium regrows over the implantation site.

species, there is evidence that humans are distinguished by the early timing of blastocyst implantation (Fig. 2; Enders and Schlafke, 1986). This contrasts with the mammalian trend for later implantation with increasing body size and gestational length. In sum, the timing of human implantation and the extent to which fetal cells promote structural changes in the maternal vasculature that contribute to the control of uteroplacental perfusion later in gestation appears to differ between humans and other haplorhines. Below, we suggest why these differences may rveal a critical function for implantation biology in humans.

Unexplored consequences of bipedalism

Following implantation, profound maternal physiological adjustments occur during pregnancy, including 40% increases in plasma volume and cardiac output as well as a 25% rise in ventilation. These function to increase uteroplacental flow, O_2 and other nutrient delivery to the developing fetus in humans as well as other mammals. But for our species, these changes must be accomplished in a habitually bipedal posture. The osteological reconfiguration of the pelvis associated with the evolution of bipedalism contributes to obstetrical complications by narrowing the dimensions the true pelvis (Tague and Lovejoy, 1986). Surprisingly little attention has been devoted to understanding the consequences of bipedalism for other aspects of maternal and fetal physiology. In a biped, the uterus, bladder, internal genitalia, and much of the lower intestines are situated within the pelvic cavity, whereas in a quadruped these organs are situated in the abdominal cavity. As human pregnancy progresses, the uterus and its contents expand to occupy much of the abdominal cavity. In the process, the uterus compresses the major blood vessels, particularly the vena cava that carries lower extremity venous blood back to the heart (Abitbol, 1993). Such compression results in a fall in cardiac output near term, especially in the supine posture where compression is greatest (Ueland et al., 1969). This vena-caval compression is due, in part, to gravity but also to the muscular tone of the abdominal wall, which, rather than acting as a supportive sling for the gravid uterus, as in quadrupeds, compresses the uterus, its contents, and supplying vessels (Abitbol, 1993). Bipedalism may compromise maternal physiological responses to pregnancy and, specifically, the rise in cardiac output not only through these mechanical effects but also via chronically elevated sympathetic tone. Increased sympathetic tone operates to oppose gravity and ensure adequate cerebral perfusion, but it also impairs venous return and hence reduces cardiac output. Indeed, an inability to override high basal sympathetic tone and a consequent reduction in plasma volume have been suggested as responsible for the known link between low plasma volume and increased risk for developing PE (Bernstein et al., 1998).

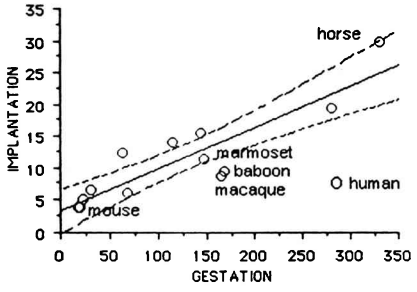

Fig. 2. Scattergram and LSR line ($y = 0.07x + 3.34$, $r^2 = 0.80$, 95% CI of the mean indicated) describing the relationship between implantation (days) and gestation (days) are shown for data from nonhuman mammals and primates (Bruggemann and Dukelow, 1980; Enders et al., 1983; Guillomot et al., 1993; Hearn, 1978; Kuster and Paul, 1984). The taxa included in the analysis are mouse, rat, hamster, guinea pig, rabbit, cat, pig, sheep, cow, horse, marmoset, macaque, baboon. The human datum (not included in regression analysis) is unusual in the extremely early timing of implantation relative to gestation.

We speculate that these mechanical and sympathetically mediated consequences of bipedalism put selective pressure on the physiological systems responsible for redistributing cardiac output to the uteroplacental circulation as a means for ensuring high uteroplacental blood flow. In other words, confronted by the cardiac output limitations imposed by bipedal posture, vasodilation and structural remodeling of the uteroplacental vasculature became critical for ensuring the exponential rise in uteroplacental blood flow required to meet the nutrient demands of the near-term fetus. If so, the adjustments characteristic of human pregnancy which establish and sustain increased uteroplacental

perfusion — early and deep invasiveness, greater placental area and larger number of maternal arteries accessed by fetal cells — are evolutionary adaptations to accommodate pregnancy in a biped. Possibly, selection for these attributes was not only important in compensating for the constraints imposed by bipedalism but, to some extent, also enabled the emergence of our species.

Trophoblast migration and preeclampsia

Incomplete trophoblast invasion and the resulting reduction in uteroplacental perfusion have been identified as underlying the human pregnancy complications of PE (Fig. 3; Gerretson et al., 1981; Van Beek and Peeters, 1998). PE occurs in an estimated 7–10% of primigravida pregnancies but is unknown in other mammals (Sharkey et al., 2001), with the exception of patas monkeys (Palmer et al., 1979; Ramsay et al., 1997). While still poorly understood and the subject of intensive investigation, incomplete trophoblast invasion and tissue hypoxia are believed to prompt the release of reactive O_2 species or some other "toxic" factor from the placental circulation. This as-yet undefined substance(s) is then thought to enter the maternal circulation, causing endothelial injury and resultant loss of the normal increased vasodilator response of pregnancy. The placenta is the source of the disorder; PE may occur under the unusual circumstance of hydatiform mole, in which there is a placenta but no fetus. Moreover, the only cure for PE is delivery. It is unknown why humans are apparently more susceptible to this disorder than are other primates in which hemochorial placentation and maternal vascular remodeling also occur. Haig (1993) proposed that the disorder is due to the genetic conflict between fetal and maternal genomes, but such a perspective does not address why humans, unlike other haplorhines, respond to poor placental perfusion with a series of changes resulting in maternal hypertension. The consequence of PE may be severe; it can advance to eclampsia, a potentially fatal condition marked by neurologic convulsions. It is more likely to result in spontaneous or induced preterm delivery of often growth-retarded (IUGR) infants with, in turn, a poorer chance of survival (Lydakis et al., 2001; Witlin et al., 2000). Even in the absence of PE, some cases of IUGR are associated with a failure of the maternal spiral arteries to undergo complete physiological transformation (Sheepard and Bonnar, 1988). Thus, both conditions may be

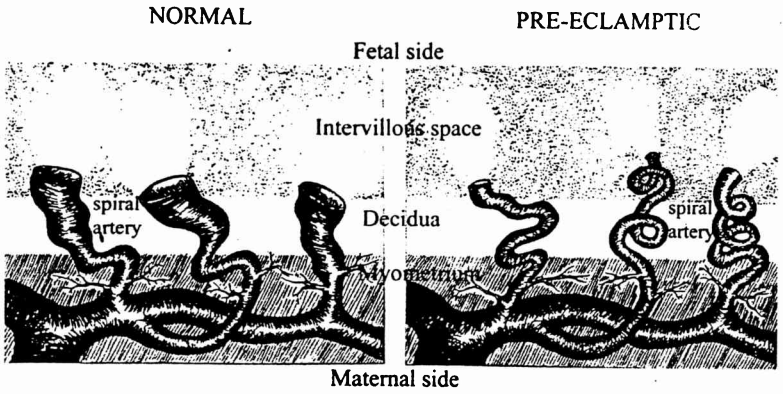

Fig. 3. The maternal placental structure in normal and preeclamptic pregnancies. Normally, endovascular invasion of the maternal spiral arteries replaces the maternal endothelium with fetal cells, destroys the muscular layer of the vessel, and renders it distended and funnel-shaped. In normal pregnancy these physiological changes appear as far proximally as the myometrial portion of the spiral arteries. In preeclampsia the physiological changes are less dramatic and appear only more distally in the arteries (modified from Van Beek and Peeters, 1998).

characterized by shallow penetration of the endometrium and a smaller number of arteries being invaded by EVCs.

We speculate that early implantation and deep, widespread invasion of fetal (trophoblast cells) into maternal uterine vessels are responses to or compensation for the biomechanical constraints imposed by bipedalism that, in turn, render our species susceptible to the pregnancy complication of PE. The endangered status of the nonhuman, large-bodied hominoids limits direct evaluation of our model in an interspecific framework. We can, however, consider data derived from intraspecific studies to examine the relationship between variation in uteroplacental blood flow, its controlling factors, and pregnancy outcome. For such an evaluation we use data from our own and others' previous studies obtained under the natural laboratory of high altitude to show how maternal cardiovascular adjustments to pregnancy impact fetal outcome.

UTERINE BLOOD FLOW AND FETAL–MATERNAL WELL BEING: THE EXAMPLE OF HIGH ALTITUDE

Adaptive challenges of the high-altitude environment

Studies of the health-related effects of high altitude occupy an important place in human biology (Beall, 2000; Brutsaert, 2001; Hochachka, 2000; Moore, 2001; Niermeyer et al., 2001; Ramirez et al., 1999). Of particular interest are the effects of high altitude that pose challenges to human adaptation, operationally defined here as the ability to reproduce successfully. Two sources of data provide convincing evidence that the high-altitude environment challenges human adaptive capacity. One is the reproductive difficulty experienced by individuals who migrate from low to high altitudes. Another is the continuing occurrence of the altitude-related increase in the frequency of the complications of IUGR and PE, both of which measurably raise mortality risk in utero, during infancy, and even in adult life.

Historical accounts reveal that some 53 years were required for the first child born of Spanish parentage to survive in the mining center of Potosí, located at 4,100 m in what is now Bolivia (Monge, 1948). For a time, this city was the focus of the Spanish Empire, as its mines were among the richest in the Americas. The difficulty appeared to be more one of survival following birth than a failure to conceive. One remedy was for the Spanish women to descend to lower altitudes to give birth and remain there for several years after the baby was born. Another may have been interbreeding with the indigenous Andean population. Similar problems are being encountered today by Han (Chinese) migrants to the Tibet Autonomous Region of western China. In the community of Nachu at 4,800 m, we found that even though Han lived there, no Han deliveries occurred over a 2-year period because the pregnant Han had descended to lower elevations in China to give birth (Moore et al., 2001a). At somewhat lower (but still "high") altitudes where Han did give birth, their babies weighed markedly less than Tibetan babies born at the same altitude, averaging 530 g lower at 3,000–3,800 m and 310 g lower at 2,700–3,000 m. Lower birthweights are known to raise mortality risk. Postnatal as well as prenatal mortality rates were higher in the Han than the Tibetans (Moore et al., 2001a). No cause of death could be established in these accounts but direct measurements of arterial O_2 saturation (SaO_2) in Tibetan and Han newborns at 3,600 m support the possibility that physiological responses to hypoxia are involved. SaO_2 was similar at delivery but the Tibetans maintained levels in a normal range, whereas Han values fell progressively during the first 4 months of life, averaging 92 to 76% during wakefulness and quiet sleep, respectively (Niermeyer et al., 1995). Such SaO_2 levels can prompt pulmonary vasoconstriction, resultant hypertension, and right heart failure. Suggesting that the Han may be more vulnerable, of the 15 babies in Lhasa dying from a syndrome marked by pulmonary hypertension and right heart failure, all but one were Han (Sui et al., 1988).

Considerable evidence from our and others' studies show that altitude continues to challenge fetal well-being, as indicated by a reduction in birthweight in populations throughout the world. In Colorado, birthweight falls an average of 100 g (1/4th lb) per 1,000 m (3,000 ft) gain, an effect which is comparable to that of maternal smoking, primiparity, or minimal prenatal care (Jensen and Moore, 1997). This is due chiefly to IUGR rather than shortened gestation. Altitude also raises the incidence of PE (Palmer et al., 1999). Until recently, the

altitude-related decline in birthweight was associated with an increase in infant mortality in Colorado (Unger et al., 1988). Such an association clearly exists in South America today, both between and within countries. That is, the countries with the highest altitudes have the highest levels of infant mortality and within the highest-altitude country, Bolivia, infant mortality rises 3–4-fold from the lowest to the highest regions (PAHO, 1994). Socioeconomic factors are no doubt involved, as the highest-altitude regions are also the poorest and have the fewest health care services (Demographic and Health Surveys, 1998). But altitude is also a likely contributor, as demonstrated by a recent comparison of the altitude-associated mortality rise in urban vs. rural regions of Bolivia (Giussani, 2002). The rural areas had higher infant mortality than the urban centers, as might be expected given their more limited health care services, but the altitude-associated rise was essentially parallel in the two regions.

Population differences in altitude-associated IUGR

While birthweight falls with increasing altitude in each geographic region of the world, when we recently summarized all published data by geographic region we noted that the magnitude of the altitude-associated birthweight reduction varied in relation to the duration of high-altitude residence (Fig. 4). In other words, birthweights fell the least in the longest-resident groups and progressively more in shorter-resident populations. Such differences were not attributable to variation in sea-level birthweights, population differences in maternal body size, or socioeconomic factors likely to affect the availability of health care. Likewise, being born and raised at high altitude appears to exert little protective effect (Moore et al., 1982; Weinstein and Haas, 1977).

Much of the Tibetan and Han data in Figure 4 came from our own work, where we could be reasonably certain of the population ancestry of the persons studied. Since Han migration to the Tibetan Plateau has occurred in significant numbers only in the last ~50 years, there is also little chance that admixture between the two groups has occurred. Most of the data for the European and Andean groups comes, however, from the published literature where the population ancestry of the groups is often not well described. In a well-controlled but small

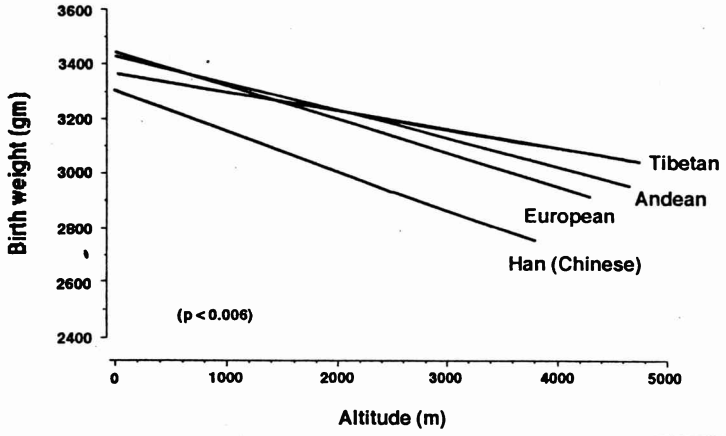

Fig. 4. Best-fit regression lines are shown for data acquired in some 90 studies or approximately 4 million infants in which birthweights were measured at the range of altitudes shown. When grouped by population ancestry, the altitude-associated fall in birthweight is least in the populations with the longest period of residence (in generations) at high altitude and greatest in the shortest-resident populations. Reprinted with permission from Moore et al. (2001a).

study, Haas and colleagues noted that birthweights of babies born to Andean women were 127 g heavier than those of European women residing at ~3,600 m in La Paz, Bolivia, or 143 g heavier after adjusting for maternal body weight. Of interest, these differences in birthweight were not as great as the ~500–600 g difference seen between Tibetan and Han residents of 3,600 m (Moore et al., 2001a,b), suggesting that differences in the duration of high-altitude residence and/or admixture may be involved. To better define the magnitude of birthweight differences between babies of Andean vs. European ancestry and the physiological mechanisms involved, we have begun collaborative studies with the Instituto Boliviano de Biología de la Altura (IBBA), the Caja Nacional de Salud, and private physicians and clinics in Bolivia.

One part of this effort has involved medical record studies of consecutive births to women receiving two or more prenatal visits at hospitals belonging to the Caja Nacional de Salud, the largest insured national health care provider, and from medical clinics specializing in obstetrical care.[7] Approximately 1,000 records were reviewed per 1,000 m altitude interval throughout the country, comprising the urban centers of Santa Cruz, Cochabamba, La Paz, and Orurro. The study aims were to determine the extent to which birthweight falls with increasing altitude in Bolivia today, the contribution of an altitude-related increase in the occurrence of PE to the reduction in birthweight, and the extent to which Andean vs. European population ancestry influences the birthweight reductions observed. Parental surnames were used to judge population ancestry, requiring three or four Aymara or Quechua maternal or paternal surnames to be considered "Andean" and, correspondingly, three or four European maternal or paternal surnames to be considered "European." All others were termed "mestizo" or mixed. This surname-based approach has been previously validated by comparison with gene markers (Chakraborty et al., 1989).

We have begun the analyses with the La Paz (3,600 m) and Santa Cruz (300 m) data since these are the largest urban centers with the most similar levels of health care. Birthweights were lower in La Paz as the result of IUGR rather than shortened gestation (Keyes et al., 2003), considering IUGR as birthweights less than the 10th percentile for a given gestational age and sex using sea-level norms (Williams et al., 1982). Because proteinuria was infrequently assessed, data were combined from women who became hypertensive while pregnant with proteinuria (PE) or without proteinuria (gestational hypertension, GH). Approximately twice as many women developed PE or GH at high vs. low altitude when all women were considered. Among primiparous women, three times as many became hypertensive at high compared with low altitude (Keyes et al., 2003). The altitude-related increase in PE/GH contributed to but could not fully account for the fall in birthweights observed. Analyses are currently being conducted to determine whether population ancestry influences the altitude-related rise in IUGR and PE/GH, taking into account differences in prenatal care, parity, and other sociodemographic characteristics. In sum, while analyses are ongoing, results to date are consistent with previous observations that Andean compared with European residents of high altitude are protected from an altitude-associated increase in IUGR, although the precise magnitude of protection has yet to be determined.

Causes of population variation in IUGR

Potentially, a great many factors could be involved in explaining such population differences in infant birthweight. We are undertaking prospective studies of pregnant Andean and European women to test the hypothesis that maternal physiological adaptations which increase O_2 delivery to the uteroplacental circulation protect babies of Andean vs. low-altitude (European) ancestry from IUGR at high altitude. To test this hypothesis, we are recruiting approximately 40 women of Andean ancestry and as many women of low-altitude ancestry as possible for measurements of the two primary determinants of O_2 delivery to the uteroplacental circulation: uterine artery blood flow and arterial oxygenation. Measurements are being made at weeks 20, 30, and 36 of pregnancy and again 3 months postpartum for characterizing the nonpregnant state. To

[7]Because a large portion of the Bolivian population does not receive prenatal care, the findings from this study cannot be generalized to the country as a whole.

date, the women in the two groups are similar in age and weight gain during pregnancy but the Andean women are shorter, lighter, and have had more prior deliveries. Studies have been completed in 25 Andean and eight European women, all of whom have resided at high altitude (~3,600 m) throughout their pregnancies. These data are summarized here by way of a preliminary report..

O_2 delivery to the uteroplacental circulation is the product of uterine artery blood flow and arterial O_2 content. We measured uterine artery blood flow as previously described (Palmer et al., 1992; Zamudio et al., 1995) using ultrasound to measure vessel diameter and Doppler velocimetry to record blood flow velocity averaged throughout the cardiac cycle. Uterine artery blood flow rose progressively during pregnancy in the Andeans due to marked increases in both vessel diameter and flow velocity (Wilson et al., 2002). However, after an initial rise, uterine artery blood flow in the European women declined near term to values that were lower than those of the Andean subjects. Both groups increased their levels of SaO_2 and the increase was similar, but a lesser fall in hemoglobin levels during pregnancy raised arterial O_2 content in the European compared to the Andean women near term (Vargas et al., 2002). However, despite their higher arterial O_2 content, the Europeans had lower uteroplacental O_2 delivery near term compared to the Andean subjects (Fig. 5). The Europeans' higher hemoglobin levels near term may have reflected a decrease in plasma volume, as hemoglobin levels were similar in the two groups when nonpregnant. Failure to expand plasma volume during pregnancy is an ominous sign since, as noted above, an increased plasma volume is vital for sustaining high levels of cardiac output and uteroplacental blood flow. We found lower common iliac as well as uterine artery blood flows in the European compared to the Andean women near term, consistent with the possibility that reduced plasma volume lowered cardiac output and contributed to the uterine artery blood flow reductions observed.

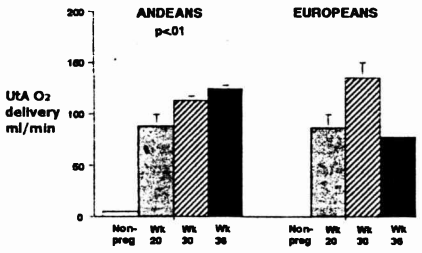

Fig. 5. Uteroplacental O_2 delivery appears to be greater in Andeans than Europeans at term. Values were calculated as the product of uterine artery blood flow and arterial O_2 content which were estimated, in turn, from measurements of uterine artery diameter and blood flow velocity, and hemoglobin concentration and arterial O_2 saturation, respectively.

Birthweight data are not yet available from these women, largely because their deliveries occurred in hospitals scattered throughout the La Paz area. Further complicating the retrieval of such information, some gave birth at home and several of the foreign women returned to their home country to give birth. However, ultrasound measurements were made of fetal dimensions during the period of study. The Andean babies tended to have larger abdominal diameters and head circumferences, suggesting greater fetal growth at a given gestational age. Interestingly, the Andean compared to the European babies in utero also tended to have a lower ratio of systolic to diastolic blood flow velocity in the umbilical artery, indicating less fetal distress.

SUMMARY AND CONCLUSIONS

An increase in uteroplacental perfusion during pregnancy is required to meet the needs of the growing placenta and fetus and to achieve reproductive success. Important determinants of this increase are a rise in blood volume and cardiac output, selective redistribution of blood to the uteroplacental circulation, growth and dilation of the uterine artery, and structural remodeling of the endometrial spiral arteries resulting from the proximally directed migration of extravillous cytotrophoblast cells. Human physiological adjustments to pregnancy resemble those of our primate relatives but differ in several key respects; namely, earlier implantation, deeper and more extensive penetration of maternal uterine tissue by fetal (trophoblast) cells, and a larger placenta relative to the uterus. We speculate that this human elaboration of haplorhine placental physiology may have been selected for, in

part, as a means for overcoming the mechanical constraints and consequent reduction in cardiac output due to bipedal posture. Such important modifications to the timing of implantation and depth of placentation reveal a possible cause for the apparent greater susceptibility of our species to PE. This suggests that variation in the mechanisms by which uteroplacental blood flow is increased during pregnancy have important evolutionary consequences. Consistent with this notion, our studies of pregnancy at high altitude indicate that variability in uterine artery blood flow has an important influence on pregnancy outcome. To date, we have found that higher common iliac flow near term and a greater increase in uterine artery diameter raise Andean uteroplacental O_2 delivery above the levels present in European women. If the present results are confirmed by ongoing studies, it will suggest that higher uterine artery blood flow is more important than higher arterial O_2 content for the previously observed protection from IUGR seen in long-resident groups at high altitude. Such findings would be consistent with our previous Tibet studies in which we observed that third trimester Tibetan women had greater uterine artery blood flow velocity and redistribution of common iliac blood flow to favor the uterine artery in conjunction with heavier weight infants when compared with Han women residing at 3,600 m (Moore et al., 2001a). Interestingly, when we compared the Tibetan and Han women to Colorado residents at 3,100 m, we found that the Tibetan women resembled healthy pregnant Colorado women in terms of their redistribution of common iliac blood flow to favor the uterine artery and infant birthweight, whereas the Han were like Colorado preeclamptic women (Moore et al., 200b). In this respect, well-adapted high-altitude populations may resemble healthy pregnant women, while less well-adapted groups may be like persons with the pregnancy complications of PE and IUGR. This suggests the intriguing possibility that the spectrum of genetic variation within a population that influences susceptibility to disorders such as PE and IUGR is similar to that which has been operated on by the evolutionary process of natural selection, consistent with our concept that the maternal vascular adaptations during pregnancy at high altitude are acting as an evolutionary gate. Identification of the mechanisms responsible for evolutionary adaptation may therefore have the additional benefit of facilitating the search for solutions to the still-significant public health problems of IUGR and PE.

ACKNOWLEDGMENTS

We thank our colleagues at the University of Colorado at Denver and Health Sciences Center campuses: Linda Keyes, Susan Niermeyer, Margueritte White, Megan Wilson, Stacy Zamudio; and at the Instituto Boliviano de Biología de la Altura in La Paz, Bolivia: Fernando Armaza, Marco Vargas, Mercedes Villena.

LITERATURE CITED

Abitbol MM. 1993. Growth of the fetus in the abdominal cavity. Am J Phys Anthropol 91:367–378.

Athanassiades A, Hamilton GS, Lala PK. 1998. Vascular endothelial growth factor stimulates proliferation but not migration or invasiveness in human extravillous trophoblast. Biol Reprod 59:643–654.

Barker DJP, Bull AR, Osmond C, Simmonds SJ. 1992. Fetal and placental size and risk of hypertension in adult life. In: Barker DJP, editor. Fetal and infant origins of adult disease. London: British Medical Journal. p 175–186.

Beall CM. 2000. Tibetan and Andean contrasts in adaptation to high-altitude hypoxia. Adv Exp Med Biol 475:63–74.

Benirschke, K. 1983. Placentation. J Exp Zool 228: 385–389.

Bernstein IM, Meyer MC, Osol G, Ward K. 1998. Intolerance to volume expansion: a theorized mechanism for the development of preeclampsia. Obstet Gynecol 92:306–308.

Blackburn RO, Clegg EJ. 1979. The survival and implantation of mouse blastocysts at varying degrees of reduced atmospheric pressure. Teratology 20: 441–446.

Bruggemenn S, Dukelow WR. 1980. Characteristics of the menstrual cycle in non-human primates. III. Timed mating in Macaca arctoides. J Med Primatol 9:213–221.

Brutsaert T. 2001. Genetic and environmental adaptation in high altitude natives. Conceptual, methodological, and statistical concerns. Adv Exp Med Biol 502:133–151.

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.

Demographic and Health Surveys. 1998. Encuesta Nacional de Demografía y Salud: Bolivia. Calverton, MD, USA: Macro International.

Enders AC, Schlafke S. 1986. Implantation in nonhuman primates and in the human. In: Dukelow WR, Rewin J, editors. Comparative primate biology, vol. 3. Reproduction and development. New York: Alan R. Liss. p 291–310.

Enders AC, Hendrickx AG, Schlafke S. 1983. Implantation in the rhesus monkey: initial penetration of endometrium. Am J Anat 167:275–298.

Gerretsen G, Huisjes HJ, Elema JD. 1981. The role of the spiral artieries in the placental bed in relation to

pre-eclampsia and fetal growth retardation. Br J Obstet Gynaecol 88:876–881.
Giussani D. 2002. High altitude and rural living are associated with increased infant mortality in Bolivia. J Soc Gynecol Invest 9:292A.
Goldman-Woh DS, Ariel I, Greenfield C, Lavy Y, Yagel S. 2000. Tie-2 and angiopoietin-2 expression at the fetal maternal interface: a receptor ligand model for vascular remodelling. Mol Hum Reprod 6:81–87.
Gruenwald P. 1972. Expansion of placental site and maternal blood supply of primate placentae. Anat Rec 173:189–204.
Guillomot M, Flechon J-E, Leroy F. 1993. Blastocyst development and implantation. In: Thibault C, Levasseur MC, Hunter RHF, editors. Reproduction in mammals and man. Paris: Ellipses. p 387–412.
Haig D. 1993. Genetic conflicts in human pregnancy. Q Rev Biol 68:495–532.
Hearn JP. 1978. The endocrinology of reproduction in the common marmoset, *Callithrix jacchus*. In: Kleiman DG, editor. The Biology and conservation of the Callithrichidae. Washington, DC: Smithsonian Institution Press.
Hochachka PW. 2000. Oxygen, homeostasis, and metabolic regulation. Adv Exp Med Biol 475:311–335.
Irving JA, Lysiak JJ, Graham CH, Hearn S, Han VKM, Lala PK. 1995. Characteristics of trophoblast cells migrating from first trimester chorionic villus explants and propagated in culture. Placenta 16: 413–433.
Jensen GM, Moore LG. 1997. The effect of high altitude and other risk factors on birthweight: independent or interactive effects? Am J Public Health 87:1003–1007.
Keyes LE, Armaza JF, Niermeyer S, Vargas E, Young D, Villena M, Moore LG. 2003. Intrauterine growth restriction, pre-eclampsia and intrauterine mortality at high altitude in Bolivia. In press.
Kuste J, Paul A. 1984. Female reproductive characteristics in semifree-ranging Barbary macaques (Macaca sylvanus, L. 1758). Folia Primatol (Basal) 43:69–83.
Lydakis C, Beevers M, Beevers DG, Lip GY. 2001. The prevalence of pre-eclampsia and obstetric outcome in pregnancies of normotensive and hypertensive women attending a hospital specialist clinic. Int J Clin Pract 55:361–367.
Moll W, Kunzel W. 1973. The blood pressure of arteries entering the placentae of guinea pigs, rats, rabbits, and sheep. Pflugers Arch 338:125–131.
Monge C. 1948. Acclimatization in the Andes. Baltimore: Johns Hopkins Press.
Moore LG. 2001. Human genetic adaptation to high altitude. High Alt Med Biol 2:257–279.
Moore LG, Rounds SS, Jahnigen D, Grover RF, Reeves JT. 1982. Infant birthweight is related to maternal arterial oxygenation at high altitude. J Appl Physiol 52:695–699.
Moore LG, Young DY, Droma TS, Zhuang JG, Zamudio S. 2001a. Tibetan protection from intrauterine growth restriction (IUGR) and reproductive loss at high altitude. Am J Hum Biol 13:635–644.
Moore LG, Zamudio S, Zhuang J, Sun S, Droma T. 2001b. Oxygen transport in Tibetan women during pregnancy at 3658 m. Am J Phys Anthropol 114:42–53.
Morrish DW, Dakour J, Li HS. 1998. Functional regulation of human trophoblast differentiation. J Reprod Immunol 39:179–195.
Morriss FH Jr, Boyd RD, Mahencran D. 1994. Placental transport. In: Knobil E, Neill JD, editors. The physiology of reproduction, 2nd edition. New York: Raven Press. p 813–861.
Niermeyer S, Yang P, Shanmina J, Drolkar T, Zhuang J, Moore LG. 1995. Arterial oxygen saturation in Tibetan and Han infants born in Lhasa, Tibet. N Engl J Med 333:1248–1252.
Niermeyer S, Zamudio S, Moore LG. 2001. The people. In: Hornbein T, Schoene RB, editors. Adaptations to hypoxia. New York: Marcel Dekker. p 43–100.
PAHO. 1994. Health conditions in the Americas. Scientific publication no. 549. Washington, DC: World Health Organization (Pan American Health Organization).
Palmer AE, London WT, Sly DL, Rice JM. 1979. Spontaneous preeclamptic toxemia of pregnancy in the patas monkey (*Erythrocebus patas*). Lab Anim Sci 29:102–106.
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.
Palmer SK, Moore LG, Young DA, Creeger B, Berman JC, Zamudio S. 1999. Altered blood pressure course during normal pregnancy and increased preeclampsia at high altitude (3100 meters) in Colorado. Am J Obstet Gynecol 180:1161–1168.
Pijnenborg R, Robertson WB, Brosens I, Dixon G. 1981. Review article: trophoblast invasion and the establishment of haemochorial placentation in man and laboratory animals. Placenta 2:71–92.
Ramirez G, Bittle PA, Rosen R, Rabb H, Pineda D. 1999. High altitude living: genetic and environmental adaptation. Aviat Space Environ Med 70:73–81.
Ramsay MM, Tame JD, Winter JA, Carbone LG, Schlafer DH, Nathanielsz PW. 1997. Proteinuric hypertension in a pregnant baboon: was this pre-eclampsia? J Med Primatol 26:207–212.
Rockwell LC, Keyes LE, Moore LG. 2000. Chronic hypoxia diminishes pregnancy-associated DNA synthesis in guinea pig uteroplacental arteries. Placenta 21:313–319.
Sharkey LC, McCune SA, Yuan O, Lange C, Fray J. 2001. Spontaneous pregnancy-induced hypertension and intrauterine growth restriction in rats. Am J Hypertens 14:1058–1066.
Sheppard BL, Bonnar J. 1988. The maternal blood supply to the placenta in pregnancy complicated by intrauterine fetal growth retardation. Trophoblast Res 3:69–81.
Stock MK, Metcalfe J. 1994. Maternal physiology during gestation. In: Knobil E, Neil JD, editors. The physiology of reproduction. New York: Raven Press. p 947–983.
Sui GJ, Liu YH, Cheng XS, Anand IS, Harris E, Harris P, Heath D. 1988. Subacute infantile mountain sickness. J Pathol 155:161–170.
Tague RG, Lovejoy CO. 1986. The obstetric pelvis of A.L. 288-1 (Lucy). J Hum Evol 15:237–255.
Ueland L, Novy MJ, Peterson EN, Metcalfe J. 1969. Maternal cardiovascular dynamics. IV. The influence of gestational age on the maternal cardiovascular response to posture and exercise. Am J Obstet Gynecol 104:856–863.
Unger C, Weiser JK, McCullough RE, Keefer S, Moore LG. 1988. Altitude, low birthweight, and infant mortality in Colorado. JAMA 259:3427–3432.
Van Beek E, Peeters LLH. 1998. Pathogenesis of pre-eclampsia: a comprehensive model. Obstet Gynecol Surv 63:233–239.
Vargas E, Niermeyer S, Vargas M, Villena M, Moore LG. 2002. Pregnancy raises ventilation and hypoxic ventilatory responsiveness similarly in Andean and

foreign residents of high altitude. High Alt Med Biol 3:112.
Weinstein RS, Haas JD. 1977. Early stress and later reproductive performance under conditions of malnutrition and high altitude hypoxia. Med Anthropol 1:25–54.
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, Armaza F, Lopez M, Niermeyer S, Zamudio S, Vargas E, Moore LG. 2002. Uterine artery blood flow and blood flow redistribution during pregnancy in Andean high-altitude women. Am J Hum Biol 14:137.
Witlin AG, Saade GR, Mattar F, Sibai BM. 2000. Predictors of neonatal outcome in women with sever preeclampsia or eclampsia between 24 and 33 weeks' gestation. Am J Obstet Gynecol 182:607–611.
Wulff C, Wilson H, Dickson SE, Wiegand SJ, Fraser HM. 2002. Hemochorial placentation in the primate: expression of vascular endothelial growth factor, angiopoietins, and their receptors throughout pregnancy. Biol Reprod 66:802–812.
Zamudio S, Palmer SK, Droma T, Stamm E, Coffin C, Moore LG. 1995. Effect of altitude on uterine artery blood flow during normal pregnancy. J Appl Physiol 79:7–14.