WOMEN AT ALTITUDE: BLOOD VESSELS

an evolutionary and integrative review

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RESUMEN: La respuesta fisiológica de las mujeres a la altura ha sido poco estudiada hasta hace un tiempo. Interesa saber si mujeres y varones difieren en su respuesta fisiológica a la altura y si las diferencias se deben a hormonas ováricas o gonadales circulantes. Para tales estudios, es importante recordar que la determinación sexual implica una considerable complejidad evolutiva, genética y de desarrollo. Los estudios de respuesta aguda y crónica a la hipoxia brindan información útil para examinar los mecanismos generales y el significado evolutivo del sexo y de las hormonas sexuales. Los períodos de gestación y desarrollo fetal están sujetos a mayor riesgo de mortalidad que cualquier otro período de la vida. En la altura, la fertilidad se mantiene en niveles de nivel del mar o por encima del nivel del mar, pero el peso al nacer disminuye un promedio de 100 gramos por cada 1000 m de altitud, principalmente como resultado de retardo del crecimiento. También hay una mayor frecuencia de complicaciones maternas durante el embarazo, que pueden contribuir al menor peso al nacer. La gestación, como resultado de acciones combinadas de hormonas ováricas y tasa metabólica incrementada, estimula varios componentes del transporte materno de oxígeno de modo que incrementa la ventilación y la oxigenación arterial. La magnitud del incremento en la ventilación materna y en la oxigenación arterial guardan relación positiva con el peso al nacer. El flujo sanguíneo úteroplacentario también parece estar reducido en la altura, particularmente en mujeres que desarrollan pre-eclampsia. El incremento en la ventilación materna y en el flujo sanguíneo úteroplacentario durante el embarazo en particular y las influencias de las hormonas ováricas sobre los procesos de transporte de oxígeno en general, probablemente han recibido el influjo de la selección natural para lograr la adaptación evolutiva a la altura.

Palabras claves: Estradiol, Progesterona, Testosterona, Transporte de oxígeno, Hipoxia, Cardiovascular, Respiración, Retardo de crecimiento intrauterino, Mortalidad infantil, Pre-eclampsia.

RÉSUMÉ: La réponse physiologique des femmes à l'altitude a été peu étudiée jusqu'à une époque récente. Or, il est intéressant de savoir si leur réponse physiologique à l'altitude diffère de celle des hommes et si les différences sont dues aux hormones ovariennes ou gonadotropes circulantes. Pour mener à bien ces études il ne faut pas perdre de vue que la détermination sexuelle implique une grande complexité évolutive, génétique et de développement. Les études de réponse aiguë et chronique à l'hypoxie fournissent des informations utiles pour examiner les mécanismes généraux et la signification évolutive de l'influence du sexe et des hormones sexuelles. Plus que toute autre période de la vie, les périodes de gestation et de développement foetal sont soumises à de grands risques de mortalité. En altitude, la fertilité se maintient à des niveaux comparables - et même supérieurs - à ceux du niveau de la mer, mais le poids à la naissance diminue de 100 g tous les 1000 m, principalement en raison du retard de croissance. On observe également une plus grande fréquence de complications chez la mère pendant la grossesse, pouvant contribuer au moindre poids à la naissance. La grossesse, résultat d'actions combinées d'hormones ovariennes et d'un taux métabolique en augmentation, stimule plusieurs composants du système maternel de transport d'oxygène, de sorte qu'il y a accroissement de la ventilation respiratoire et de l'oxygénation artérielle. On observe un rapport positif entre l'ampleur de cet accroissement et le poids à la naissance. Le flux sanguin utéro-placentaire semble être également en diminution du fait de l'altitude, particulièrement chez les femmes présentant une pré-éclampsie. L'augmentation de la ventilation respiratoire maternelle et du flux sanguin utéro-placentaire pendant la grossesse en particulier et les influences des hormones ovariennes sur les processus de transport d'oxygène plus généralement, ont probablement reçu l'influx de la sélection naturelle pour parvenir à l'adaptation évolutive à l'altitude.

Mots-clés : Oestradiol, Progestérone, Testostérone, Transport d'oxygène, Hypoxie Cardiovasculaire, respiration, Retard de croissance intra-utérin, Mortalité infantile, Pré-éclampsie.

SUMMARY: The physiological response of women to altitude has received comparatively little study until recently. Of interest is whether women and men differ in their physiological response to high altitude and if so, whether differences are due to circulating ovarian or gonadal hormones or to gender differences unrelated to levels of circulating hormones. It is important to recall that the determination of gender involves considerable evolutionary, genetic and developmental complexity. Studies of acute and chronic response to high altitude provide are useful for examining the general mechanisms and evolutionary significance of the influences of gender and sex hormones on processes of oxygen transport. The period of pregnancy and fetal development is subject to greater mortality risk than any other period during the life cycle. At high altitude, fertility is maintained at or above sea level values but infant birth weight decreases an average of 100 gm per 1000 m altitude gain, principally as a result of fetal growth retardation. An increased frequency of maternal complications of pregnancy also has been reported at high altitude and may, in turn, contribute to the birth weight decline. Pregnancy stimulates several components of maternal O_2 transport, raising ventilation and arterial oxygenation as the result of the combined actions of ovarian hormones and increased m!etabolic rate. The magnitude of the rise in maternal ventilation and arterial oxygenation relates to infant birth weight at high altitude. Uteroplacental blood flow also appears to be reduced at high altitude, particularly among women developing preeclampsia. Thus the maternal ventilatory and cardiovascular adjustments by which fetal-placental O_2 and other nutrient

delivery is maintained may be crucial in attaining successful adaptation to high altitude.

KEY WORDS: Estradiol, Progesterone, Testosterone, Oxygen Transport, Hypoxia, Cardiovascular, Respiration, Pregnancy, Intrauterine growth retardation, Infant mortality, Preeclampsia

INTRODUCTION

To date there has been little systematic study of women's physiological response to acute or chronic hypoxia. Despite the early, inclusive studies conducted on residents of high altitude by Mabel Purefoy Fitzgerald (1), most of the extensive literature on newcomers or long-term residents of high altitude has not included female subjects. Such an omission is consistent with much of the cardiovascular, respiratory and exercise physiology literature. One suspects that it is due, in part, to a concern that cyclic variation in female hormones may contribute an additional source of variation. Ironically, this very possibility is actively being investigated in contemporary studies of women at altitude.

As described in the preceding papers (2-6), gender comparisons are currently underway on the effects of high altitude on exercise performance and symptoms of acute mountain sickness. Also being studied are the influences of menstrual cycle phase on ventilatory, cardiovascular, hematological, and nutritional acclimatization to high altitude. Progress is being made toward understanding of the factors causing the incidence of the high-altitude disorder of chronic mountain sickness (CMS) to differ between the sexes.

The purpose of this article is to consider the general mechanisms and significance of the influences of gender and sex hormones on hypoxic responses. An evolutionary and integrative approach is used in order to address the importance of gender and sex hormonal influences on human adaptation to high altitude. This approach is developed by considering 1) the evolutionary determinants and influences of gender, 2) the effects of hypoxia on reproductive success, and 3) the influences of reproductive hormones and pregnancy on processes of oxygen transport and their implications for fetal and maternal well-being.

EVOLUTIONARY PERSPECTIVE ON SEX AND GENDER

While sex and gender are often used synonymously, here we use "sex" to refer to the biological attributes of being male or female and "gender" to those attributes generally ascribed to members of a given sex. As such, gender includes socially as well as biologically acquired or assigned attributes and includes the possibility that the attributes ascribed to one gender may vary and at times, include those traits assigned to the other.

For humans and other mammals, sex is determined by having received from one's parents either two X chromosomes (females) or one X and one Y chromosome (males). This chromosomal determination of sex is not universal. Among birds, males are XX and females are XY. Sex determination in most insects is the same as mammals but in two orders, the lepidoptera (moths and butterflies) and trichoptera (caddisflies), is like that of birds (XX males and XY females) (7). In humans, the presence of two X's vs one X and one Y chromosome is usually but not always associated with the presence of female vs. male genitalia and other secondary sexual characteristics. The regulation of secondary sexual characteristics is a function of a gene or genes on the Y chromosome that, together with a brief period of elevation in androgen levels during embryonic life, prompt the formation of testes. If this gene(s) on the Y chromosome is lacking, an XY individual will develop into a female; likewise a prenatal surge in androgens can cause a genetic female to develop testes. Since, in the absence of a stimulus to become male, a female will result, female features appear to be the underlying, primary attribute of mammalian life.

Darwin recognized that sex is subject to natural selection and termed this "sexual selection". For reasons that remain unclear, males in utero are subject to higher mortality than females. Hence the majority of spontaneous abortions are male. Even so, there is an excess of males relative to females at birth; the average sex ratio at birth is 106 males for every 100 females. By adulthood in most societies the sex ratio has evened, again indicating greater male than female mortality. Female mortality remains generally lower than male mortality at every age except during childbearing years. As a result, life expectancy is longer for females than males at nearly every age in most societies. These differences in mortality between males and females indicate that sex and/or gender influences Darwinian (evolutionary) fitness.

One of the mechanisms by which sex and gender influence evolutionary fitness is the presence of sex-specific genetic material. Among mammals, both mother and father contribute an equal, haploid number of chromosomes to form the zygote. In addition, the mother contributes her mitochondrial DNA to the fertilized egg. This mitochondrial DNA reproduces itself with each ensuing cell division. In a somewhat analogous fashion, Ychromosomal DNA is transmitted only by the father. However an important difference is that Y-chromosomal DNA

is acquired only by males whereas both females and males possess the maternally-derived mitochondrial DNA. Thus the developing organism is subject to nuclear genetic influences from both parents but to mitochondrial genetic influences from its mother only.

Imprinting or the disproportionate influence of maternal or paternal genetic material is another mechanism by which maternally and paternally-derived genes influence the developing organism. Recent studies have revealed that, for example, paternal genes exert a greater influence on placentation whereas maternal genes appear to predominate in fetal development (8).

EFFECTS OF HYPOXIA ON REPRODUCTIVE SUCCESS

From an evolutionary perspective, the period of pregnancy and fetal development is subject to greater mortality risk than any period during the life cycle. In this section, we consider whether chronic hypoxia serves to increase selective pressure during this critical period.

Severe, acute hypoxia impairs reproductive function (9) but the effects of more sustained or moderate hypoxia are less clear. Earlier studies suggested a reduction in fertility in South American high- compared with low-altitude populations, as judged by completed family size and an increase in completed fertility in persons who migrated from high to low altitudes, but this has not been supported more recently (10). While menarche is later and menopause earlier, a 1990 survey in Peru demonstrated higher completed fertility in the high than low altitude-departments (11). The high-altitude residents achieved higher fertility by shortening the intervals between menarche and the birth of the first child and between the births of subsequent children and conceiving more often during lactation in comparison with low-altitude residents.

There are a number of factors which might be expected to influence fertility levels in the Andean region. In the setting of high infant mortality (Figure 1), fertility may be elevated, perhaps in an attempt to assure surviving offspring. Alternatively, the reporting of births may be reduced in Peru and Bolivia where most births occur outside of hospitals (12). Cultural considerations pertaining to the contribution and costs of children also influence childbearing patterns. In traditional areas of highland Peru, high completed fertility is desirable in that children from ages 6 - 18 yr generate more resources than they consume (13).

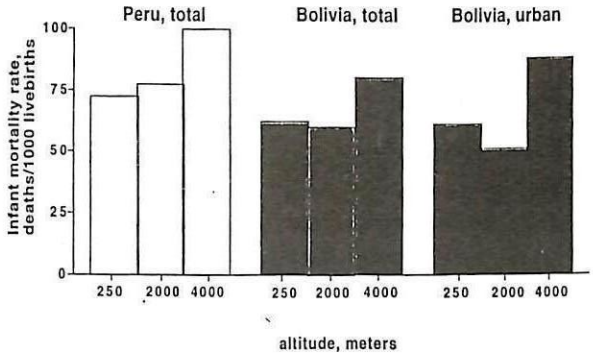

Figure 1: Infant mortality increases with altitude in Peru and Bolivia (12).

An important but unanswered question pertains to the influences of short-term hypoxia in women who are already pregnant. Large numbers of persons travel to Colorado and other mountainous regions (14). Medical advice is inconsistent regarding the safety of travel to high altitude for pregnant women and their babies. The only published data, to our knowledge, is a brief report concerning 13 newcomer residents of La Paz, Bolivia (Table 1) (15). While the numbers are extremely small, it is noteworthy that the women who arrived at high altitude in their first trimester appeared to develop maternal or fetal complications more frequently than those who conceived at high altitude. Needed is an expanded, systematic comparison of maternal and neonatal complications and birth outcome in newcomers exposed to high altitude before vs. during pregnancy. In order to control for the effects of migration independent of altitude, such a study should include an assessment of pregnancy and birth outcomes in women who move from one low altitude to another.

Chronic hypoxia has long been associated with a reduction in infant birth weight, averaging a 100 gm decline per 1000 m altitude gain (9, 16). There is a corresponding increase in the percentage of low-birth-weight babies (< 2500 g) (17). The reduction in birth weight is likely due to high altitude rather than maternal body size or some other population-specific factor since a generally similar reduction in birth weight is seen in most (but not all) human populations and can be observed when comparing birth weights of infants born to the same woman at low vs. high altitude (18). The reduction in birth weight at high altitude has historical significance; the first recognition that fetal growth and length of gestation were separable influences on birth weight was made at high altitude (19).

Table 1. Pregnancy outcome in 13 La Paz newcomers (adapted from 15)

Arrival	No.	Complication(s)	Birth
weight. Gm	1	none	2900
Before conception	2	none	2600
	3	none	3000
	4	none	3000
	5	none	3000
	6	none	3100
	7	C-section	2900
		mean ± sem	
		2920 ± 70	
1st trimester	8	eclampsia, preterm, C-section	2100
	9	preterm	2000
	10	preterm	1800
	11	threatened abortion, C-section	2800
		mean ± sem	
		2175 ± 220	
2nd trimester	12	none	3300
	13	preterm, C-section	2500

The primary cause of the reduction in birth weight at high altitude appears to be intrauterine growth retardation (IUGR) (Figure 2). In Colorado, the reduction occurs principally in the third trimester as demonstrated by a progressive decline in fetal weight after 32 weeks at high compared with low altitudes (20 - 21) (Figure 2). Recent data included in Figure 2 from Peru appear consistent with the North American results when the higher altitudes of Peru are taken into account (22 - 23). Growth curves from Peru and Bolivia across the full range of gestational ages at low vs high altitudes are needed but will be difficult to construct given that birth records are not available for most of these countries' population (12). Average gestational ages at high vs. low altitude are similar in North America (16, 19 - 21) but modest reductions, which are generally not sufficient to explain the birth weight reduction observed (24), have been reported in some South American studies (22 - 23). Such altitude-associated reductions in gestational age may be due to differences in medical interventions for preventing preterm births or the extent to which complete samples have been obtained.

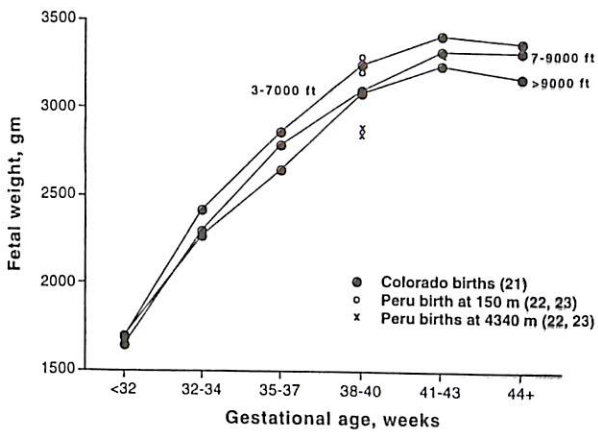

Figure 2: Fetal growth is retarded at high altitude beginning after 32 weeks gestational age (comparison of curves, $p < 0.05$) (21 - 23).

The magnitude of retardation of fetal growth at high altitude appears to vary among populations in relation to their duration of high-altitude exposure. Populations have resided at high altitude for the shortest period in the Rocky Mountains, an intermediate length of time in the Andes, and the longest in the Himalayas (25). Comparing well-matched studies by the same investigator across a 0-3500 m gradient, Zamudio and co-workers found that the reduction in birth weight was greatest in North Americans (-352 grams, p<.001), intermediate in South Americans (-270 grams in Peru, -282 grams in Bolivia, p<.001) and least in Tibetans (-72 grams, p=NS) (24). Of note was that the Tibetans, residing at an altitude equivalent to that present in the South American studies, did not appear to have altitude-associated IUGR (24, 25). This suggests that the Tibetans have adapted to high altitude in a fashion that permits normal fetal growth.

Twenty years ago, infant and neonatal mortality rates were above nationwide levels in Colorado and the other USA mountain states (19). Currently, infant mortality is the same as national values and does not increase with altitude within Colorado (21). The mortality decline in Colorado was associated with a modest increase in birth weight and a fall in the percent preterm births (21) but much of the decline remains unexplained. Being small (reduced birth weight) does not reduce infant mortality at high altitude (26) since low birth weight infants are an increased mortality risk at every altitude (2 .mproved

medical technol gy and greater utilization of tertiary medical facilities by women from the highest compared with the lowest-altitude areas in Colorado are likely to have contributed to the mortality decline.

Bolivia and Peru currently have the highest infant mortality in South America. The excess mortality compared to other countries has not changed appreciably over the past 20 or more years (12). Within both countries, infant mortality is greatest in the highest altitude regions when all infants or only urban infants are compared (Figure 1). However, the infant mortality data are of poor quality. Payment is required to register a birth or death and only about one-third of the deaths are certified by a physician (12). Such problems are particularly acute in rural regions and other settings where infant mortality is likely to be highest.

The IUGR and greater frequency of preterm deliveries in some studies may be the result of an increased frequency of pregnancy complications, best documented of which is an increased incidence of placental abruptions and preeclampsia. A review of all deliveries in La Oroya, Peru (3750 m) over a 15-year period indicated that placental abruptions were three-fold more common than at sea level and demonstrated an age- and parity-associated relationship, occurring in 6.8% of women over 40 yr and in 3.4% with parity greater than 4 (27). Preeclampsia is the leading cause of maternal and fetal mortality in the industrialized world (28). Preeclampsia is defined as an elevation in blood pressure (>140/90 mmHg, a systolic rise > 30 mm Hg, or a diastolic rise > 15 mmHg) accompanied by proteinuria and/or upper extremity edema in a woman who is normotensive when nonpregnant. - Abnormalities of liver function, coagulation, and the central nervous system are sometimes observed as well. The incidence of preeclampsia increases about three-fold from low to high altitudes in Colorado (29 - 30) but data from South America are equivocal as to whether the incidence of preeclampsia is increased (22, 31).

An increased occurrence of maternal complications during pregnancy is likely to contribute to an elevation in maternal as well as infant mortality. Maternal mortality in Peru and Bolivia is more than twice the South American average (12), rising from 13.2 maternal deaths per 10,000 live births on the coast, to 21.5 in the 2-3000 m region and to 43.1 at elevations above 3000 m in Peru (32).

Impaired placentation and uteroplacental ischemia may be a common pathway whereby pregnancy complications are increased and intrauterine growth retarded at high altitude. Uteroplacental ischemia has been associated with preeclampsia at low altitude (33). An attractive hypothesis is that the uteroplacental ischemia, in turn, is due to impaired trophoblast invasion and remodeling of maternal spiral and other uterine arteries (34).

Historic as well as more recent observations indicate that behavioral adjustments, in addition to alterations in maternal O_2 transport, are important responses to high altitude. Out-migration serves as a mechanism for avoiding the challenges of high altitude. As Antonio de la Calancha observed in 1632 when the Spaniards entered what is now Bolivia, pregnant women of Spanish origin would descend to give birth at lower altitudes and not return until the child was more than a year old (35). A similar practice occurs among Han women living on the Tibetan Plateau who often return to their home districts at lower altitude during pregnancy. After birth, their infants customarily stay with extended family until approximately two years of age, at which time they are brought to high altitude (36).

MATERNAL OXYGEN TRANSPORT RESPONSES TO PREGNANCY AND THEIR IMPLICATIONS FOR MATERNAL AND FETAL WELL-BEING

Because not all women at high altitude deliver growth-retarded babies, we have conducted a series of studies to test the hypothesis that altitude-associated IUGR is due to insufficient maternal O_2 transport to meet fetal-placental demands. The alternate possibilities are that placental diffusing capacity is impaired in such a way as to limit O_2 or other nutrient transfer or that other, fetal-specific factors limit growth. Early reports indicated that the placenta at high altitude was similar in absolute size and larger in relation to fetal size than at low altitude (37). Recent studies indicate that the placenta at high altitude is more vascularized and has a greater diffusing capacity than at low altitude (38, 39). Thus, impaired placental O_2 transfer is unlikely to be the primary cause of altitudeassociated IUGR.

In normal pregnancy, elevated levels of progesterone and estrogen in combination with increased metabolic rate raise peripheral (carotid bódy) and central chemosensory sensitivity and resting ventilation (40 - 42). Investigation of gender differences in ventilation is often framed in terms of the effects of ovarian hormones. It is important, however, to recognize that other factors also contribute to gender differences. Gender may influence ventilation in ways that are unrelated to circulating levels of sex hormones due to, for example, prior hormonal exposure or to other, gender-linked factors. When normalized for differences in body size, neutered as well as intact females have higher alveolar ventilation and HVR than their intact or neutered male counterparts (43, 44). The male hormone testosterone also affects ventilation (45). The rise in resting ventilation after exogenous testosterone administration is due to an increase in metabolic rate but testosterone treatment also raises hypoxic and hypercapnic ventilation responsiveness. Interestingly, the increase in HVR appeared due to a diminution in descending central inhibitory influences on the carotid boy (45).

At low altitude, the increase in ventilation during pregnancy does not appreciably raise arterial O_2 saturation, since it is already nearly maximal. At high altitude, arterial O_2 saturation rises with pregnancy. Our studies in Peru and Colorado have demonstrated that the magnitude of the rise in maternal ventilation, hypoxic ventilatory sensitivity, and arterial O_2 saturation during pregnancy related positively to the birth weight of their infants (18, 46, 47). While suggesting that the factors serving to raise maternal arterial oxygenation help to preserve fetal growth at high altitude, a puzzling aspect of these observations is that arterial O_2 content is similar at high and low altitude as the result of the pregnancyassociated rise in arterial O_2 saturation and higher hemoglobin concentration characteristic of the high-altitude residents (18). Because uteroplacental blood flow increases some 50fold during pregnancy, it is a major influence on uteroplacental O_2 delivery (i.e. the product of uteroplacental blood flow and arterial O_2 content). We therefore asked whether uterine blood flow was altered by residence at high altitude.

Several factors combine to increase uteroplacental blood flow during pregnancy. Of major importance is the remodeling of the uteroplacental circulation. The uterine and radial arteries (the vessels branching from the uterine artery and,entering the uterine wall) at least double in diameter. The downstream, basilar and spiral arteries also enlarge as a result of the trophoblast invasion from the developing placenta. In preeclamptic pregnancies, however, the increase in vessel diameter occurs only in the decidual portion and not in the myometrial region of the uterine vascular wall, resulting in a narrow segment with retained pressor sensitivity that likely raises uterine vascular resistance and diminishes blood flow.

Changes also occur outside the uteroplacental circulation which contribute to the increased uteroplacental blood flow during pregnancy. Blood volume increases approximately 40%, cardiac output rises similarly, and the distribution of blood flow is altered to increase the proportion of flow directed to the uteroplacental circulation as opposed to the lower extremities (48). Blood pressure falls, implying a decrease in systemic vascular resistance, which may in turn be due to altered response to vasoconstrictor, vasodilator, or myogenic stimuli. The increased blood volume implies that venous capacitance is increased, since the major portion of blood volume resides in the venous circulation.

Near term, approximately 1 l/min or 15% of the total cardiac output is directed toward the uteroplacental circuit. In studies conducted at low altitude (1600 m), we demonstrated that the rise in uteroplacental blood flow is accomplished in approximately equal part by a doubling of uterine artery diameter, that was complete by mid-gestation, and a rise in uterine artery flow velocity that continued until term. The overall increase in uteroplacental blood flow during human pregnancy is similar to that observed in other mammals when normalized per kg of fetal weight (48). In studies at

high altitude (3100 m), we found similar external and common iliac artery diameters but smaller uterine artery diameters, resulting in 1/3 lower unilateral uterine artery blood flows in the high-altitude women (49). Pelvic blood flow distribution was also altered near term; 74% of common iliac flow was directed toward the uterine artery in normal pregnant women at low altitude whereas only 47% was directed to the uterine artery at high altitude. Women who developed preeclampsia at high altitude had less redistribution of common iliac flow to favor the uterine artery and no increase in uterine artery flow near term. These differences were present prior to the onset of hypertension, suggesting that lower uterine blood flow may be a cause rather than an effect of preeclampsia (50). Compilation of data from human and experimental animal studies indicates that reductions in uterine or uteroplacental blood flow relate exponentially to declines in birth weight (figure 3), suggesting that an altitude associated decline in uteroplacental blood flow may be a major contributor to the birth weight reduction observed.

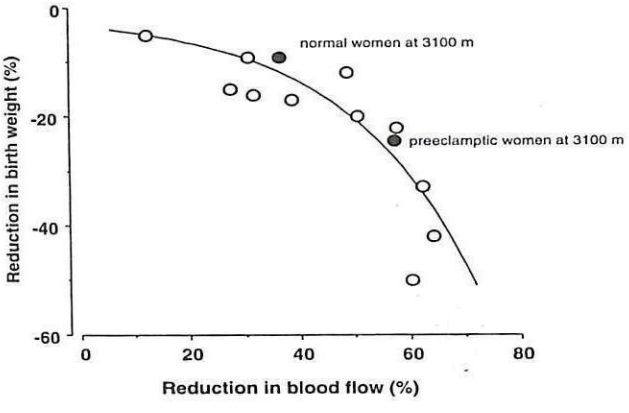

Figure 3: Reduction in birth weight and uterine blood flow in women at high altitude (closed circles) is consistent with that observed in models of IUGR in experimental animals (open circles) (adapted from 51).

SUMMARY AND CONCLUSIONS

The influences of gender and sex hormones on physiological responses to acute and chronic hypoxia are complex. This complexity is due to the many factors determining or, conversely, being determined by sex or gender. While operative under low- as well as high-altitude circumstances, the influences of gender and sex hormones at high altitude may be particularly important given the probable increase in selective pressure demonstrated by the more frequent occurrence of maternal, fetal and neonatal complications.

In general, stimulatory effects of ovarian hormones appear to help defend maternal arterial O_2 saturation and birth weight at high altitude. This has been demonstrated in a series of studies in which we and others have shown that ovarian hormones raise ventilation and are likely involved in the vascular alterations of pregnancy that serve to increase blood flow to the uteroplacental circulation. A lesser rise in uterine artery blood flow, particularly among preeclamptic women, may underlie the reduction in birth weight observed at high altitude and may, in turn, be due to an impaired growth response and/or alterations in responsiveness to vasoconstrictor, vasodilator or myogenic stimuli.

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