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Does Hypoxia Impair Ovarian Function in Bolivian Women Indigenous to High Altitude?

VIRGINIA J. VITZTHUM,[1] P.T. ELLISON,[2] S. SUKALICH,[2] E. CACERES,[3]
and HILDE SPIELVOGEL[3]

ABSTRACT

Fertility appears to be reduced in at least some high altitude populations relative to their counterparts at lower elevations. Inferring from the difficulties with reproduction of newcomers to high altitude and from animal experiments, it has been hypothesized that this apparent reduction is the result of hypoxia acting to reduce fecundity and/or increase fetal loss. In humans, however, several behavioral as well as biological factors may affect fertility levels. These many factors have been organized by demographers into a framework of seven proximate determinants that includes fecundability (the monthly probability of conception) of which successful ovulation is one component. To test whether ovarian function is impaired in women indigenous to high altitude, we measured salivary progesterone (P) in a sample (*n* = 20) of Quechua women (aged 19–42 years) residing at 3100 m. It was found that mean luteal P = 179 pmol/L and mean midluteal P = 243 pmol/L, levels that fall about midway in the range of known values for several populations and are higher than some lower altitude populations. These findings suggest that hypoxia does not appear to significantly impair ovarian function in those with lifelong residence at high altitude. There are, however, several factors common to many high altitude populations that may act to reduce fecundability and fertility including intercourse patterns (affected by marriage and migration practices), prolonged lactation, dietary insufficiency, and hard labor.

Key Words: progesterone; fecundity; proximate determinants; Quechua

INTRODUCTION

WHILE THERE IS SOME EVIDENCE for reduced fertility in Andean and Himalayan populations at higher altitudes compared with their counterparts at lower elevations (James, 1966; Clegg and Harrison, 1971; Baker and Dutt, 1972; Hoff and Abelson, 1976; Bangham and Sacherer, 1980; Gupta, 1980), the mechanisms underlying these observations are under debate (Goldstein et al. 1983, 1984a, 1984b; Abelson, 1984; Hoff, 1984). The first Spaniards to arrive in the Andean region noted difficulties in reproduction, both among themselves and their domesticated animals. These reports, in conjunction with medical and animal data, led Monge (1948) to propose that low oxygen pressure reduces fertility (the number of live births), perhaps by reducing fecundity (the capacity to conceive) and/or increasing fetal loss. Later evidence, principally drawn from animal experiments, suggested that environmental

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[1] Department of Anthropology, Binghamton University, Binghamton, NY.
[2] Department of Anthropology, Harvard University, Cambridge, MA.
[3] Bolivian Institute of High Altitude Biology, La Paz.

conditions at high altitude, including cold as well as hypoxia, can have a direct and negative bearing on at least some aspects of reproductive functioning.

In humans, however, social and cultural factors may also underlie any apparently lowered production of offspring at high altitude. Marriage, labor, and migration patterns as well as prolonged lactation and sterility from sexually transmitted diseases have all been implicated (Stycos, 1963; Heer, 1964; Weitz et al., 1978; Goldstein et al. 1983; Kashiwazaki et al., 1988; Vitzthum, 1989; Wiley, 1998). Hence, the demonstration of relatively fewer live births at greater elevations, even when well substantiated, is not, in and of itself, evidence of the influence of hypoxia. Conversely, similarity in fertility among populations at different altitudes does not disprove hypoxic effects, as other factors may compensate for physiological changes caused by varying oxygen pressure. Clearly, as with all humans, several determinants contribute to fertility levels in populations at high altitude. To evaluate the relative contribution of hypoxia to fertility, the approach we advocate is the integration of bioanthropological and other data with Bongaarts and Potter's (1983) demographic model delineating the Proximate Determinants of Fertility. Refining the model proposed by Davis and Blake (1956), they identified a complete set of seven proximate determinants through which any and all socioeconomic and environmental factors can affect fertility. These are: natural fecundability (the monthly probability of conception, itself a function of four probabilities that we examine in greater detail in the Discussion below), marriage and marital disruption, onset of permanent sterility, spontaneous intrauterine mortality (fetal loss), induced abortion, postpartum infecundability (including lactational subfecundity), and the use and effectiveness of contraception.[1]

Of this complete set of proximate determinants, hypoxia is hypothesized to affect fertility by increasing fetal loss and/or reducing fecundability by impairing fecundity. However, previous studies have not directly measured fecundity in women indigenous to high altitude. Rather, reduced fecundity has often been inferred for a high altitude population if fertility appears to be reduced, especially if fetal loss does not appear to be increased.

To test the hypothesis that fecundity is reduced in women at high altitude, we measured salivary progesterone (P) levels in a sample of Quechua women residing at 3100 m (10,000 ft). P has a characteristic profile during the menstrual cycle, being relatively low and flat during the follicular (preovulatory) phase, then rising and peaking about halfway through the luteal (postovulatory) phase before returning to basal levels, signaled by the onset of menstrual bleeding. Because absence or reduction of a rise and peak in P is considered indicative of subfecundity, P levels are an excellent proxy for measuring fecundity. For a variety of reasons, measurements of reproductive steroids have typically been restricted to the laboratory study of relatively few subjects. However, the development of methods for measuring steroids in saliva, found to be well correlated with serum steroid levels, has greatly expanded our ability to evaluate ovarian functioning in nonclinical settings (Ellison, 1988; Lipson and Ellison, 1989). Salivary sample collection is quick, easy, noninvasive, requires no special handling or storage, is acceptable where there are cultural reservations about blood collection, and can be done repeatedly through the day and/or every day throughout a cycle. In addition to presenting these new data on salivary P, we discuss the other determinants of fecundability so as to better identify factors other than hypoxia that may be operating to determine fertility levels in high altitude populations.

MATERIALS AND METHODS

Study participants comprise nearly all nonlactating/nonpregnant women of reproductive age from two isolated rural agropastoral Quechua communities (3100 m and 3200 m), Ayopayo Province, Bolivia. Women were recruited according to procedures approved by

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[1] Note that variation in neonatal survival, sometimes invoked as an explanation for lower fertility at high altitude, is not a component of the model as fertility is, by definition, the production of a live birth.

the Institutional Review Board, University of California, Riverside, and were free to withdraw without consequence at any time; no remuneration was given. All women in the sample (n = 20, 19 to 42 years old) reported experiencing regular menstrual cycles, an absence of sexually transmitted diseases, and an absence of contraception or other fertility control methods. All are lifelong high altitude residents (>3000 m), engage in arduous agricultural labor, and are subject to at least occasional nutritional constraints, most notably, seasonality in food abundance. Data presented here were collected during a season of relative adequacy in food supplies (July–August 1992).

Each woman was interviewed in her native language regarding her reproductive history, infant feeding practices, familial dietary practices, subsistence and income-generating activities, and characteristics of her menstrual cycle. Standard anthropometrics, made by a single observer (V.J.V.), included height, weight, and mid-arm circumference. Following a previously established protocol (Vitzthum et al., 1993), serial saliva samples were collected from each woman every other day through the course of the luteal phase of a single menstrual cycle. Samples were maintained at ambient temperature and shipped within 90 days of collection to the Reproductive Laboratory at Harvard University, under the direction of Ellison, whereupon they were frozen at −20 degrees centigrade.

Samples were subsequently radioimmunoassayed for P according to previously published protocols (Ellison and Lager, 1986). After centrifugation, 1.75 mL of each sample was extracted twice in anhydrous diethyl ether before being added to a radioimmunoassay of P. Specific antiserum #337 (Gibori et al., 1977) was supplied by Dr. Gordon Niswender, Colorado State University, and four-position tritiated P was obtained from Amersham-Searle (Arlington Heights, IL). Procedural losses during extraction were monitored by addition of an internal standard to each sample, and averaged 90%. Assay sensitivity, the smallest amount of steroid distinguishable from zero with 95% confidence, averaged 10 pmol/L. Average intraassay variability, assessed at the 50% binding point of the standard curve, was 9.3%. Interassay variability, estimated from pools containing various levels of P, averaged 26% for low pools ($y = 96$ pmol/L), 14% for medium pools (y = 375 pmol/L), and 15% for high pools (y = 663 pmol/L). The effects of interassay variability were minimized by running all samples from an individual woman in one assay. Assay blanks were indistinguishable from zero. Correlations of P concentrations in matched saliva and serum samples over the course of the menstrual cycle in three separate subjects (not from the Bolivia sample) ranged from 0.80 to 0.97.

RESULTS

The anthropometric characteristics of the Bolivia sample are similar to those of other high altitude populations (Table 1). Average stature is fairly short (147.7 cm), suggesting lifetime chronic undernutrition, while average body mass index (BMI) (22.7) is within what is considered a normal range (WHO, 1998). BMI values, however, are influenced not only by weight and height but also by body proportions, being inflated in those with relatively shorter limbs, as is typical in Andean peoples

TABLE 1. RURAL ANDEAN POPULATIONS: ANTHROPOMETRICS

	Ayopayo, Bolivia (3100 m) mean (SD) [range]	*Nuñoa, Peru (4000 m) mean [range]*
Age (years)	30.6 (8.3) [18.5–42.1]	[20–40]
Stature (cm)	147.7 (4.5)	147.4
Weight (kg)	49.4 (4.3)	50.3
BMI	22.7	23.1
MAC (cm)	25.8 (1.5)	24.2

BMI, body mass index; and MAC, mid-arm circumference.

(Vitzthum et al., 2000). Hence, these women are likely more nutritionally stressed than might be inferred from the average BMI value.

P levels are expressed by two indices. Because of the variable length of the follicular (preovulatory) phase of the menstrual cycle and the relatively invariable duration (approximately 14 days) of the luteal (postovulatory) phase, P data are aligned to the beginning of the subsequent cycle, operationally defined as the first day (the hours between awaking and retiring) of observable bleeding. Counting backwards from this anchor, average luteal P is the mean of sample average values over the days −1 to −14; average midluteal P (which should include the greatest P levels) is calculated as the mean of all values observed on days −5 to −9. In the Bolivia sample, mean luteal P is 179 pmol/L (SE = 18.7) and mean midluteal P is 243 pmol/L (SE = 21.0).

As has been previously reported (Ellison, 1990), P levels were observed to vary with age, being relatively highest from about 23–35 years old, and lower at younger and older ages. Subdividing the Bolivia sample accordingly, mean luteal P and mean midluteal P for the three age groups reflect this age-dependent variation (Table 2). In the youngest group (19–21 years) mean luteal P is 165 pmol/L (SE = 21.8), rising to 200 pmol/L (SE = 13.2) in the mid-aged group (23–35 years), then falling to 149 pmol/L (SE = 14.4) in the oldest group (39–42 years). Similarly, mean midluteal P is only 219 pmol/L (SE = 29.8) among the younger women, rises to 264 pmol/L (SE = 17.3) in the midaged subsample, and then drops to 203 pmol/L (SE = 21.4) among the older subjects.

DISCUSSION

Observed fertility levels in Andean populations

The first analyses in the Andes of fertility differences according to ethnicity and/or altitude (Stycos, 1963; Heer, 1964; James, 1966) relied on national-level census data. Unfortunately, many would agree that "a rural Third World survey is the careful collection, tabulation, and analysis of wild guesses, half-truths, and outright lies meticulously recorded by gullible outsiders during interviews with suspicious, intimidated, but outwardly compliant villagers" (Chen and Murray, 1976). While there has been much improvement over the last 35 years in the implementation of national surveys, ethnographic observation over the course of several years of fieldwork in the rural Andes by the first author confirms that the problem persists even today. This difficulty aside, the measures of fertility used in these early analyses were likely biased. As suggested by James (1966) and Whitehead (1968), and later confirmed by Dutt (1980), the ratio of the number of children under 5 years of age to the number of women aged 15–49 is downwardly biased by the greater infant and child mortality known to exist in higher regions. Similarly, at higher elevations the average number of children ever born to women aged 45–49 is disproportionally biased downward by the omission in reporting infants dying shortly after birth.

Recognizing these limitations, later studies in the Andes concentrated on community level estimates of fertility (summarized in Table 3). The CFR (completed fertility rate) for high and low altitude populations in these studies

TABLE 2. SALIVARY PROGESTERONE INDICES IN FIVE POPULATIONS

	N	Mean [SE] luteal P (pmol/L)	Mean [SE] mid-luteal P (pmol/L)		Data source
			all ages	25–35 years old	
Bolivia	20	179 [18.7]	243 [21.0]	251 [17.1]	this study
younger (19–21)	4	165 [21.8]	219 [29.8]		
mid (23–35)	10	200 [13.2]	264 [17.3]		
older (39–42)	6	149 [14.4]	203 [21.4]		
Poland					G. Jasienska
postharvest	20	226 [9.5]	283 [16.9]	299 [19.6]	
harvest	20	188 [6.9]	224 [12.5]	237 [14.7]	
Nepal (winter)	21	117 [7.2]	138 [21.0]	253 [53.0]	Panter-Brick et al. (1994)
Zaire	56	132 [11.0]	167 [6.5]	201	P.T. Ellison
Boston	124	232	333	373	Lipson and Ellison (1992)

TABLE 3. FERTILITY MEASURES FOR ANDEAN SAMPLES

Sample	*High altitude*		*Middle altitude*		*Low altitude*		*Source*
	CFR	*CBR*	*CFR*	*CBR*	*CFR*	*CBR*	
Aymara (Chile)	7.3	82			6.4	48	Cruz-Coke (1966)
	8.5				7.2		Cruz-Coke (1966)
	5.8						Cruz-Coke (1966)
			7.1				Schull et al. (1990)
Mestizo (Chile)	6.9		6.7		4.6		Schull et al. (1990)
Quechua/Mestizo (Peru)	6.7						Hoff (1968)
	9.1*				8		Way (1972)
					8.3		Abelson (1976)
		49					Baker and Dutt (1972)
		54					Baker and Dutt (1972)
				46			Alers (1971)
				56			Alers (1971)
Aymara (Bolivia)	5.9		7.2		6.9		Dutt (1976, 1980)
			5.3		5.4		Dutt (1976, 1980)
Quechua (Bolivia)		51		46			Godoy (1984)

CFR, completed fertility rate for women >45 years old; and CBR, crude birth rate.
*Number of pregnancies.

ranges from 5.8 to 9.1 and 4.6 to 8.3, respectively. Similarly CBR (crude birth rate) ranges from 51 to 82 in high altitude populations, 46 to 56 in populations at middle altitudes, and is as low as 48 in a low altitude sample. Clearly, as one might expect, fertility levels vary considerably at any altitude, and in specific comparisons made by the various authors, fertility is higher at greater elevations in several cases. It has been noted that there are low altitude populations (i.e., the Hutterites) displaying an elevated fertility not seen in any high altitude population, thus suggesting that hypoxia is somehow responsible for lowering fertility at high altitude. But the observation is not relevant. Not only has no other human population been found to have a fertility as high as the Hutterites, but worldwide there are many more low than high altitude populations; hence, greater variation is to be expected among the former. Thus the lowest fertility levels (in noncontracepting populations) are found, for example, among the Lese (average # of live births in women >35 years of age = 2.8; Ellison et al., 1989) and the !Kung (completed fertility for a post-menopausal cohort = 4.7; Howell, 1979).

Although it is clear that a range of fertility levels characterize Andean populations at high altitude, this does not necessarily indicate an absence of an effect of low oxygen pressure on fertility. Other determinants of fertility may compensate for any loss due to hypoxia. Hence, it is necessary to directly examine the principle mechanisms by which hypoxia may influence fertility. Because hypoxia has been hypothesized to reduce fertility by influencing fecundity, below we discuss what is known of the determinants of fecundability in high altitude human populations.

Animal and experimental studies

Although there are many intriguing studies on animals suggesting that hypoxia may directly affect reproduction, these are not discussed here for two reasons. First, while these studies on rats and other mammals are clearly valuable for revealing potential lines of inquiry and for gaining an understanding of physiological pathways, extrapolation in a consideration of fertility determinants in humans is at best speculative and should be reserved until after an evaluation of those factors known to influence human fecundity and fertility. Second, many of the studies draw their conclusions based upon acute exposure to low barometric pressure. The relevance of these laboratory experiments to ascertaining the effects of chronic hypoxic exposure, occurring from the moment of conception to full sexual maturity, is unknown. In the same vein, experimental studies of humans exposed to a dramatic change in barometric conditions do not mimic the cumulative lifetime experiences of high altitude indigenous residents nor the possible multigenerational adaptations of these populations.

That ontogenetic adaptation of the reproductive system to hypoxia is likely is evidenced by Father Cobo's observation (1891–1892, cited by Monge 1948) that "The Indians are healthiest and where they multiply the most prolifically is in these same cold air-tempers, which is quite the reverse of what happens to the children of the Spaniards, most of whom when born in such regions do not survive. But where it is most noticeable is in those who have half, a quarter, or any admixture of Indian blood; better they survive and grow; so that it is now a common saying based on everyday experience that babes having some Indian in them run less risk in the cold regions than those not having this admixture." Hence, we focus our discussion below on what is known of the determinants of fecundability in indigeous populations residing at high altitude.

Fecundability

In the model developed by Bongaarts and Potter (1983), spousal fecundity (the capacity to conceive) is operationalized as fecundability (the monthly probability of conception) and is dependent upon four probabilities, specifically: (1) $p1$ = the probability of an ovulatory cycle, (2) $p2$ = the probability that insemination occurs during the midcycle fertile period, (3) $p3$ = the probability that insemination during the fertile period leads to fertilization, and (4) $p4$ = the probability that fertilization results in a recognizable conception. Reasoning that $p1$ and $p3$ are consistently high (each estimated at 0.95), that $p4 = 0.50$, and that all three probabilities are relatively invariant across populations, Bongaarts and Potter concluded that fecundability is largely the result of $p2$, which is dependent upon the frequency and timing of intercourse.

Unfortunately, data on intercourse patterns are rare and, at least according to some (Muggeridge 1965), highly suspect. Certainly caution is warranted as selectivity bias and recall error, both difficult to avoid, will confound any intended deception regarding personal sexual activities. These biases are probably exacerbated in nonindustrialized settings where, as we have already noted, interviewer–interviewee interactions are typically far less than ideal. At best, in the absence of some specific prohibition against sexual intercourse (e.g., postpartum taboos, which are not known to occur in Andean culture), one is forced to assume that the frequency of sexual relations between cohabitating partners is approximately the same in all populations. What little data there is, however, suggests this may not be the case. For example, married women in Belgium reported monthly coital rates approximately 25% higher than those reported by Japanese married women (Udry et al., 1982). It is not possible to say, however, if the reported difference reflects true behavior or cultural norms about what one may do and then say about what one has done.

An important exception to the assumption of uniformity of coital rates is the case of spousal (i.e., partner) separation, when clearly spousal fecundability is zero. In settings where male migration occurs, either seasonally or long term, because of subsistence cycles or to secure employment, fertility would clearly be reduced. Such migration patterns are not uncommon in populations residing at high altitude, where the harsh environmental conditions often necessitate a subsistence strategy that includes exploiting resources at altitudes lower and higher than one's permanent residence. Spousal separation is also found among rural and/or very poor individuals, driven by necessity to seek employment at some distance from their home. Historically, some colonial powers have sometimes enforced spousal separation to exploit the labor of males, and remnants of such practices persist today in some locales. Unfortunately, while fecundability during periods of spousal separation is certain to be zero, the frequency and duration of such separations is usually not recorded, unlike occurrences of marital dissolution, and hence, it is difficult to measure and evaluate the impact of temporary separations on fertility. Nonetheless, relative to their lowland counterparts, it is clear that there are several factors likely to increase spousal separation and reduce *p2* to zero, hence leading to a decrease in fertility, among impoverished rural populations at high altitude.

The probability that insemination during the fertile period leads to fertilization (*p3*) is partly dependent upon sperm quality and quantity, another mechanism by which hypoxia has been hypothesized to influence fecundity at higher elevations. However, to date the evidence suggests that there is no impairment of spermatogenesis among men indigenous to high altitude (Sobrevilla et al., 1967). In addition, the levels of urinary gonadotropins (Donayre, 1966) and urinary excretion of testosterone (Guerra-Garcia et al., 1965) appear to be the same in low and high altitude men. It seems unlikely that fecundability is negatively impacted in high altitude populations as a result of any hypothesized effects of hypoxia on male fecundity. Given the time since these studies, however, with the development of new techniques, the question certainly warrants reinvestigation.

Among healthy women, fecundity has been assumed to be relatively invariant except in the immediately postmenarcheal and premenopausal periods. Hence, Bongaarts and Potter set *p1* at 0.95. However, a growing body of data suggests that there is considerable natural variation among women and populations in ovarian function (Ellison et al., 1993). Recall that progesterone is low and flat during the follicular phase but rises after ovulation; P remains relatively low if ovulation does not occur. Thus, a study of P levels affords an opportunity to directly evaluate interpopulational variation in the probability of an ovulatory cycle (*p1*). However, because there is no known threshold of P below which ovulation does not occur, the observed absolute level of P is not itself very useful. Rather, it is instructive to compare P levels in the Bolivia sample with those of samples from four other populations, all of which have also been assayed in the same laboratory at Harvard.

The mean luteal P in the Bolivia sample is 179 pmol/L (Table 2), a value much lower than that of both the Boston sample (232 pmol/L) and the post-harvest Polish sample (226 pmol/L), but considerably higher than the samples of agriculturalists from Zaire (132 pmol/L) and Nepal (117 pmol/L; this value is for the winter season, a period of relatively less work and greater food resources, as was the case for the period during which the Bolivia data were collected. Note also, this value is slightly higher than the published value which was calculated from the means of days −1 to −16 rather than −1 to −14). In other words, the Bolivia sample is approximately in the middle of the range of observed salivary P levels.

However, because of variation in the length of the follicular phase, values for mean luteal P in these samples may inadvertently include some follicular P values. It may be more useful, therefore, to compare the values of mean midluteal P, which would exclude such bias. Once again, the mean midluteal P (Table 2) is highest in the Boston sample (333 pmol/L) and lowest in the sample from Nepal (138 pmol/L); the Zaire sample is also quite low (167 pmol/L), being just half of the Boston value. Of the samples from nonindustrialized populations, the Polish peasants are once again the highest (283 pmol/L in the post-harvest season) though still substantially lower than Boston. As was the case with mean luteal P, the Bolivia sample (243 pmol/L) falls in the middle of this range, being somewhat more similar to Poland than to Zaire. In sum, when considering either index of ovarian function, the Bolivia sample falls within the range of P levels observed for several low altitude populations and is substantially higher than the Nepal sample, drawn from a population residing at 1870 m.

Then again, P is known to vary with age, and the age distribution of these five samples are not identical. A more appropriate comparison is to examine P levels solely for mid-aged women (Table 2, column 4; only those Bolivia women from 25–35 years of age are included here to ensure comparability with the published findings of other studies). Reflecting the greater similarity in age among the samples, mean midluteal is also more similar. It is particularly noteworthy that, once adjusting for age, the lowest value is no longer found in the Nepal sample but rather in the Zaire sample (201 pmol/L). Both higher altitude samples (Bolivia and Nepal) are nearly identical (251 pmol/L and 253 pmol/L, respectively) and substantially higher than the low altitude Zaire sample. Interestingly, while lower than Polish women (299 pmol/L) during the post-harvest season (a period roughly comparable to the seasons during which the Nepal and Bolivia data were collected), these samples from higher altitudes display P levels greater than the low altitude (700-m) sample of Polish women during the peak of harvesting (237 pmol/L). Although these comparisons are not conclusive, it does not appear that the P level observed in the high altitude Bolivia sample is unusual or necessarily suggestive of an effect of hypoxia on ovarian function.

Our findings, however, appear to be at odds with a study of the menstrual cycle in high altitude women in Peru (Escudero et al., 1996). Beginning with the second day of menses and until the subsequent menses, a daily venous blood sample was obtained from 10 women native to Lima (150 m) and 10 women native to Cerro de Pasco (4340 m). Inclusion criteria included regular menstrual cycles, good general health, no obesity, and no pregnancy or lactation in the previous 6 months. Serum P levels were similar in the two samples during the follicular phase but found to be significantly higher ($P < 0.05$) in the sea level sample on 6 of 15 days during the luteal phase. A number of other similarities and differences were noted in the menstrual cycles of the two samples, the authors concluding that the differences are "probably an effect of low barometric pressure."

While this may be the case, there are other factors known to affect P levels, and other characteristics of the menstrual cycle, that could explain the observed differences in these two Peru samples from different altitudes. As demonstrated above, age is a significant determinant of P levels. In the Peru study, the average age of the high altitude sample was almost 3 years less than that of the Lima sample, and the variance was somewhat greater (28.5 ± 3.9 years vs. 31.3 ± 3.6 years). The age range is not given for these samples but, while the means are not statistically significantly different, the sample statistics suggest that perhaps somewhat younger women made up a greater proportion of the high altitude sample. In a sample of only 10 individuals, the impact of even a single younger woman is proportionally greater, a frustrating fact when one considers how difficult it is to conduct investigations of reproductive hormones. This point is dramatically illustrated by the near doubling of the mean midluteal P in the Nepal sample (Table 2, column 4) once only mid-aged (25- to 35-year-old) women are considered rather than the entire sample from 17–46 years of age (253 pmol/L vs. 138 pmol/L, respectively).

Substantial differences in salivary P can also occur as a result of changes in energy intake and expenditure. In Zaire and Nepal, P levels were found to fall with a loss in weight during the leaner seasons. But the Peru study took care to recruit women who had no recent weight change, therefore it is unlikely that recent weight loss might account for the observed differences in the menstrual cycle. However, it has recently been found (Jasienska and Ellison, 1998) that in Polish women midluteal P levels during the harvest season were only 79% of the levels observed post-harvest (Table 2, column 4), even though energy balance was in equilibrium (i.e., weight stayed constant). Similarly, during the harvest season, those women with high total energy expenditure displayed a mean luteal P only 68% of the value seen in women with moderate total energy expenditure (158.4 pmol/L vs. 231.6 pmol/L). In other words, the level of activity itself can dramatically change P levels. In the Peru samples, the inclusion criteria included "daily mild or moderate physical activity." It is not possible to say, however, what defines these levels of activity, or whether one sample included more women engaged in mild versus moderate activities. Assuming that the women self-reported their activity levels, women from the rural high altitude population may have a different conception of mild or moderate than women in the urban sea level sample. Hence, it is not unreasonable to suggest that the relatively lower P levels seen on some days of the menstrual cycle in the Peru high altitude sample may be the result of greater physical activity rather than hypoxia.

Socioeconomic factors may also play some role in determining P levels. Both Peru samples "belonged to a low socioeconomic class assessed by their place of residence." Assuming that the women in each sample are necessarily equivalent presupposes relative homogeneity within socioeconomic classes and similarity of classes among different locales. This is unlikely to be the case when comparing urban and rural settings, particularly at different altitudes. In some cases, poor urban individuals would be relatively affluent in a rural setting; in others, urban poor are worse off than rural poor. Any differences in resources between these populations would affect growth and possibly P levels. It has been hypothesized that under chronically poor conditions during the developmental period, P levels will be lower in adulthood (Ellison, 1990, 1996; Vitzthum, 1990, 1997). Chronic undernutrition during growth typically results in a relative stunting of stature in adulthood, but the anthropometrics of the two Peru samples are not presented. If the women at higher altitude are relatively shorter than the sea-level sample, this is likely a reflection of differences between the samples in socioeconomic resources that could decrease P levels in the high altitude sample. Although it has been proposed that relatively short stature at high altitude is a result of hypoxia, more recent studies (cf. Vitzthum et al., 2000) have found that socioeconomic conditions figure prominantly in determining the heights of Andean peoples.

It is also the case that diet may affect P levels, and dietary differences are likely to exist between the high and low altitude samples. In addition, although none of the participants were currently using oral contraceptives or other steroids, it is not clear how long before recruitment they may have been. While it is not possible to know without direct inquiry of the participants, it may be that women in the Lima sample had more recently used steroids than women in the rural high altitude sample.

It would appear, then, that the differences in P and some other aspects of the menstrual cycles observed in the Peru study may be the result of low barometric pressure and/or differences in age distribution of the samples and/or differences in physical activity and/or differences in socioeconomic resources and/or differences in diet and/or differences in recency of steroid use.

CONCLUSIONS

In sum, the question of whether low oxygen tension has a negative impact on fecundity among women indigenous to high altitude remains open. Despite the meticulous effort of the Peru study, it is exceedingly difficult to control for all of the factors that may affect P levels, or any other measure of reproductive functioning. The data presented here on salivary P in an Andean sample, exhibiting levels that fall about midway in the range of known values from populations at lower altitudes, suggest an absence of a difference in ovarian function according to altitude. And there are not, as yet, any data that are not explainable by some variable, other than hypoxia, already known to affect ovarian function.

Nonetheless, it is yet to be determined if the levels of P we observed are associated with maintenance or change in fecundity (i.e., conceptions) per se. As well, much more needs to be learned about which factors determine intra- and interpopulational variation in P levels. These and other issues of reproductive functioning are being addressed by the REPA (Reproduction and Ecology in Provincia Aroma) Project, a longitudinal study in the Bolivian altiplano serially measuring levels of reproductive steroids every other day and monitoring for conceptions as they occur (Vitzthum et al., 1998). Perhaps the most well-considered conclusion at this time is that if hypoxia does negatively impact ovarian function in women indigenous to high altitude, its effect appears to be far less than that of several other factors common to populations living at high altitude.

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Address reprint requests to:
V.J. Vitzthum
Department of Anthropology
Binghamton University
Binghamton, NY 13905

E-mail: vitzthum@binghamton.edu

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