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The Ecology and Evolutionary Endocrinology of Reproduction in the Human Female

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ABSTRACT Human reproductive ecology (HRE) is the study of the mechanisms that link variation in reproductive traits with variation in local habitats. Empirical and theoretical contributions from biological anthropology, physiology, and demography have established the foundation necessary for developing a comprehensive understanding, grounded in life history theory (LHT), of temporal, individual, and populational variation in women's reproductive functioning. LHT posits that natural selection leads to the evolution of mechanisms that tend to allocate resources to the competing demands of growth, reproduction, and survival such that fitness is locally maximized. (That is, among alternative allocation patterns exhibited in a population, those having the highest inclusive fitness will become more common over generational time.) Hence, strategic modulation of reproductive effort is potentially adaptive because investment in a new conception may risk one's own survival, future reproductive opportunities, and/or current offspring survival. The hypothalamic-pituitary-ovarian (HPO) axis is the principal neuroendocrine pathway by which the human female modulates reproductive functioning according to the changing conditions in her habitat. Adjustments of reproductive investment in a potential conception are manifested in temporal and individual variation in ovarian cycle length, ovulation, hormone levels, and the probability of conception. Understanding the extent and causes of adaptive and non-adaptive variation in ovarian functioning is fundamental to ascertaining the proximate and remote determinants of human reproductive patterns. In this review I consider what is known and what still needs to be learned of the ecology of women's reproductive biology, beginning with a discussion of the principal explanatory frameworks in HRE and the biometry of ovarian functioning. Turning next to empirical studies, it is evident that marked variation between cycles, women, and populations is the norm rather than an aberration. Other than woman's age, the determinants of these differences are not well characterized, although developmental conditions, dietary practices, genetic variation, and epigenetic mechanisms have all been hypothesized to play some role. It is also evident that the reproductive functioning of women born and living in arduous conditions is not analogous to that of athletes, dieters, or even the lower end of the "normal range" of HPO functioning in wealthier populations. Contrary to the presumption that humans have low fecundity and an inefficient reproductive system, both theory and present evidence suggest that we may actually have very high fecundity and a reproductive system that has evolved to be flexible, ruthlessly efficient and, most importantly, strategic. Yrbk Phys Anthropol 52:95–136, 2009.

> It would be instructive to know not only by what physiological mechanisms a just apportionment is made between the nutriment devoted to the gonads and that devoted to the rest of the parental organism, but also what circumstances in the life-history and environment would render profitable the diversion of a greater or lesser share of the available resources towards reproduction. Ronald Fisher, 1930.

Fisher's two questions are clearly linked, yet historically the answers to each have been pursued largely independently. With rapidly advancing laboratory technologies, physiologists have exposed many of the fine details of how organisms function as they do, and with sophisticated analytical tools, evolutionary theorists have generated testable explanations of why organisms vary as they do. Propitiously, the relatively recent and invigorating exchange of ideas and data between these lines of inquiry has fostered the rapidly expanding field of evolutionary endocrinology. The study of whole organism physiology, morphology and behavior in natural, and sometimes cleverly modified, settings is at the nexus of these exciting developments in the evolutionary sciences.

Anthropologists are well positioned to contribute to and gain from these advancements, as evidenced by findings from field studies during the past three decades that have broadened our understanding of human, especially female, reproductive functioning (e.g., Konner and Worthman, 1980; Wood et al., 1985; Leslie and Fry, 1989; Ellison et al., 1989; Vitzthum, 1989; Holman, 1996; Strassmann, 1997; Bribiescas, 2001; Nepomnaschy et al., 2006 and others discussed later). But there is much more work to be done. A cursory examination of medical texts on women's reproductive biology could leave one

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thinking that the functioning of the ovarian cycle is well understood in extraordinary detail. But in fact, there is not much that is unequivocally certain about the specifics of women's reproductive biology. Moreover, for all that is known at the cellular level, there is but a modicum of data on populational variation in these processes, and the determinants of that variation are almost entirely conjectural. Fortunately, anthropologists' preoccupation with variation, our willingness (even eagerness) to work outside the confines of our own populations, and our capacity for adapting laboratory methods to remote field sites predisposes us better than most to undertake the fascinating and necessary task of discovering the nature and extent of variation in human reproductive functioning.

For the most part, contemporary biological anthropologists investigate human reproductive variation within a somewhat fuzzy framework that has come to be known as human reproductive ecology (HRE). Reflecting different intellectual traditions, there are several definitions of this field of inquiry (e.g., Campbell and Wood, 1994; Hill and Hurtado, 1996; Morbeck et al., 1997; Winterhalder and Smith, 2000; Ellison, 2001; Leslie and Little, 2003). For the purpose of the present discussion, I define HRE as: *the study of the mechanisms that link variation in reproductive traits with variation in local habitats*.

Habitats comprise the physical, biological, and social conditions that an individual must accommodate and exploit for survival and reproduction. I emphasize "local habitats" because these are the contexts within which natural selection acts on individuals and because human "biological uniformitarianism," the assumption that all humans respond in a similar manner to comparable stimuli across varied habitats, is demonstrably incorrect (Leslie and Little, 2003).

Mechanisms subsumes both physiological and behavioral processes that modulate reproductive traits. These two sets of mechanisms have rarely been studied in tandem, in part because of the technical challenges of measuring biomarkers outside a clinical setting. Nonetheless, reproductive behavior, as a manifestation of the neurohormonal mechanics of the human brain, is necessarily physiological, at least in part. Moreover, reproductive behaviors exert much of their influence on fertility by modulating physiological determinants. Unlike others, this definition stresses the study of "mechanisms" over that of "relationships" to encourage a more specific examination of *how* differing habitats generate variation in reproductive traits.

Reproductive traits are the suite of physiological, morphological, developmental, and behavioral phenotypes concerned with the production and nurturance of offspring (e.g., age at puberty, mating strategies, number of offspring, age at menopause). Collectively, these traits determine the magnitude and temporal patterning of an individual's lifetime reproductive investment.

The full breadth of thinking and relevant evidence regarding human reproductive investment is beyond the scope of a single article. My focus here is on the functioning of the hypothalamic-pituitary-ovarian (HPO) axis, the principal neuroendocrine pathway by which the human female modulates reproductive functioning according to the changing conditions in her habitat. Adjustments of reproductive investment in a potential or recent conception are manifested in temporal and individual variation in ovarian cycle length, probability of ovulation, hormone levels, probability of conception, and early pregnancy maintenance. Modulation at these early stages of reproductive investment, even to the extent of rejection of the current opportunity (anovulation or early pregnancy termination), is largely under maternal control and not costly, as only one or very few opportunities for reproduction may be lost. Figure 1 is a schematic presentation of the principal approaches used by reproductive ecologists to investigate women's reproductive functioning. Whichever explanatory framework one prefers, understanding the extent and causes of variation in ovarian functioning is fundamental to ascertaining the proximate and remote determinants of human reproductive patterns.

Many investigators, particularly those concerned with the role of energetics in reproduction, have focused on measuring ovarian functioning, "the 'linchpin' of the female reproductive system, with steroid levels being the most useful, readily detectable reflection of ovarian function" (Ellison, 1990, p 936). Proponents of this approach presume that variation in measures of ovarian functioning is associated with variation in fecundity and have been less concerned with measuring fertility, considered by some to "provide for second-order inferences only" (Ellison, 1990, p 934).

On the other hand, fertility differentials are at the heart of demographic frameworks, which delineate a finite set of proximate determinants by which all the potential causes of variation in fertility must exert their effects. Wood and Weinstein (1988), Campbell and Wood (1988), and Wood (1990, 1994a) have developed a model of the proximate determinants of natural fertility (PDNF; Table 1, Fig. 1 [middle panel]). Ovarian hormone levels are not a PDNF but might influence several PDNF including ovarian cycle length and the proportion of cycles that are ovulatory. A sensitivity analysis of the potential contribution to fertility differentials of each fecundability factor in this model suggested that variation in the frequency of insemination is the least important factor whereas differences in cycle length and ovulation frequency can have greater impacts (Wood and Weinstein, 1988). They concluded (1988, p 108) that "both total and effective fecundability change throughout life in response to changes in the efficiency of the ovarian function and in the level of intrauterine mortality ... Intrauterine mortality appears to be particularly important in explaining the decline, if any, ... in effective fecundability before age 40." These observations derived from a demographic model mesh well with the physiologists' view of the ovarian cycle as a "linchpin" and with the life history hypothesis that varying the functioning of the HPO axis is a low-cost effective mechanism for modulating reproductive investment.

Physiological and demographic approaches inform answers to Fisher's first question, how "a just apportionment is made," but cannot address his second question, why there is a "diversion of a greater or lesser share of the available resources towards reproduction." Simply claiming that the observed pattern must be selectively advantageous because, after all, it works so well, merely begs the question (Williams, 1966a). Life history theory (LHT) provides the framework, models and tools for generating testable hypotheses concerning the costs and benefits of human reproductive patterns in different habitats, in other words, the answers to why human reproduction varies as it does. Human reproductive investment lasts far beyond the production of a live neonate, a pattern that incurs competition among different reproductive opportunities (see Fig. 1). A given opportunity is not considered successful until the offspring is grown

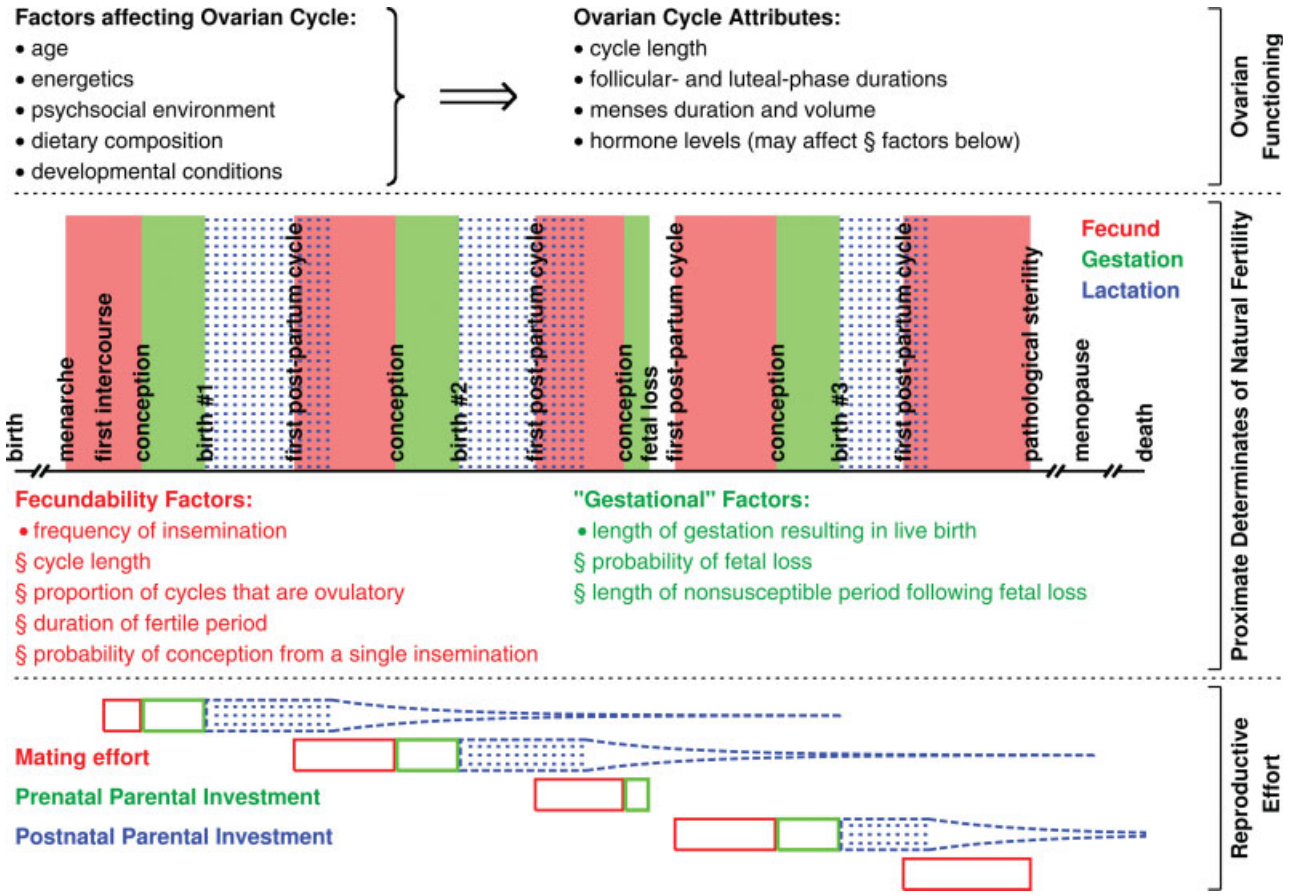

Fig. 1. Three approaches for the study of human female reproductive patterns. Top Panel: Physiological studies may focus on how different factors influence ovarian functioning, manifested as variation in ovarian cycle attributes. Center Panel: Demographic studies evaluate the relative contributions of the PDNF. The schematic depicts a hypothetical reproductive history: red = fecund periods, green = gestation, blue dots = lactation [*post-partum* amenorrhea = blue on white, fecundity resumes during lactating = blue on red]. * = PDNF linked directly to ovarian functioning. Bottom Panel: A life history approach analyses the components of reproductive effort, depicted schematically over a lifetime: red = mating effort, green = prenatal parental investment, blue = postnatal parental investment including, but not limited to, lactation (blue dots). Parental investment in sequential offspring typically overlaps.

and reproducing, yet other opportunities must be engaged before prior ones are completed. The unavoidable trade-offs in resource allocation, including those necessary for maternal survival, generate a delicate balancing act that we have long appreciated but are only beginning to understand.

To consider what is known, and what still needs to be learned, of the ecology of women's reproductive biology, I begin this review with a discussion of the principal explanatory frameworks in HRE. I next describe the biometry of ovarian functioning and, reflecting presumed reader interests, give particular attention to field-friendly protocols; a basic familiarity with these methods facilitates an understanding of the relevant literature. In the subsequent sections I examine modulation of reproductive effort in a new opportunity for reproduction, manifested as variation in ovarian cycle attributes. My principal focus is on women from about 20 to 40 years of age. Of course, this age span is part of a continuum that encompasses both menarche and menopause, but there are good reasons for limiting the scope of the present inquiry, not the least being that these are the years of greatest reproductive investment, which largely determines evolutionary fitness.

TABLE 1. Proximate determinants of natural fertility[a]

I. Exposure factors:
Age at menarche
Age at menopause
Age at entry into sexual union
Age at onset of pathological sterility
II. Susceptibility factors:
Fecundability factors:
Length of ovarian cycles
Probability of ovulation
Duration of the fertile period
Frequency of insemination
Probability of conception from a single insemination in the fertile period
Probability of pregnancy loss
Length of the nonsusceptible period following fetal loss
Length of gestation resulting in a live birth
Duration of post-partum infecundability

[a] Modified from Wood (1990, 1994).

FRAMEWORKS FOR THE STUDY OF HUMAN REPRODUCTION

HRE arose from a confluence of somewhat disparate approaches to human fertility, and its origins are not

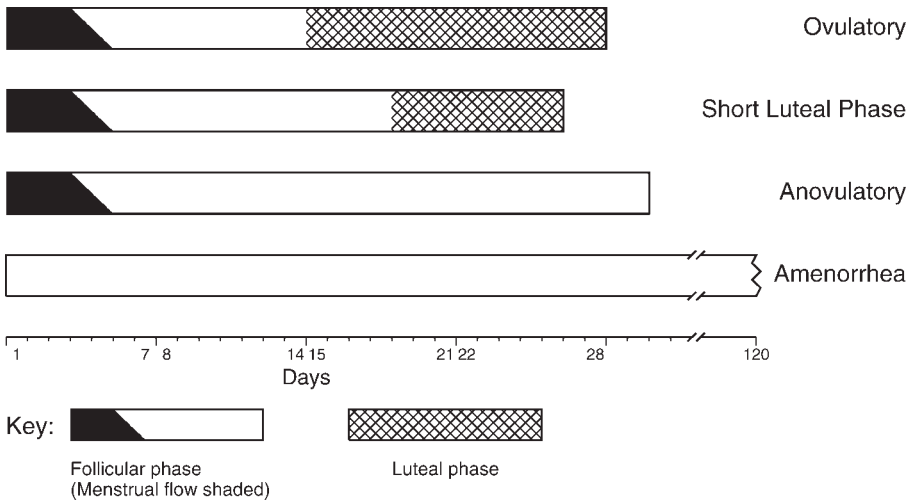

Fig. 2. Prior's (1985a) model of ovarian functioning as a series of graded responses to escalating stress, from a normal ovulatory cycle to shorter luteal phases to anovulation to a complete absence of menstrual bleeding.

readily traceable to a single seminal paper or project. Over time the emergent HRE framework has adopted, if not quite integrated, intellectual contributions from biological anthropology, demography, physiology, behavioral ecology, medicine, and evolutionary biology.

Demographers (e.g., Henry, 1956; Tietze, 1961) were among those who first recognized and documented the substantial contribution of lactation to post-partum suppression of ovarian functioning, a behavior-physiology-fertility linkage that became a cornerstone of research in HRE (Konner and Worthman, 1980; Vitzthum, 1994a; Sellen, 2007). Roger Short (1976), a physiologist, squarely placed human fertility patterns within an evolutionary framework in his essay, "The evolution of human reproduction". Rose Frisch's (1978; Frisch and Revelle, 1970, 1971a,b; Frisch and McArthur, 1974) arguments regarding the roles of energy intake and expenditure in human reproductive functioning sparked wide debate and laid the foundation for energetics models of ovarian functioning. At about the same time, the increases in menstrual dysfunction that accompanied women's burgeoning participation in physical fitness programs inspired models in HRE and prompted some physicians (e.g., Prior, 1982, 1985a,b) to reconceptualize apparent pathology as an adaptive response to energetic stressors (see Fig. 2).

Anthropological approaches

Although insights from outside anthropology were significant, the substantial bulk of empirical and theoretical work in HRE is the contribution of several intersecting research lineages within anthropology. Nancy Howell's (1979) rigorous study of fertility and mortality in the Dobe !Kung was both a thorough demographic analysis of a hunter-gatherer population and a perceptive consideration of the ecological and biological determinants of these patterns. Melvin Konner and Carol Worthman's (1980) groundbreaking integration of meticulous behavioral observation with hormonal measures to investigate the mechanism linking lactation and fertility in the !Kung San marks the beginning of human evolutionary endocrinology. James Wood and his collaborators injected greater analytical rigor into anthropological research and greater biology into classic demographic models than had been previously customary (Campbell and Wood, 1988; Wood and Weinstein, 1988; Wood, 1994a). Working independently, Samuel Wasser and David Barash (1983), Nadine Peacock (1990, 1991) and Virginia Vitzthum (1990; Vitzthum and Smith, 1989) proposed evolutionary models grounded in LHT to explain reproductive suppression and pregnancy termination. Technological advancements expanded the collection of biomarkers outside clinical settings, thereby affording empirical tests of evolutionary hypotheses. Peter Ellison and his collaborators (1993a,b) demonstrated significant seasonal and interpopulational differences in salivary progesterone in several non-industrialized populations, and advanced energetics models of ovarian functioning (1990). Using urinary biomarkers, Paul Leslie, Kenneth Campbell and Michael Little (1993) documented unexpected differences in pregnancy loss between nomadic and settled Turkana pastoralists. By the mid-1990s, theoretical and empirical efforts had laid a solid foundation for the ecological study of human reproductive biology.

Concurrent with efforts to model and measure variation in reproductive *functioning*, another somewhat independent tradition developed within anthropology that focused on modeling and measuring variation in reproductive *behavior* (i.e., mating strategies, parental investment) and associated outcomes (e.g., reproductive success). This side of HRE, embedded within human behavioral ecology (HBE), is less concerned with elucidating biological mechanisms per se (rather assuming their necessary existence) than with the application of "evolutionary ecology models and concepts to the study of human behavioral diversity" (Winterhalder and Smith, 2000). Hence, while intellectually vigorous and highly productive, HBE has not devoted much attention to variation in reproductive biology. There are, however, good reasons to unify biological and behavioral approaches to human reproduction, not least because ovarian physiology is much more variable and complex than assumed in many behavioral studies.

Reflecting the field's focus on adaptation (Washburn, 1951; Lasker, 1969; Mazess, 1975; Wiley, 1992; Leslie and Little, 2003; Vitzthum, 2008b), several anthropologists have sought to integrate evolutionary (ultimate)

and proximate (mechanistic) explanations (Tinbergen, 1963; Mayr, 1983) for women's reproductive functioning. Evolutionary hypotheses are, however, difficult to test in humans because of the daunting task of accurately measuring fitness (for notable approaches, see Borgerhoff Mulder, 2000; Strassmann and Gillespie, 2002; Beall et al., 2004; Julian et al., 2007). Rather, investigators have, of necessity, tested other predictions from evolutionary models and, if supported, inferred that adaptive modulation of reproductive investment is occurring. This tack has, for example, yielded substantial evidence of statistically significant associations between the occurrence of some stressor and changes in the ovarian cycle (Prior, 1985a,b, 1987; Ellison and Lager, 1986; Ellison et al., 1989; Panter-Brick et al., 1993; Jasienska and Ellison, 1998; Nepomnaschy et al., 2004; Vitzthum et al., 2006, 2009a), but it remains possible that such changes are non-adaptive disruptions of normal functioning.

In addition to the difficulties of measuring differential fitness among phenotypic variants, evolutionary explanations of ovarian functioning have also been slow to find acceptance in some quarters because of different views, each having merits and limitations, on the nature of evolutionary adaptation (Williams, 1966a; Lasker, 1969; Jacob, 1977; Gould and Lewontin, 1979; Caro and Borgerhoff Mulder, 1987; Wood, 1994a; Rose and Lauder, 1996; Vitzthum, 2008b). With regard to ovarian functioning, a given instance of not investing in reproduction is rightly considered adaptive if (and only if) the total lifetime reproductive success (LRS) is greater than would be the case if some effort at investment in that instance had occurred (Clutton-Brock and Harvey, 1979; Caro and Borgerhoff Mulder, 1987; Vitzthum, 2008b). Natural selection maximizes LRS (and over time, multigenerational reproductive success), not individual well-being, congruity with the environment, or fertility (Williams, 1966a; Stearns, 1992; Rose and Lauder, 1996; Voland, 1998; Vitzthum, 2008b). High fertility is evolutionarily inconsequential if all the offspring die before reproducing themselves.

Demographic models

Malthus (1798) viewed the human reproductive system much like an unflagging machine without any internal controls or capacity to respond to changing conditions. Population growth was held in check only by external factors (famine, disease, war, homicide), old age, and conscious restraint. This metaphor of man as machine, traceable to Descartes (1647), remains a powerful image today, particularly when coupled with Platonic typologies. A normal healthy body is expected to approximate an ideal in form and function. Hence, for example, most women "should have" 28-day menstrual cycles. Because a fundamental goal is detecting and eliminating disease, biomedical paradigms often equate variation from an ideal with pathologies in need of correction. Thus, if a woman's reproductive machinery deviates from the relentless productivity envisioned by Malthus, she must be malfunctioning. This "pathology framework" underpins the medicalization of women's normal, if variable, reproductive functioning (Ginsburg and Rapp, 1991; Rueda Martinez de Santos, 1997; Lock, 2001; Meyer, 2001; Sievert, 2003).

A principal concern of demographers trained in sociology or economics is organizing the seemingly innumerable behavioral and sociopolitical influences on fertility into a small tractable set of proximate determinants through which all other factors must operate. These demographic frameworks (Davis and Blake, 1956; Bongaarts and Potter, 1983) can be useful tools for comparing the relative impact of fertility determinants within and across populations. However, influenced by Malthusian and biomedical models, many demographers implicitly conceptualized reproductive physiology as a mechanical constant for the entire species, a reproductive machinery faithfully reflecting fertility determinants external to the individual's physiology.

Demographic studies within anthropology (e.g., Kertzer and Fricke, 1997; Roth, 2004) differ in many respects from classic demography including, for some, an interest in linking variation in vital rates to biological mechanisms, ecological conditions, and selection differentials. For example, Wood (1990) emphasized the importance of giving "attention to the fine details of the reproductive process" in demographic analyses, and Hill and Hurtado (1996) took an explicitly adaptationist approach to reproduction in their richly detailed analyses of the ecology and demography of the Ache foragers. Reflecting an intellectual grounding in HBE and LHT, they forcefully argued that "the ultimate theoretical goal of anthropological demography should be a complete *explanation* of why certain demographic patterns are expressed."

The interdisciplinary exchanges of the past two decades (e.g., Low, 1993; Campbell and Wood, 1994; Kaplan, 1994; Holman and Wood, 2001; Metcalf and Pavard, 2007; Sear and Gibson, 2009) strengthened both anthropological and demographic approaches to human reproduction. In particular, Wood and Weinstein (1988), Campbell and Wood (1988) and Wood (1990, 1994a) have dramatically advanced the proximate determinants approach by specifying the biological mechanisms through which behavioral and sociocultural factors could have any impact on fertility. The PDNF (Table 1) comprises exposure factors, which determine if there can be any non-zero risk of conception and may be thought of as on–off switches, and susceptibility factors, which govern the probability of successful reproduction if exposure has occurred. Of the five fecundability factors contributing to the duration of the fecund waiting time to conception (which begins with the initial capacity to conceive and ends with a conception), only cycle length has been studied in a number of populations (see later section on "Variation in the Ovarian Cycle").

The PDNF framework has afforded new insight into old questions. For example, there is a long-running debate on whether hypoxia depresses fertility in indigenous high altitude populations (Monge, 1948; Baker, 1978; Escudero et al., 1996; Gonzales et al., 2002). The PDNF model can be used "as an accounting frame" (Wood, 1990) to organize and evaluate the paths by which all relevant environmental, sociocultural and behavioral variables might affect fertility. Such analyses suggest that hypoxia plays little, if any, role in determining fertility levels in high altitude populations (Wiley, 1998; Vitzthum, 2001a; Vitzthum and Wiley, 2003). Rather, variation in behavioral repertoires is of far greater importance. Prolonged breastfeeding, modified by a wide variety of infant feeding practices reflecting local resources and customs, is a major determinant of fertility differentials. In the Andes (Vitzthum, 1989, 1992a, 1994b). In the Himalaya, later age at first marriage, non-monogamous marital patterns, religious celibacy, and marital instability generate high rates of non-

marriage that dampen fertility (Goldstein et al., 1983, 1984a,b; Laurenson et al., 1985; Elford, 1994; Wiley, 1998).

Energetics models

The hypothesis that natural selection favors efficient energy utilization has a long history (Lotka, 1922a,b). Building on this and other theoretical arguments (e.g., Frisch, 1978; Prior, 1985a,b; Ellison, 1990), contemporary energetics models of women's reproductive functioning have garnered empirical support from studies on changes in ovarian functioning associated with exercise and/or caloric deprivation (e.g., Prior, 1982; Pirke et al., 1985, 1989; Ellison and Lager, 1986; Schweiger et al., 1987; Cameron, 1996; Loucks and Thuma, 2003; Warren and Goodman, 2003), from reports that the duration of post-partum amenorrhea is modestly influenced by maternal nutritional status (Huffman et al., 1978a,b; Bongaarts and Delgado, 1979; Lunn, 1985, 1994; Worthman et al., 1993), and from the series of investigations composing the Human Adaptability Project (HAP) (Weiner, 1964; Lasker, 1969; Baker, 1978; Little and Garruto, 2000; Leslie and Little, 2003). Apropos to energetics models, these studies documented the influence of developmental conditions on adult biology and the effects of low energy availability, and used measures of energy efficiency as an indicator of adaptation (Baker and Little, 1976; Thomas, 1976; Thomas et al., 1989). HAP did not investigate ovarian biology, but once it became possible to measure hormones in women living in energetically demanding environments (e.g., van der Walt et al., 1978; Ellison et al., 1986, 1989), it was a logical extension to attribute relatively low ovarian steroid levels to energetic stress.

In an influential synthesis of current knowledge, Ellison (1990) examined ovarian functioning in relation to age and other variables, and proposed a developmental energetics model, which he and his colleagues subsequently elaborated to explain variation in human reproduction (Ellison, 1994, 1996a,b, 2003; Ellison et al., 1993b; Jasienska, 2001; Lipson, 2001). This model predicts that women born in energetically demanding conditions will grow more slowly, mature later, have a greater sensitivity to energetic stress, have lower fecundity (evidenced by lower ovarian steroid levels), and have fewer offspring during their lives than would be the case if they had developed in resource-rich conditions. This pattern of growth and reproduction is seen as adaptive because it avoids investment in a pregnancy with a poor probability of success, thereby conserving energy, maintaining long-term maternal energy balance and increasing the probability of maternal survival. Energetics models posit that selection favors reproducing only if a woman's nutritional status is substantially adequate and/or there is some indication of "the potential for sustaining an ongoing investment" (Ellison, 2003, p 345); fecundity is hypothesized to be a function of trends in energetic status and/or current energetic status.

Despite the logical appeal of energetics models, they have always been controversial. The details of Frisch's model were criticized by both demographers (Trussell, 1980, Menken et al., 1981) and human biologists (Cameron, 1976; Ellison, 1981, 1982; Malina, 1983; Quandt, 1984; Scott and Johnston, 1985). Bongaarts (1980) argued that, barring famine, chronic malnutrition has only a very small effect on fertility relative to any of the proximate determinants of fertility. Noting the significant differences between physiology and demography in measurement, study design and model specifications, and the difficulties in operationalizing either fecundity or energetic stress, Wood (1994b, p 113) concluded that "it may never be possible to collect the data needed to establish" whether nutritional suppression of ovarian functioning is adaptive. These analyses were atheoretical. Bongaarts did not ask *why* the effect of malnutrition on fertility was so small but simply sought to quantify that impact. Wood evaluated the methodological constraints that hampered quantification.

Throughout these debates on the role of energetics, proponents on either side usually implicitly assumed a biological uniformitarianism regarding women's reproductive functioning. In other words, the ovarian steroid level thought necessary for a U.S. woman to be fecund was presumed to be the same level necessary for comparable fecundity in any woman in the world. Likewise, the same level of energetic stress was assumed to have the same impact on fecundity. Thus, when population samples had lower salivary progesterone levels than did U.S. women, it was inferred that fecundity must also be relatively lower (Ellison et al., 1986, 1989). Wood's analysis (1994b) focused on the limits of tools and time in studies of the energetics-fertility link, taking the relationship itself, if any, to be equivalent across human populations.

Perhaps because the driving issue in much of the relevant research has been whether there is *any* effect of energetics on human reproductive functioning, little attention has been directed to understanding either the extent or the causes of variable responsiveness to such stressors. But it was this variability itself that struck me as demanding an explanation and which, I proposed (Vitzthum, 1990, 1992b, 1997, 2001b), could best be understood by applying the principles of LHT to women's reproductive functioning.

Life history models

LHT is an analytical framework within evolutionary theory for studying behavioral and physiological resource-allocation mechanisms and related maturational and reproductive traits (Lessells, 1991; Borgerhoff Mulder, 1992; Stearns, 1992; Charnov, 1993; Hill and Kaplan, 1999; Vitzthum, 2008b). A *life history strategy* (LHS) comprises a suite of reproductive and developmental traits (e.g., age and size at initiating reproduction; the number, quality and timing of offspring; age at death) and the associated schedule of investments in growth, reproduction, and somatic maintenance. Depending on the species, *resources* comprise the availability of a suitable habitat, mate, and social group; the energy and other nutrients available to support a growing conceptus, live offspring, and one's own soma; the physical and psychological status of the parents; time (Promislow and Harvey, 1990, 1991; Hill and Kaplan, 1999); and information (Worthman, 2003).

LHT is concerned with the fundamental challenge faced by all life forms: What is the optimal allocation of finite resources within a finite lifetime? (Gadgil and Bossert, 1970; Stearns, 1992). Alternative LHSs are potential solutions to this question. Under the assumption that any unit of resource may only be allocated to one function, the fitness advantage of any given investment is traded off against the fitness advantages of any other

potential investments (Zera and Harshman, 2001). Fisher (1930) defined reproductive value (*RV*) as the mean future reproductive success (i.e., how many offspring the organism can expect to produce) for those of a given age and sex in that population. Williams (1966b) divided *RV* into that which is immediately at stake (the current reproduction, *CR*) and the residual reproductive value ($RV = CR+RRV$). He defined a to be the proportional gain to *CR*, and c to be the proportional cost to *RRV*, when a positive allocation decision is made by the organism (e.g., forage, ovulate, defend, or mate). In the case of a negative allocation decision (e.g., do not forage or do not ovulate), he defined b to be the proportional decrement to *CR*. Hence, RV_p [positive decision] = $(1+a)CR + (1-c)RRV$ and RV_n [negative decision] = $(1-b)CR + RRV$. If RV_p (the gain from investing in *CR* plus the reduced *RRV* because of the current investment) exceeds RV_n (the reduced *CR* by not investing plus the *RRV*) then selection will favor the positive allocation decision over evolutionary time and it will become the normative decision. Alternatively, the negative allocation decision would become normative if $RV_n > RV_p$. The availability (or deficiency) of all resources contribute to the relative values of RV_p and RV_n. Hence, selection favors reproductive effort whenever $RV_p > RV_n$, even if some resource (e.g., food availability) is not particularly propitious. Likewise, selection favors delaying or avoiding reproductive investment whenever $RV_n > RV_p$, even if some relevant resources are favorable (Williams, 1966b).

Time until the end of reproductive capacity (either death or menopause) is a particularly critical resource contributing to the relative values of RV_p and RV_n. Hence, mortality schedules are a strong determinant of LHS (Promislow and Harvey, 1990, 1991; Charnov, 2001). Analytically, the impact of time on the trade-offs among life history traits is represented by the Euler-Lotka equation, which is parameterized by age-specific fertility and mortality schedules, and allows *RV* to be expressed as a function of these demographic variables (Stearns, 1992). Conceptually, one should appreciate that the optimal LHS for an organism is a consequence of numerous competing trade-offs, which vary with locally specific risks of mortality.

LHT clarifies the fitness costs and benefits of modulating reproductive investment in any given opportunity. For example, lactational infecundity increases LRS so long as investment in an infant outweighs the fitness gain from a new conception (Vitzthum, 1994a; McDade and Worthman, 1998; Sellen, 2007). So might LRS be increased by suppressing reproductive functioning under other circumstances. Such strategic modulation of reproductive effort is potentially adaptive because investment in a new conception may risk one's own survival, future reproductive opportunities, and/or the survival of current offspring. Three independently developed applications of LHT have examined the potential adaptiveness of reproductive suppression in non-human primates and women (Wasser and Barash, 1983; Peacock, 1990, 1991; Vitzthum, 1990, 1997, 2001b).

Wasser and Barash (1983) proposed the Reproductive Suppression Model, a special case of Williams' (1966b) model. They suggested that a female might increase her own reproductive success by manipulating reproduction in the other members of her social group, and that if social competition is high, it could be beneficial to delay reproduction until less socially competitive times. Peacock (1990, 1991) used LHT to explain when and why pregnancy wastage in humans and other animals could be adaptive, and proposed that selection will favor mechanisms that permit reproduction under persistently suboptimal conditions.

Drawing on LHT and work in genetics, developmental biology and human adaptability, I developed the Flexible Response Model (FRM) of reproductive functioning to explain variation in reproductive suppression to seemingly comparable conditions (Vitzthum and Smith, 1989; Vitzthum, 1990, 1992b, 1997, 2001b). I had been struck by an apparent paradox. Studies in industrialized countries reported that even moderate exercise, dieting, or the stress of exams could perturb ovarian functioning (e.g., Ellison and Lager, 1986). But in the rest of the world, most women engage in often arduous physical labor and face chronic undernutrition, perhaps punctuated by periods of even greater food scarcity. Economic and psychosocial stressors that threaten their health and even their lives are commonplace. But despite these demands, each of these same women may experience up to a dozen pregnancies in her lifetime (Bongaarts, 1980).

I argued that the sensitivity of ovarian functioning in well-off women and its resiliency in poorer women could be reconciled by recognizing that a current reproductive decision depends on both the absolute quality of current conditions *and* the relative quality of these compared with prior conditions, which are predictive of future conditions. I proposed that a woman's physiology "judges" current environmental conditions based on those she experienced as she matured. Given temporarily poorer conditions, delaying reproduction may be advantageous because conditions are likely to improve. But if habitats are typically arduous, delaying reproduction may not increase fitness because there is no expectation of improved conditions within a finite time period. Of course, if a demanding context becomes even worse, then a woman may gain from delaying reproduction temporarily. However, if worsened conditions persist and the probability of successful conception in these is >0, those who acclimate over time and resume reproductive functioning may have a fitness advantage over those who do not. The FRM applies to both pre- and post-conception reproductive decisions. Women accustomed to poor conditions may maintain their pregnancies in the face of stressors that would prompt termination in better-off women.

In contrast to energetics models, the FRM proposes that fecundity is a function of current conditions (including one's own status) relative to long-term average conditions (an estimate of likely future conditions). Reproductive effort depends on: (1) the probability of successful reproduction (conception and live birth) in the present conditions, (2) the probability of conditions changing (for better or worse) within a finite period, (3) the risk to future reproductive opportunities, and (4) the expected duration until the end of the reproductive lifespan.

Both the FRM and energetics models generate hypotheses that can be tested with empirical data on ovarian functioning. In 1989, Dr. Hilde Spielvogel (Instituto Boliviano de Biología de Altura, La Paz) and I initiated cross-sectional studies of reproductive functioning and health in Bolivian Quechua and Aymara populations (e.g., Vitzthum et al., 1993, 2000a). Building on these, in 1995 we implemented Project REPA (Reproduction and Ecology in Provincía Aroma), a longitudinal study of rural Aymara communities, to test the predictions of these

models. Over the course of 2 years, more than 300 women at various reproductive stages were followed; conceptions were monitored from occurrence to either loss or a live birth. In brief, the findings from Project REPA support the Flexible Response Model (Vitzthum et al., 2004, 2006, 2009a).

BIOMETRY OF OVARIAN FUNCTIONING

> "When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind . . ." William Thomson (aka Lord Kelvin), 1883.

In this section I review terms, concepts and the hormonal regulation of the ovarian cycle, and summarize the methods used in quantitative studies of human ovarian functioning. Reflecting the most common interests of anthropologists, I emphasize approaches suitable for population-based research requiring the non-invasive collection of biological samples and, in particular, undertaken in locales having little or no facilities for cold storage of samples.

Terms and concepts

For analytical purposes, the World Health Organization (WHO, 1981) refers to a menstrual interval as a *segment* to avoid the presumption of normal cycling and defines *segment length as* the interval from the first day of menses up to and including the day before the subsequent menses (Snowden and Christian, 1983). Very few studies have used WHO's terminology, but most have defined cycle length thusly, hence segment and cycle are *de facto* synonyms.

A menses *episode* is defined as the period from the first through the final appearance of blood during waking hours (Snowden and Christian, 1983). For example, if bleeding is first detected upon waking on Monday and persists through retiring on Thursday, but is absent at waking on Friday, the episode is 4 days long. If there is 1 bleed-free day, the episode is also 4 days. If there are two or more bleed-free days, then bleeding on Monday and on Thursday are two separate episodes of 1 day each. There are very few studies in which spotting has been distinguished from more substantial flow.

Fertility is the production of a live offspring, *fecundity* is the biological capacity to conceive, and *fecundability* is the monthly probability (from 0 to 1) of conception. Fertility is relatively easy to measure if there is an observer and records are kept (e.g., nurse and/or birth certificate) but can be biased if relying on recall (e.g., a neonate's birth and death may be forgotten, not mentioned, or called a stillbirth even if born alive). Fecundity is difficult to operationalize. Pre-menarcheal and post-menopausal females are infecund. The post-menarcheal and pre-menopausal years, and the post-natal period, are subfecund compared with periods of peak fecundity but by how much? Fecundability quantifies fecundity, but is usually unknown because conceptions are not readily detected at occurrence. Instead, a*pparent fecundability* is estimated from conceptions that are detected (Wood, 1994a), usually by hormonal biomarkers. Following WHO's (2001) definition of fetal loss, *pregnancy loss* is defined here as any conception not ending in a live birth regardless of the pregnancy duration, development stage, or detection method (if detected).

Hormonal regulation of the ovarian cycle

The principal hormonal changes that occur during an ovulatory cycle, absent conception, are depicted in Figure 3. Negative and positive feedback mechanisms involving hormones from the ovary (steroids [estradiol and progesterone] and proteins [inhibins A and B]), anterior pituitary (the gonadotrophins: follicle stimulating hormone [FSH] and lutenizing hormone [LH]), and hypothalamus (gonadotrophin-releasing-hormone [GnRH]) regulate follicle maturation, the timing of ovulation, and the proliferation of the endometrium (Messinis, 2006).

Determining segment (cycle) length and episode duration

Many studies have relied on a woman's recollection of her cycle patterns, but comparative studies found that recalled reports of segment length and variability are inconsistent with prospectively recorded data (Burkhart et al., 1999; Steiner et al., 2001; Creinin et al., 2004; Jukic et al., 2008). To assess both between- and within-woman variation in cycle variables, WHO (Snowden and Christian, 1983) recommends a 90-day observation frame during which a woman notes on a calendar whether or not bleeding has occurred on that day. Most women with a segment length <36 days will complete at least two segments during 90 days. A 120-day observation frame is needed to record at least two completed segments from all women having segment lengths ≤ 40 days. These calendars could also be used to note the time of day at which bleeding was first observed and self-assessments of bleeding volume, but such record keeping requires high participant motivation and is prone to subjectivity and failure to record data.

Detecting ovulation and conception

Non-invasive methods for detecting the presence and timing of ovulation depend upon measuring one or more biomarkers (Table 2), either through self-examination or assayed in a body fluid (Campbell and Rockett, 2006); see O'Connor et al., 2006 for a combined hierarchical method for detecting ovulation). Implantation is associated with a rise in human chorionic gonadotrophin (hCG), detectable in maternal urine within a few days using an over-the-counter "early pregnancy test" and closer to the time of initiating implantation using very sensitive laboratory assays (Holman and Wood, 2001; Baird et al., 2003). Pregnancy loss is accompanied by a sustained drop in hCG.

Neglecting to distinguish ovulatory and anovulatory segments seriously confounds cross-populational comparisons of hormone levels. Anovulation is typically characterized by low (even flat) progesterone and estradiol profiles during the second half of the segment. Combining these with ovulatory cycles will yield average steroid profiles that are easily misinterpreted as a dampening of these hormones in every cycle (i.e., luteal deficiency). Whether a sample consists of ovulatory cycles having high ovarian steroid levels plus a few anovulatory cycles, or several cycles all having reduced ovarian steroid levels, leads to different conclusions regarding ovarian functioning and the theories that seek to explain that functioning (see Fig. 4).

Particular caution is required when comparing ovulation frequencies across studies that used different methods or sampling regimes. For example, some authors

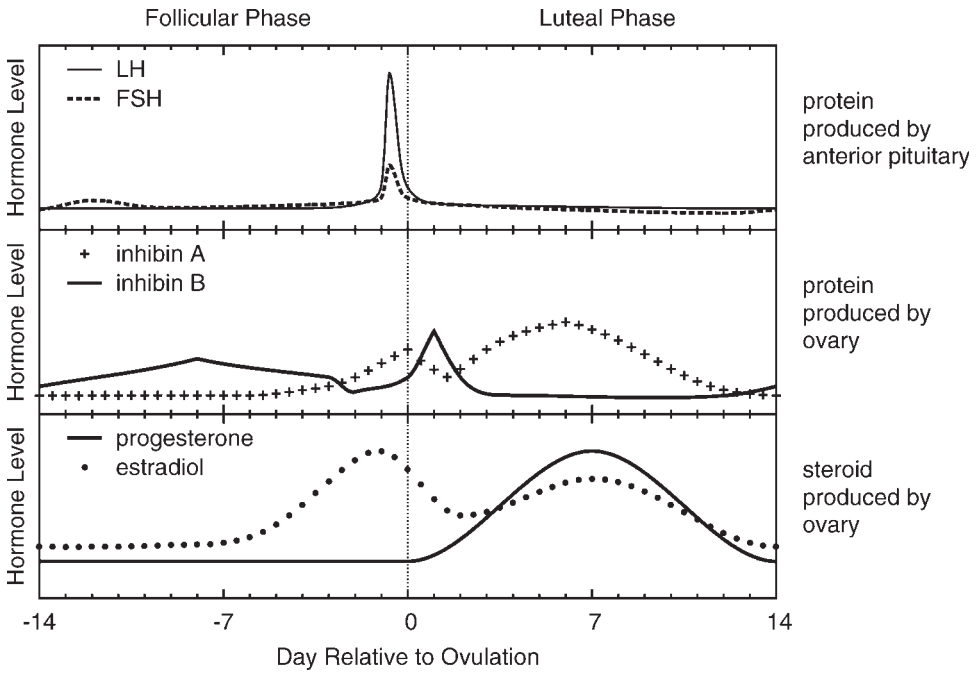

Fig. 3. Hormonal profiles during an idealized ovulatory cycle. Follicular and luteal phases are demarcated by ovulation (dominant follicle releases the ovum, day = 0). At the transition between cycles, FSH rises slightly because of low estradiol (E2), progesterone (P4), and inhibin A levels. Rising E2 and inhibin B, produced by the dominant follicle, then suppress FSH. High E2 triggers the LH surge that induces ovulation and, subsequently, causes the dominant follicle to redifferentiate into the corpus luteum ("yellow body"), which produces P4, inhibin A, and some E2. Without conception, falling LH is insufficient to maintain the corpus luteum, which regresses. Dropping hormone levels eventually prompt endometrial shedding (menses), denoting the beginning of the next cycle.

TABLE 2. Change in biomarkers relative to day of ovulation[a]

Biomarker	Time relative to ovulation				Source
	Mean (days)	SD	Minimum	Maximum	
Rise of basal body temperature	1.1	2.0	−2	7	Flynn et al. (1988)
Rise of salivary progesterone	1.5				Riad-Fahmy et al. (1987)
					Vitzthum et al. (2004)
Rise of urinary pregnanediol-3-glucuronide (PdG)	0.2	3.0			Flynn et al. (1988)
Rise of serum progesterone	−0.3	0.3	−1.3	0	Collins (1985)
Peak of serum LH	−0.7	0.2	−1.9	−0.3	Collins (1985)
Rise of serum LH	−1.3	0.3	−2.3	−1	Collins (1985)
Peak of serum estradiol	−1.0	0.3	−2	0	Collins (1985)
Peak of salivary estradiol	−1.5				Riad-Fahmy et al. (1987)
Rise of serum estradiol	−3.4	0.9	−7	−2	WHO (1980)
Rise of salivary estradiol	−5.0				Riad-Fahmy et al. (1987)
Peak of urinary estrone-3-glucuronide (E_1G)	−1.3	1.9	−9	4	WHO (1983a)
Rise of urinary estrone-3-glucuronide (E_1G)	−5.6	1.9	−11	−2	WHO (1983a)
Peak of E_1G/PdG	−2.5	2.3	−10	0	WHO (1983a)
Rise of E_1G/PdG	−7.2	2.8	−15	−2	WHO (1983a)
Drop of E_1G/PdG	±2				Baird et al. (1991)
Peak of fertile mucus	−0.4	2.2	−10	5	WHO (1983a)
Peak volume of mucus	−2.0	1.0	−4.5	−1.5	Usala and Schumacher (1983)
First day of fertile mucus	−5.1	2.6	−12	−1	WHO (1983a)

[a] Modified from Campbell and Rockett (2006).

have assumed a cycle is ovulatory if ≥1 observed luteal progesterone value was >2 standard deviations above the daily mean of follicular progesterone (Ellison et al., 1986; Panter-Brick et al., 1993). However, even without a systematic rise in progesterone due to ovulation, there is a non-trivial chance, depending on the number of luteal observations, of meeting this threshold (Vitzthum et al., 2002). This chance probability is 0.16 (= $1-0.975^7$) in every-other-day sampling and 0.30 in daily sampling. Hence, for example, in the hypothetical case where all the cycles in all samples were, in fact, anovulatory, a set of women sampled daily would appear to have a rate of ovulation twice that of another population sampled less frequently, simply because of differences in the sampling regimes. Even with identical sampling regimes, the bias by chance alone in this algorithm makes it unsuitable for ascribing ovulation in any case. Other methods to identify ovulatory cycles lack this bias

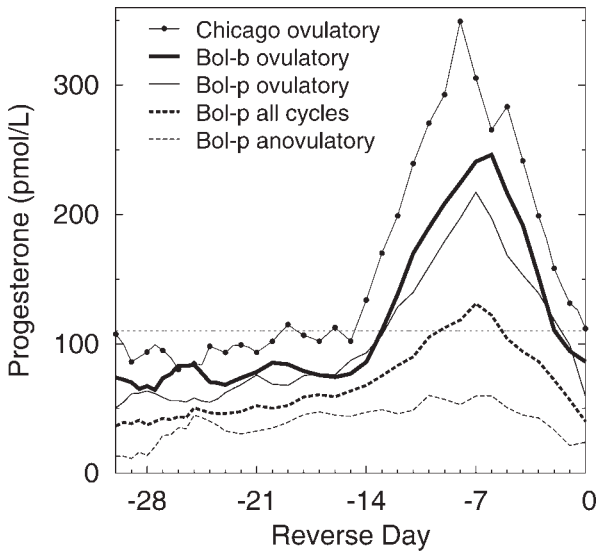

Fig. 4. Progesterone profiles in Chicago, better-off Bolivian (Bol-b) and poorer Bolivian (Bol-p) samples. Cycles are aligned on the first day of the subsequent cycle, and days are numbered backward from that point (reverse day). The poorer Bolivian sample comprising all cycles appears to have very suppressed progesterone levels, but is, in fact, a mixture of two types of cycles: anovulatory (with flat progesterone profiles) and ovulatory (with a substantially higher progesterone profile than the samples of all cycles). (Modified from Vitzthum et al., 2002.)

(Table 2; Krieg et al., 1999; Vitzthum et al., 2004; O'Connor et al., 2006).

Reported correlations among cycle and phase lengths (WHO, 1983b; Liu et al., 2004) may arise from imprecision in pinpointing the day of ovulation and/or the start of a cycle (Potter et al., 1967; McIntosh et al., 1980). If the true correlations are 0, then an indicator of the accuracy and precision of indirect methods for estimating the day of ovulation is a low correlation between phase lengths.

Measuring reproductive hormone levels

Rosalyn Yalow and Solomon Berson's (1960) development of a radioimmunoassay (RIA) for the measurement of endogenous insulin in human plasma heralded a still burgeoning approach for measuring the levels of biological molecules (biomarkers) in living organisms. RIA is very sensitive and specific, but because RIA uses radioactive substances, enzyme immunoassays (EIA) are often preferred. Extension of these technologies to measuring biomarkers in saliva, urine, and dried blood spots (Walker et al., 1978; Ellison, 1988; Campbell, 1994; Lasley et al., 1994; Worthman and Stallings, 1994, 1997; O'Connor et al., 2003; Knott, 2005; McDade et al., 2007; Valeggia, 2007) has been a boon for anthropologists and others studying natural variation in community-dwelling individuals. Space constraints necessitate only a brief review of these methods here, focusing on the measurement of female reproductive hormones in non-industrialized populations and highlighting information not readily available elsewhere.

Several challenges face the use of these methods for studies in remote locales (Ellison, 1988; Campbell, 1994; Worthman and Stallings, 1997; Valeggia, 2007). Collection procedures must be culturally acceptable to study participants, and sample contamination and degradation must be prevented in the field and during transport. There is no ideal body fluid or collection protocol for investigating ovarian functioning in all situations. Favoring a familiar technique over a novel approach may neglect an opportunity to gain greater insight into the questions under investigation. Rather, one needs to weigh the demands of the available technologies against the reality of specific field conditions and select the options that are both feasible and hold the greatest promise for scientific advancement. The advantages and limitations of each body fluid that could be collected and assayed are noted below and in Table 3. In any study, written agreements with laboratories should specify responsibilities, ownership of samples, transfer and storage of samples, and intellectual property rights (see "Materials Transfer in Academia: 20 Questions and Answers" and "Access to and Retention of Research Data: Rights and Responsibilities" at www.cogr.edu; more information is at www.ott.nih.gov).

Blood samples. Serum levels of biomarkers are the "gold standard" for evaluating salivary and urinary assays. Measurements in a venous blood sample represent the circulating levels of the molecules at the time the sample is taken (Campbell, 1994). Circulating levels of steroids comprise a portion bound to carrier (binding) proteins (e.g., sex-hormone-binding globulin or albumin) and a free (unbound) portion, generally considered to be the biologically active form that is available to diffuse into target cells. Changes in the levels of binding proteins help dictate changes in the levels of circulating

TABLE 3. Advantages and disadvantages of different body fluids

	Saliva	Urine	Blood
Number of biomarkers that can be assayed	Few	Several	Many
Common biomarkers of reproductive functioning	P4, E2	PdG, E1G, E2G, LH, FSH, hCG	PdG, E1G, E2G, LH, FSH, hCG
Tolerates lengthy storage at ambient temperature	Yes	Variable	No
Cultural proscriptions	None reported	None reported	Some
Can be self-collected	Yes	Yes	Not easily
Easy daily sampling	Yes	Yes	No
Risk of sample contamination	Some	Low	Low
Invasive	No	No	Yes
Risk of disease transmission	Low	Low	Some

P4, progesterone; E2, estradiol; PdG, pregnanediol-3-glucuronide; E1G, estrone-3-glucuronide; E2G, estradiol-3-glucuronide; LH, lutenizing hormone; FSH, follicle stimulating hormone; hCG, human chorionic gonadotrophin.

free steroids. Methods exist to measure both free and unbound portions of circulating steroids (Campbell, 1994).

The apparent superiority of assaying blood samples is offset by the difficulty of serial sample collection in both clinical and field settings. Venipuncture requires trained personnel and special equipment for sample preparation and cold storage. Blood spots, drawn from a finger prick and dried on filter paper, are easier (Worthman and Stallings, 1994, 1997; Shirtcliff et al., 2001; McDade et al., 2007), but correct self-collection may be discouraging for some participants, and most people seem disinclined to give or self-collect blood daily for an extended period.

Saliva samples. Samples are stable for ≥6 months at ambient temperature if preserved with sodium azide (Ellison, 1988), but only a few biomarkers can be assayed in saliva. Some preservatives can interfere with assays (e.g., sodium azide interferes with EIA), and some collection materials or devices may be unsuitable (e.g., steroids "stick" to many plastics but not polypropylene) (Krüger et al., 1996; Gröschl et al., 2001; Mylonas et al., 2006; Wood, 2009). Ovarian steroid levels are much lower in saliva than in blood, hence sample contamination from blood is a serious problem as is that from food, drink, coca, and/or betel nut (Ellison, 1988; Vitzthum et al., 1993; Gröschl et al., 2001; Núñez-de la Mora et al., 2007a; Wood, 2009).

Bound steroids cannot diffuse into the salivary glands, but because unbound steroids diffuse rapidly, a salivary steroid level is thought to represent the synchronous unbound steroid level in serum (Ellison, 1988; Campbell, 1994). Correlations of paired saliva and serum steroid levels are generally high (Walker et al., 1978; Riad-Fahmy et al., 1987). The ratio of saliva to serum levels varies among individuals but is thought to be, on average, about the same across populations.

A single study has challenged this assumption. On the basis of paired saliva and serum samples from Bolivian (n = 26) and Chicago women (n = 20), Chatterton et al. (2006) reported that mean Bolivian salivary progesterone (P_{SAL}) was 48% of mean Chicago P_{SAL} but that mean Bolivian serum progesterone (P_{SER}) was 197% of mean Chicago P_{SER}. However, additional analyses of the identical data set revealed that Chatterton et al.'s (2006) statistical approach is seriously flawed, casting substantial doubt on their conclusions (Thornburg et al., 2008).

Figure 5 is a bivariate scatter plot of P_{SAL} versus P_{SER} for both study samples. In an ideal data set (i.e., P_{SAL} and P_{SER} highly correlated), all points would fall on a narrow diagonal band of nearly-constant diffusion fraction (the fraction of unbound serum progesterone that has diffused to saliva), with biologically reasonable values and ranges for P_{SAL}, P_{SER} and the diffusion fraction. These data are far from this ideal. Two of the Chicago P_{SAL} values are implausibly high (>900 pmol/L) and one Bolivian has an unlikely combination of very low P_{SAL} (51 pmol/L, typical of an anovulatory cycle) with moderately high P_{SER} (13,700 pmol/L, suggesting an ovulatory cycle). These outliers severely bias the mean values of the samples, rendering invalid any analyses based on sample means, as was done by Chatterton et al. (2006). Also note the extremely wide range of P_{SER} concentrations. The largest Chicago P_{SER} value is 44 times the smallest, and the largest Bolivian P_{SER} is 21 times the smallest. These ratios are far greater than the known range of inter-individual variation for this hormone (Wood, 1994a). Likewise, typical diffusion fractions are 3%–8%, but for two Chicago women the fractions are 45% and 70%. Such implausibly high values suggest blood contamination of these Chicago saliva samples. These and other anomalies (Thornburg et al., 2008) suggest that, rather than some unknown aspect of Bolivian women's biology, sample contamination and/or inaccurate assays are more parsimonious explanations for the differences in sample means reported by Chatterton et al. (2006).

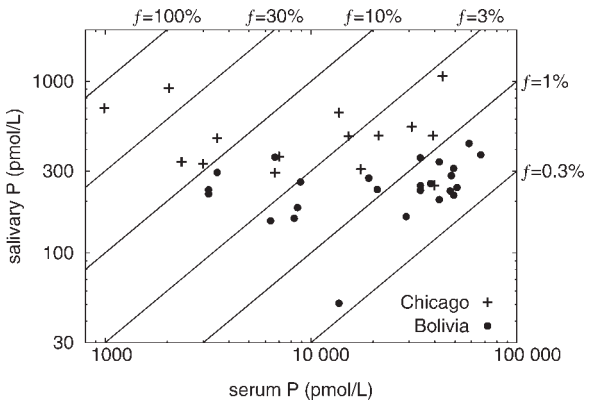

Fig. 5. Scatter plot of paired measurements of serum (x-axis) and salivary (y-axis) progesterone (P) for each study participant in samples of Chicago and Bolivian women. Lines of constant diffusion fraction (f, ratio of saliva P/serum P) from 0.3% to 100% are also indicated. Typical f range from 3% to 8%. In these samples, f is as high as 70%, suggesting sample contamination. (Reproduced from Thornburg et al., 2008.)

Urine samples. Urine and saliva collection share several advantages (Campbell, 1994; O'Connor et al., 2003, 2004; Brindle et al., 2006; Valeggia, 2007), but fluid urine requires refrigeration not long after collection (≤8 days if assayed for estrone glucuronide (E1G) or pregnanediol-3-glucuronide (PdG) (O'Connor et al., 2003). Urine dried on filter paper and stored at 28°C for up to 6 months yielded measurements of E1G and PdG that were highly correlated (r > 0.81) with those from frozen liquid urine (Wasalathanthri et al., 2003), although additional extraction steps are needed in laboratory processing (Knott, 2005).

The level of a urinary biomarker is an internally integrated reflection of varying serum levels since the last void (Campbell, 1994), which precludes observation of short term fluctuations in the urinary biomarker but minimizes the misinterpretation that can arise from measuring a single serum or saliva sample that may have been inadvertently collected during a secretory pulse or nadir (O'Rourke and Ellison, 1990). The choice of integrated or transient readings depends upon the research question. Urinary assays must be standardized for hydration status of the sample, which requires assaying for urinary creatinine or, more easily and cheaply, measuring the specific gravity of the urine sample (Miller et al., 2004; Anestis et al., 2009).

Sampling frequency. Sampling regimes range from every few minutes (e.g., catheterized participants in a clinic) to a single sample per subject. Sampling frequency must be sufficiently dense to accurately represent the hormonal variation relevant to the specific research question (see Shannon, 1949; Jerri, 1977; Press et al., 1992). Even if practicality must take precedence

over an ideal sampling frequency, it is instructive to recognize the limits of the data that have been collected in field studies of ovarian functioning.

Daily sampling is generally considered desirable and sufficient to characterize functioning of the HPO-axis over several weeks. Less frequent sampling can miss hormonal peaks and inaccurately represent changes in hormone levels during an ovarian cycle, particularly if the rise and fall of a hormone occurs quickly (e.g., an LH surge takes place within 48 h or less; daily first-morning-urine sampling in a study of U.S. women missed this surge in 25%–30% of their cycles [Baird et al., 1991]). Biologically significant individual and populational variation in hormone levels, and the associations with potential covariates, may be obscured if sampling frequency is too sparse. But trade-offs between sampling frequency and sample size may be unavoidable, particularly if collection is labor intensive and logistically complex.

A participant in an industrialized literate population usually self-collects urine and/or saliva at home. Labeled tubes may be refrigerated/frozen until returned to the laboratory. As there is little contact between subjects and researcher during the sampling period, investigator labor is low. But this protocol risks contaminated samples, missed sampling, and incomplete records.

In typical anthropological fieldwork, a researcher seeks out a participant at a frequented locale (e.g., her home or fields) to retrieve a previously self-collected sample or to collect the sample, taking pains to avoid sample contamination. Because individual collection is labor intensive, it is difficult to achieve large sample sizes and each woman may be visited only every 2–3 days. Longer gaps between sampling can occur if a woman cannot be located or there is a holiday or weekly day of rest. These gaps increase the chance that hormonal peaks, which vary more among women than do basal levels, are missed (posing a significant problem for studies comparing peak hormone levels across populations). If a hormone varies diurnally (e.g., cortisol), statistical methods may help to correct for different collection times, but diurnality may differ among persons and/or populations (Hellhammer et al., 2007; Vitzthum et al., 2009b).

Initiating sample collection. Accurate and precise estimates of total hormone levels require sample collection for a full cycle, best initiated on the first day of menses and continued until the first day of the next menses. This protocol has some drawbacks that became evident during my fieldwork in Bolivia. In particular, scheduling visits proved logistically daunting if several widely distant participants were expected to start menses on the same day. Also, the first cycle days went unsampled if a woman began menses between visits.

These and other problems can be avoided by initiating sampling regardless of a participant's cycle day and continuing long enough to span a completed cycle. I successfully used this protocol in Bolivian schools, where menstrual status had to be concealed from other classmates. All students gave daily samples and private interviews with each girl provided menses dates; compliance was nearly 100%. I also adapted this protocol to the collection of saliva and urine samples from dispersed Mongolian nomads. Daily self-collection began with the day of recruitment and continued for up to 60 days (see Supporting Information Table S1).

Analyzing hormone levels. Because cycle and follicular-phase lengths are variable within and between women, calculating and comparing indices of steroid levels requires aligning cycles on a day other than the first day of menses. Cycles may be aligned on the day of ovulation, estimated by a biomarker (Table 2) or, if unavailable, on the first day of subsequent menses (Day 0) and reverse numbered; ovulation is assumed to have occurred at Day -14.

A suitable, and commonly used, index of the level of any hormone (H) during some defined period of an ovarian cycle is to estimate the mean daily value under the hormone's profile during that defined period. This is given by (area under the curve of H from x to y)/($y-x$) where x to y is any span of days and H at any time is defined by linear interpolation of the observed hormone data (Vitzthum et al., 2002, 2004); details on calculating hormonal indices are given in supplementary materials (Supporting Information Table S2). Interpolating missing values avoids having different subsets of women contributing data on different days for a composite profile of the sample, which has the effect of spuriously increasing the day-to-day variance in the sample.

Common pitfalls in study designs

Reproductive ecologists often compare different populations and subpopulations, both to document the extent of variation in human biology and to test hypotheses. Several common problems in some study designs and analytical approaches can seriously bias estimates of sample parameters and hamper comparisons of data on ovarian functioning.

Selection bias. An unavoidable selection bias characterizes cross-sectional studies of the ovarian cycle. In general, the most fecund women can be expected to be either pregnant or lactating; those who are menstruating and available to a study are likely to be less fecund and are not representative of the population. This bias is especially severe in non-contracepting populations. The significance of this bias was recently examined with data from Project REPA (Thornburg and Vitzthum, 2009). Progesterone levels were 18% higher in lactating cycling women than in those not lactating for $\geq$180 days. Similarly, cross-sectional studies restricting samples to nonlactating cycling women are likely to significantly underestimate hormone levels.

Age distributions. The data regarding hormonal variation between the ages of 20 and 40 years is inconsistent (see "Variation in the Ovarian Cycle"), but samples that are heavily weighted toward younger and older women, who are less likely to be pregnant or lactating in a noncontracepting population, may have lower or higher hormone levels than samples of women aged 25–35 years (Ellison, 1994; Ferrell et al., 2005, 2007). Compared samples should have the same age distribution or control for this confounder with appropriate statistical techniques.

Observation period. Some study designs are biased toward the collection of more observations from some categories of women than others. If observation is for some specified period, women with shorter cycles will contribute more observations than those with longer cycles. In a longitudinal study of sexually active non-contracepting women, the more fecund are more likely to conceive quickly, leaving the less fecund to be observed for longer. Comparing women through time or in different seasons

can be particularly tricky, especially if the sample composition varies. Censoring and truncation can also bias the estimates of cycle variables.

Unit of analysis. Multiple observations (e.g., cycles or days of a cycle) from each subject in a study are not statistically independent. To treat non-independent observations as if they are separate data points contributing to a sample violates the assumptions of most statistical tests, and a computed significance level in such cases is meaningless. Analyses must also account for unequal numbers of observations from each study participant. Multi-level models (West et al., 2007) or bootstrap methods (Efron and Gong, 1983; Efron and Tibshirani, 1986) may be more appropriate approaches for evaluating ovarian-cycle data in some study designs.

Sample composition. Clinical studies typically recruit subjects meeting a strict set of criteria (e.g., no more than light exercise, no pregnancy or lactation within some number of months, no known illnesses or fertility problems, have "regular" cycles). It is usually acknowledged that such samples do not represent any population. There may also be some selection bias in population-based U.S. studies (e.g., Windham et al., 2002; Ferrell et al., 2005), but the problem is less severe. Field studies of human variation may have fewer subject criteria, hence the study sample more closely represents the population from which it was drawn. But such a sample may be less suited for comparison to a strictly selected sample. For example, if the disease burden is high in a population, subject exclusion on the basis of illness may be untenable but illness of the study subjects could confound comparison to a sample of healthy U.S. women. A large swath of central Africa that includes the Ituri Forest is known as "the infertility belt," the result of high levels of sexually transmitted diseases (Belsey, 1976; Collet et al., 1988; Ericksen and Brunette, 1996). The impact of STDs on ovulation and ovarian steroid levels is difficult to evaluate, but may not be negligible (Svensson et al., 1983; Alvarez-Sanchez et al., 1981; Csemiczky et al., 1995).

Assay comparability. Salivary and urinary assays are not comparable across laboratories and, absent rigorous quality controls, even across batches within the same laboratory (Cauley et al., 1991; Potischman et al., 1994; Hankinson et al., 1994; Toniolo et al., 1994; Dabbs et al., 1995; Gail et al., 1996; Falk et al., 1999; Fears et al., 2000; Gröschl, 2008). Comparisons require a conversion factor or curve based on laboratories assaying a single set of samples.

Ecological (epidemiological) fallacy. This problem concerns analyses using population-level variables (e.g., a sample mean for progesterone versus national caloric consumption) and arises from the assumption that correlations among aggregate measures are a reflection of causal relationships at the individual level (Robinson, 1950). As well as the presumption that hormone levels in a selected sample represent a nation, spurious associations can occur because of the difficulty of controlling for all the differences among the populations that could confound the true relationship if any. In epidemiology, cross-population comparisons are a first step in detecting patterns and generating hypotheses, but they are not a compelling test of the hypothesis itself (unless one has controlled for all of the relevant variables and has unbiased aggregate variables).

VARIATION IN THE OVARIAN CYCLE

> Scientific curiosity was quick to invade almost every aspect of human behavior, yet it long neglected this most obvious one. Arey, 1939.

This summary of what is known of variation in cycle characteristics serves as a foundation for subsequent discussions of how ovarian functioning varies with individual and ecological factors, and for testing evolutionary models of women's reproductive functioning. Fecundability is sensitive to cycle length (which determines the number of opportunities for conception in a given time span) and the incidence of anovulatory cycles (Wood and Weinstein, 1988). Yet surprisingly little is known about variation in these and other features of the ovarian cycle.

Segment (cycle) length

Arey (1939) gives a fascinating account of early 20th Century debates on cycle "regularity." Analyses based on self-recorded data clearly demonstrated substantial variability in women's cycles (Foster, 1889; Allen, 1933; Fluhmann, 1934; Gunn et al., 1937). Yet these were summarily dismissed in favor of reports that relied on a woman's recall of her "typical" cycle patterns (Sanes, 1916; Nakagawa, 1931; Kennedy, 1933) because these supported the prevailing medical opinion that normal women invariably had 28-day cycles. Arey's own analyses of 20,000 calendar records from 1500 persons did little to dissuade the entrenched opinion nor did subsequent studies (e.g., Haman, 1942) have any greater impact.

Perhaps prompted by the lack of attention given to then-available data, in 1934 Treloar began what remains the largest longitudinal study of ovarian cycles with the recruitment of 2350 students at the University of Minnesota (Treloar et al., 1967; Tremin Research Program on Women's Health, www.pop.psu.edu/tremin/tremin.htm). Since then >5000 participants, principally white women of middle to high socioeconomic status, have recorded their daily menses patterns, most for several decades. The publication of these data firmly established the reality of substantial variation in the ovarian cycle, not only among healthy women but during the course of their lifetimes. Nonetheless, despite the evidence of several studies (Supporting Information Table S3; Figs. 6, 7, S1), the extent of cycle variability remains underappreciated. "Natural family planning" (aka "fertility awareness") methods are still widely promoted even though they require an uncommon level of cycle regularity (Burkhart et al., 1999; Vitzthum et al., 2000b), and many behavioral studies unjustifiably assume a 28-day cycle having an idealized hormonal profile (Shirtcliff et al., 2001).

On the heels of Treloar's report, Chiazze et al. (1968) published the findings of a 2-year longitudinal study of self-recorded menstrual diaries from 2316 predominantly Catholic pre-menopausal women, aged 15–44 years, from 65 geographical locations in Canada and the U.S. Although not specified, this sample may have been more ethnically and economically varied than the pre-dominantly white, middle-class Minnesota students. Nonetheless, the two studies reported comparable segment lengths and variability at a given age. The findings from large prospective studies of European women (Bailey and Marshall, 1970; Vollman, 1977; Münster et al., 1992; Monari and Montanari, 1998; Kolstad et al., 1999) were

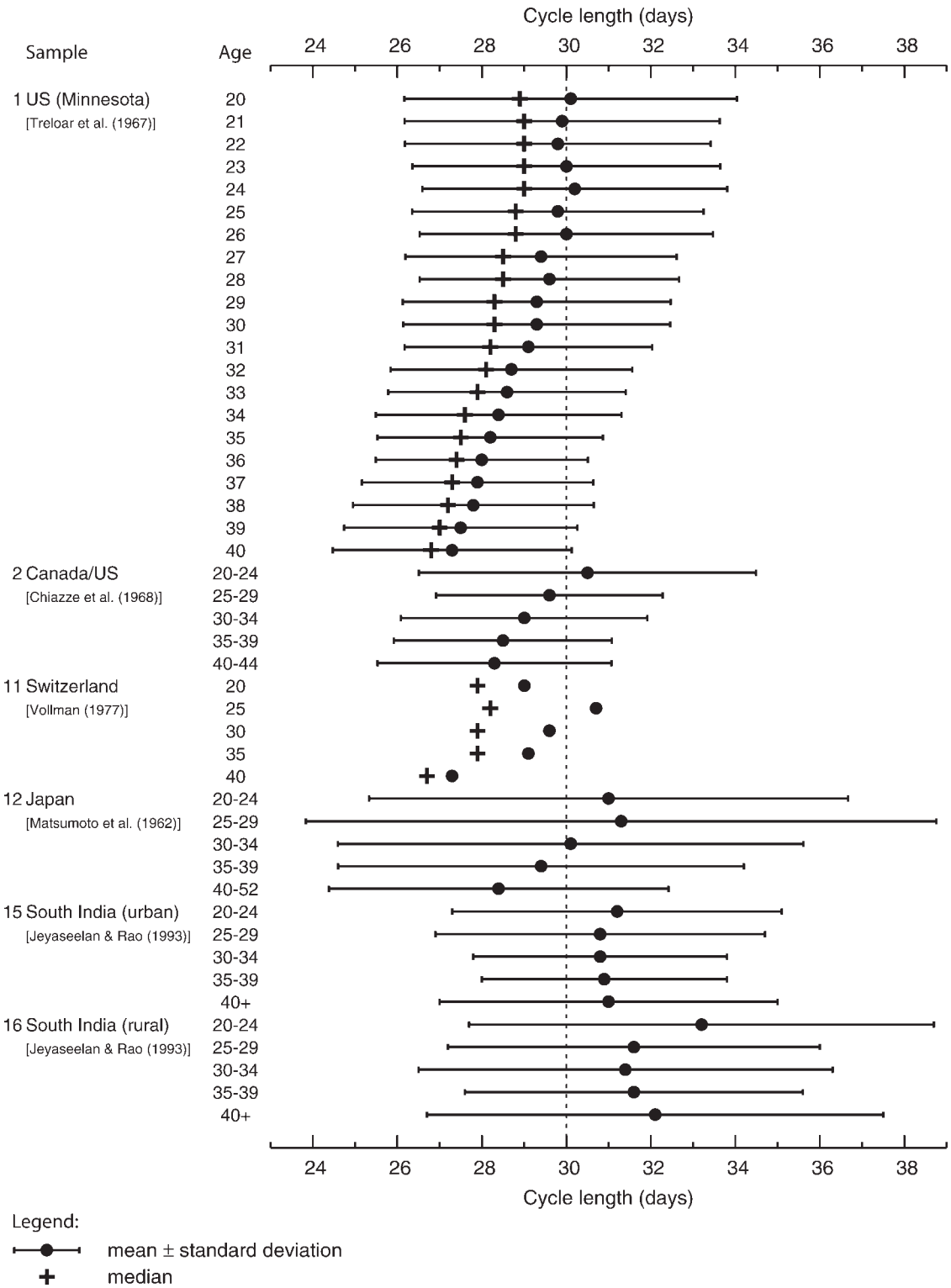

Fig. 6. Cycle length distributions, based on recorded data, for selected subsamples of various age ranges. The numbers at the far left of each sample identify the corresponding sample and data in Supporting Information Table S3.

also entirely consistent with those in North American women (Supporting Information Table S3; Figs. 6, 7).

The largest self-recorded data set from women not of European ancestry is that of 701 wives of Japanese coal miners (Matsumoto et al., 1962). At a given age, cycle length averaged 1–2 days longer than that observed in some studies of women of European ancestry. Whether such differences between those of Asian and European ancestry are consistent or an artifact of sampling and analytical difference between the studies requires fur-

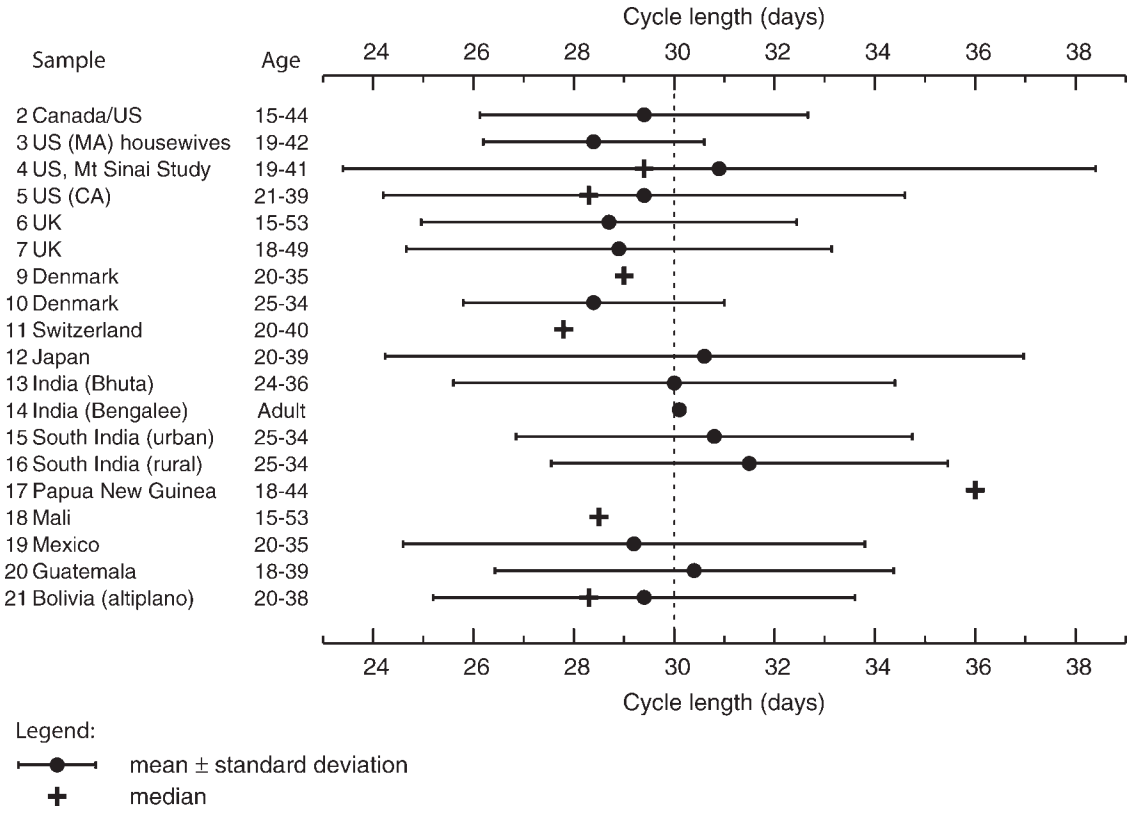

Fig. 7. Cycle length distributions, based on recorded data, for selected samples from various human populations. The numbers at the far left of each sample identify the corresponding sample and data in Supporting Information Table S3.

ther investigation. A single study has reported that, having controlled for several covariates, both Asian and Hispanic Californians had cycle lengths averaging 2 days longer than "white" women (Waller et al., 1998).

There are only a few studies of non-industrialized populations that reported on either recorded data or menstrual events reported to a researcher within a short time of their occurrence (Supporting Information Table S3; Fig. 7). Mean segment lengths in Mali, Guatemala, Bolivia, and Mongolia are similar to those observed in women of European ancestry. The Indian samples more closely resemble the Japanese sample. The Papua New Guinea sample has the longest reported segment length.

There is marked within-woman (inter-cycle) variability in segment length (e.g., Foster, 1889; Ferrell et al., 2005), often referred to as cycle "irregularity." This characterization is unfortunate as it connotes something amiss rather than normal, but the term is unlikely to be replaced. Most studies of regularity have been within the context of family planning trials or programs and, hence, women have been included for their self-reported "regularity." Despite this selection bias, comparisons with subsequently collected data on these participants revealed significant discrepancies from the woman's initial report, a finding that suggests variability is even greater in the larger population. For example, of 303 Guatemalan women who self-identified as having regular cycles every 26–32 days, more than half were then observed to have $\geq$1 of 3 consecutive cycles fall outside this range (Burkhart et al., 1999). Bolivian, Indian, U.S. and European women all had similarly high levels of variability (Gunn et al., 1937; Chiazze et al., 1968; Münster et al., 1992; Belsey and Pinol, 1997; Vitzthum et al., 2000b; Creinin et al., 2004; Williams, 2006). About half or more of the woman in each study sample (Supporting Information Table S4) had a range in cycle length of $\geq$6 days and about a quarter had a range >2 weeks, even if only a few cycles were recorded by each woman. Recent reanalyses (Ferrell et al., 2006; Gorrindo et al., 2007) of subsets of the Tremin Study longitudinal data corrected computational and study design limitations in the original report (Treloar et al., 1967) and reconfirmed, yet again, the normality of "irregularity."

Age is a well-documented covariate of variation in cycle length. Women <20 years old tend to have longer and more variable cycles. From 20 to 40 years of age, mean segment length shortens by ~2 days, there are progressively fewer long cycles, and variability is at a minimum (Gunn et al., 1937; Collett et al., 1954; Matsumoto et al., 1962; Treloar et al., 1967; Chiazze et al., 1968; Bailey and Marshall, 1970; WHO, 1983b; Münster, 1992; Jeyaseelan and Rao, 1995; Monari and Montanari, 1998; Rowland et al., 2002; Liu et al., 2004). In the years prior to menopause, variability increases again (Supporting Information Table S3, Fig. 6). Substantial variation within and between women's cycles underlie these general age-associated trends (Ferrell et al., 2005).

BIMORA, a prospective 5-year study of U.S. women (mean age = 47.6 years, ~10% of sample <40 years old) confirmed the aggregate cycle length patterns reported by earlier studies and greatly expanded what was known of age-associated variation in cycle lengths in an individual. In most women, length declined with age through the early 40s, increasing thereafter. Cycle variability

began to increase between 33 and 40 years of age, subsequently increasing more rapidly at older ages. At all ages, cycle length variance was greater within-woman than between-woman, even more so at older ages. In brief, "Each woman has a wide range of cycle lengths that cannot be easily distinguished from other women's ranges of cycle lengths" (Ferrell et al., 2005, p 574).

Phase durations

Ascertaining the extent and causes of variation in lengths of follicular and luteal phases is key to understanding segment length variation. Determining phase lengths requires physiological data and calendar records and, hence, is only available for a few samples (Supporting Information Table S5).

Early studies on phase lengths relied on daily self-monitoring of basal body temperature (BBT), which usually rises 0.2°C–0.5°C at about the time of ovulation (Matsumoto et al., 1962; Döring, 1969; Bailey and Marshall, 1970). Although BBT is not a very reliable indicator (Barron and Fehring, 2005), a BBT-based estimate has ~60% probability of being within ±1 day of the true day of ovulation (Dunson et al., 1999). Different algorithms to interpret the chronological pattern of recorded BBT are not necessarily comparable; even within a study, phase-length estimates should be viewed cautiously. BBT's limitations are well recognized, but it is still widely used in clinical and research settings because it is relatively easy and not costly (Dunson et al., 2002).

On the basis of large trials to evaluate self-monitoring of changes in cervical mucus as a natural family planning method, mean follicular phase = 15 days and mean luteal phase = 13.5 days (WHO, 1983b). These estimates agree with a study of 80 women using ultrasound: mean follicular phase = 14.6 days and mean luteal = 13.6 days (Ecochard and Gougeon, 2000).

All studies (Supporting Information Table S5), excepting that using ultrasound, reported marked variation in phase lengths in women and cycles. In general, the follicular phase varied more than the luteal. Hormonal biomarkers more accurately indicate the day of ovulation than BBT or cervical mucus, and thus give better estimates of phase-length variability. Of 68 Swedish women, more than one-third of the pre-ovulatory estradiol and LH peaks (marking the end of the follicular phase) occurred before Day 12 or after Day 18 of the cycle; 31% of the women had luteal phases <12 or >15 days (Landgren et al., 1980). Of 141 U.S. women (mean age = 29 years), each contributing ≥3 cycles, 34% had a range of follicular-phase lengths >7 days and 9% had a range of luteal-phase lengths >7 days (Fehring et al., 2006). Given such variation, any study that assumes ovulation occurs on a specific day, absent any supporting biological data, is on shaky ground.

Age-associated changes in mean follicular-phase length and mean cycle length are roughly comparable; from 20 to 40 years of age, both shorten by ~2 days (Lenton et al., 1984a; Monari and Montanari, 1998). Luteal-phase duration is less variable with age. However, Lenton et al. (1984b) found that luteal phases <11 days are more common in 18–24-year-olds and 45–50-year-olds, suggesting that changes in luteal duration with age may not be linear. More accurate methods to detect ovulation may also reveal greater variation in the luteal phase than currently recognized. Using ultrasound, a U.K. clinical study of 53 women (aged 21–45 years) reported later ovulation in the oldest women but cycle length the same as in younger women; i.e., the follicular phase was longer and the luteal phase shorter at older ages (Fitzgerald et al., 1994).

Probability of ovulation

The probability of ovulation is less during the years immediately after menarche and just prior to menopause (Döring, 1969; Mansfield and Emans, 1984; Lipson and Ellison, 1992; Apter, 1997). However, data from New Zealand suggest that cycles of 21–35 days duration are as likely to be ovulatory in pre-menopausal women >40 years old as in women <40 years old (Metcalf, 1979).

The few data for women 20–40 years old in industrialized countries suggest probability of ovulation is typically ≥85% (Supporting Information Table S6), but may be much lower in segments that are <21 days or >42 days, and in some subsamples. Ovulation frequency in married 20–29-year-old New Zealanders was 99% but only 63% in unmarried same-aged women who were not living with relatives (Metcalf and Mackensie, 1980; Metcalf, 1983). During a season of food scarcity, ovulation frequency was 45% in poor Bolivians (23–35 years old) but 88% in same-aged members of the local medical school and 91% in Chicagoans (Vitzthum et al., 2002). Even in carefully screened samples, anovulation risk can be significant. In a prospective study of Swedes (20–37 years old) recruited for testing contraceptives, 7 of 43 (16%) subsequently did not ovulate, based on hormone profiles, despite meeting very strict selection criteria (Landgren and Diczfalusy, 1980; Landgren et al., 1980).

Bleeding episode (menses) duration

Menses duration and/or volume may be proxies for reproductively significant variation in ovarian functioning (e.g., endometrial development). In two studies (Vitzthum et al., 2001; Small et al., 2006), menses immediately preceding an implanted conception were longer than those not followed by an implanted conception. Assuming that endometrial development in successive cycles is correlated, the most plausible mechanism for this finding is that greater endometrial development increases the probability of successful implantation (Gonen et al., 1989; Zhang et al., 2005). But putative links between menses duration, hormone levels and endometrial development still require verification. In fact, the causes and significance of the striking variation in menses duration (almost two-fold worldwide) are unknown.

A multi-country WHO study (Snowden and Christian, 1983) concluded that geographical location is the best predictor of episode duration (Belsey and Peregoudov, 1988). In general (Supporting Information Table S7, Fig. 8), those of European ancestry have the longest menses, although duration among Pakistani women is as long. South Americans and Indians reported the shortest menses. Samples from northern and southeast Asian populations fall between these extremes.

Most studies report that a woman's menses rarely varies by more than a day or two which, for a 4-day episode, is comparable to a 28-day cycle varying by 7 days. However, because episode measurements are usually quantized in whole days (the first and/or last day of menses is counted as 1 day even if bleeding lasted only a brief period), the true within-individual variation in episode duration may, in fact, be low. In a large subsample

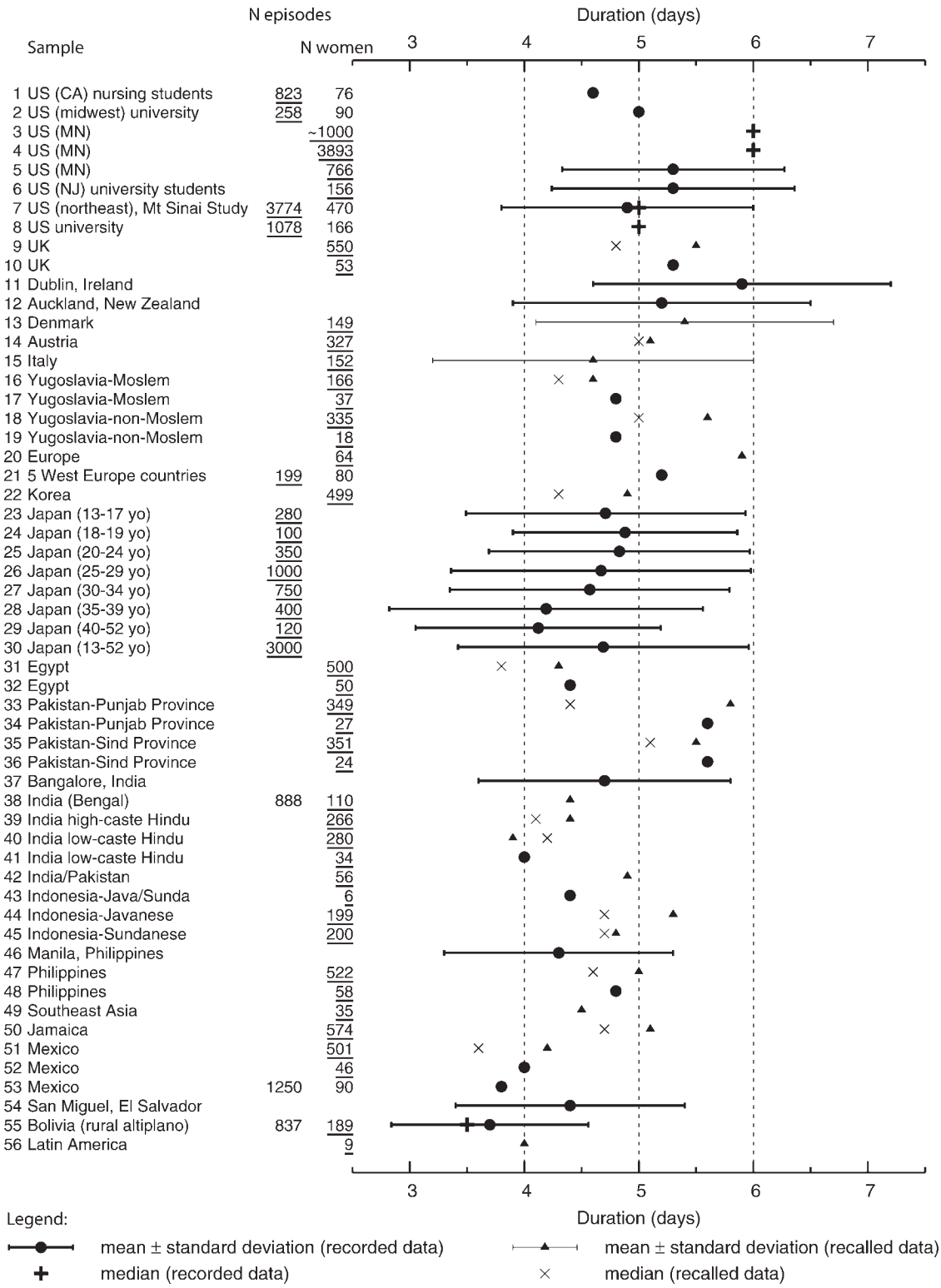

Fig. 8. Menses duration distributions for selected samples from various human populations. The numbers at the far left identify the samples in Supporting Information Table S7, which also lists sources. For each sample, the *N* for the units of analysis (episodes or women) is underlined. Note the distinction between recorded data (which is quite reliable) and recalled data (which may be subject to various recall biases).

of the Treloar longitudinal data set, median episode duration was 6 days; <25% of the women at a given age had an episode duration that ranged by more than 1 day during the year (Belsey and Pinol, 1997). In Bolivians, more than half had a range of ≤1 day, and only 6% had a range >3 days (Vitzthum et al., 2001). The vaginal

bleeding accompanying early pregnancy loss is at most ~0.4 days longer than a woman's average menses, primarily due to more days of light bleeding, and is unlikely to be distinguishable from menses (Vitzthum et al., 2001; Promislow et al., 2007).

Menses duration appears to shorten ~0.5 day over the course of adulthood (Matsumoto et al., 1962; Datta, 1957, 1960), but most studies either did not assess age variation or reported an absence of age-related changes. Such lack of evidence may, however, reflect measurement difficulties (e.g., quantifying episodes in whole days). Likewise, the absence in most studies of a relationship between episode and segment lengths may be a consequence of methodology. Two studies of non-hormonal family planning methods reported a significant positive correlation between episode and segment lengths among women who reported regular cycles (Creinin et al., 2004; Fehring et al., 2006). Perhaps those in family planning trials are more highly motivated to keep accurate records of their cycles than women in population-based studies.

The studies to date (Supporting Information Table S7) differ in definition of menses, data collection method, number of episodes per woman, unit of analyses, participant age, and inclusion of clinic patients or those with sexually transmitted diseases. Much of the data were recalled and most of the recorded data were from small samples (the "Latin America" sample had only 9 women). Almost none of the studies distinguished spotting versus full flow or partial versus full days of bleeding. In sum, there is not yet an accurate and complete picture of menses variation among women and populations, or the causes of that variation. Perhaps clothing style, cultural attitudes about blood, and personal hygiene practices explain the observed regional differences. Or perhaps there are significant biological differences among women that are obscured by these behavioral variables.

Reproductive hormone levels

A handful of studies (Supporting Information Table S8), almost all on clinical samples in industrialized countries, have described hormonal changes during the ovarian cycle (e.g., Mishell et al., 1971; Thorneycroft et al., 1971, 1974; Kletzky et al., 1975; Sherman and Korenman, 1975). Few samples were large enough to reveal the substantial variation among pre-menopausal women within a population (Landgren et al., 1980). Up to half of all cycles from fertile women have hormone profiles that deviate markedly from clinical standards of "normal" profiles (Renaud et al., 1980; DeCherney et al., 1982; Alvarado et al., 1988; Alliende, 2002). The BIMORA project (Ferrell et al., 2005) observed that during a 5-year period most of the substantial variance in levels of the urinary metabolites, estrone-3-glucuronide (E1G) and pregnanediol-3-glucuronide (PdG), was attributable to differences between women.

Whether hormone levels and segment or phase lengths consistently covary is unclear (Table 4). Landgren et al. (1980) noted that high initial estradiol combined with low initial LH was associated with relatively short cycles, and the opposite pattern with relatively long ones. Smith et al. (1985) concluded that a short luteal phase did not necessarily indicate poor corpus luteum function or poor follicle development. The implications of these or other patterns for fecundity remain unknown. The one certainty is that reproductive hormone profiles, regardless of cycle length, cannot be assumed to mimic those in an idealized cycle.

Age variation. The preponderance of evidence suggests that there is very little, if any, age-associated ovarian steroid variation (in ovulatory cycles) from 20 to 40 years of age (Metcalf, 1979; Lipson and Ellison, 1992; Fitzgerald et al., 1994; Reame et al., 1996; Westhoff et al., 1996; Windham et al., 2002). Studies not distinguishing ovulatory and anovulatory cycles have reported significant age-related variation in ovarian steroid levels (Ellison et al., 1993b; Lipson and Ellison, 1994; Ferrell et al., 2005). But because the risk of anovulatory cycles is higher in the years immediately preceding menopause than during the peak reproductive years (Döring, 1969; Mansfield and Emans, 1984; Lipson and Ellison, 1992; Apter, 1997), at least some, perhaps most, of the apparent age variation may be spurious.

To appreciate the consequences of including anovulatory cycles in analyses of ovarian steroid levels, consider the measurements (Fig. 9A) of mid-luteal salivary progesterone from a sample of Boston women (Lipson and Ellison, 1992; Ellison et al., 1993b). If all cycles, regardless of ovulatory status, are included in analyses then a quadratic (the black curve) is a plausible fit to the data; progesterone appears to peak at ~32 years and is lower at younger and older ages (of course, if there is a peak, a quadratic is symmetrical about it). But if only ovulatory cycles are considered, the mean progesterone levels are nearly constant from ages 20–39 years.

Whether steroid levels (in ovulatory cycles) vary from 20 to 40 years of age in non-industrialized populations is uncertain. Data from Nepal (Fig. 9B) suggests progesterone decreases at the extremes of the age distribution (Panter-Brick et al., 1993; Ellison et al., 1993b). Figure 9B includes the quadratic curve fitted to the 45 data points by Ellison et al. (1993b: Fig. 5C), the ovulation fraction in winter, and the mean (± standard deviation) progesterone level in the ovulatory cycles for each of the three age cohorts (Panter-Brick et al., 1993). The data appear to show a strong age variation in progesterone levels, but this is primarily due to only three very high data points in the middle-age cohort. Evaluating the stability of hormone levels from 20 to 40 years of age is very difficult because the younger cohort spans 17–23 years, the older cohort spans 37–46 years, and there are no women aged 24–28 years. In addition, this study's method of identifying ovulatory cycles (see discussion in section on " Biometry of Ovarian Functioning) is biased toward classifying anovulatory cycles as ovulatory; when combined with the large apparent variation in ovulatory fraction with age, this may further distort the pattern of age variation in progesterone in this population.

The BIMORA project reported striking differences between aggregate and individual age-related variation in gonadotrophin levels (Ferrell et al., 2007). Aggregate LH levels did not increase until >45 years of age, but longitudinal changes in individuals varied greatly. Before 45 years of age, women had uniformly low LH, but these might be constant, increasing or decreasing during the 5 years of observation. From 45 to 55 years old, LH sharply increased in some women, but in others, LH levels were comparable to those at younger ages. Aggregate FSH levels increased throughout the participant age range (25 to >60 years), and nearly all individuals also had increasing FSH with age. But at <45 years, FSH levels were low with only moderate increases; at

TABLE 4. Hormonal variation versus cycle and phase lengths

	Estrogen		Progesterone		Gonadotrophins				
	Follicular	Luteal	Follicular	Luteal	FSH	LH	Method	*N*	Source
Cycle length					No relation		Blood	39	Schipper et al. (1998)
Cycle length	Negative corr. with several indices	No relation	No relation	No relation	No relation	Positive corr. with several indices	Blood	68	Landgren et al. (1980)
Follicular phase (days):									
Length					No relation			39	Schipper et al. (1998)
Length	Negative corr. with mean of Days 1–6, and peak		No relation	No relation	No relation	Positive corr. with mean of days −3 to −7 before ovulation	Blood	68	Landgren et al. (1980)
Length	No relation	No relation	No relation	No relation	No relation	No relation	Blood	51	Broom et al. (1981)
>23 vs. shorter	No difference						Urine	258	Harlow et al. (2000)
>23 vs. 12–23	Higher total	Higher daily mean	No difference	No difference			Urine	411	Windham et al. (2002)
<12 vs. 12–23	Higher baseline and daily mean; lower total	No difference	Higher	Higher peak			Urine	411	Ibid.
Luteal phase (days):									
Length	Negative corr. with peak	No relation	No relation	Positive corr. with peak	No relation	No relation	Blood	68	Landgren et al. (1980)
>14 vs. 11–14	No difference	No difference	Higher	Higher total and peak			Urine	411	Windham et al. (2002)
<11 vs. 11–14	Higher total	Higher daily mean	No difference	Lower total and peak			Urine	411	Ibid.
<12 vs. longer	No difference	Higher		No difference in mid-luteal; lower in late luteal phase	No relation to mid-cycle levels; lower during luteo-follicular transition		Blood	31	Smith et al. (1985)

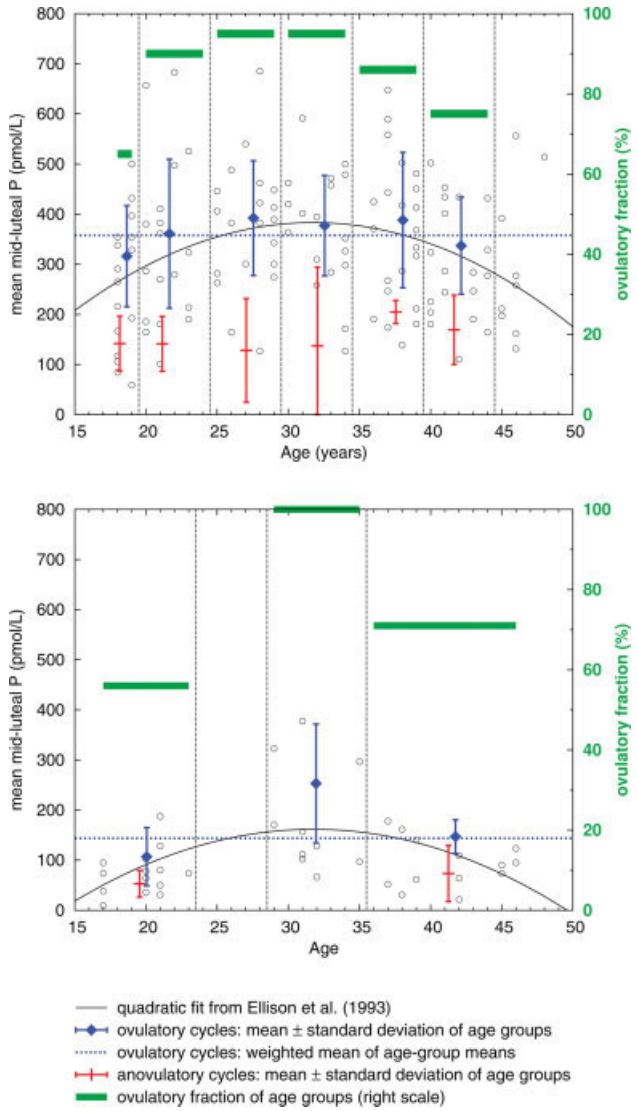

Fig. 9. Plots of mid-luteal progesterone values derived from Lipson and Ellison (1992; Table 3), Panter-Brick et al. (1993), and Ellison et al. (1993), subdivided by woman's age and ovulatory status: Boston sample (upper plot) and Nepal sample (lower plot). For each age group, the frequency of ovulation (green horizontal bars), the mean and standard deviation for progesterone level in only ovulatory cycles (blue ◆ and vertical lines), and the mean and standard deviation for progesterone level in only anovulatory cycles (red — and vertical lines) are depicted. Solid black curve = quadratic fit to all data for all cycles, regardless of ovulatory status. Horizontal blue dashed line = weighted mean in ovulatory cycles of age groups' mean progesterone levels, all of which fall within one standard deviation of the weighted mean. This pattern in ovulatory cycles suggests that there is little variation in mean progesterone levels in the Boston sample across ages 20–39 years.

>55 years, FSH levels were all significantly higher and increased rapidly with age.

In two cross-sectional studies restricted to ovulatory cycles (53 U.K. women aged 21–45 years [Fitzgerald et al., 1994]; 32 U.S. women aged 19–50 years [Reame et al., 1996]), FSH and LH both rose with age. Maximum FSH levels did not, however, vary with age in the ovulatory cycles of 39 women aged 20–35 years (Schipper et al., 1998), suggesting that an increase in FSH starts later in life rather than incrementally throughout adulthood.

Inter-populational variation. Populations differ markedly in the average levels of ovarian steroids in pre-menopausal adult women. In general, the highest concentrations are found in industrialized populations and the lowest are seen among the poorest women in developing countries, but, for unknown reasons, there are exceptions to this pattern.

Much of the early research on populational differences was prompted by the hypothesis that high breast cancer rates in women of European ancestry, compared with women in Asia, are attributable to elevated estrogens, thought to result from high dietary fat intake (Tannenbaum and Silverstone, 1953; Armstrong and Doll, 1975). The merits of this idea aside, these studies reported estrogen levels in Asians to be anywhere from 55% to 90% of those observed in U.S. and U.K. "white" women (MacMahon et al., 1974; Dickinson et al., 1974; Trichopoulos et al., 1984; Key et al., 1990; Shimizu et al., 1990; Wang et al., 1991). The wide range among studies in estrogen levels of Asians relative to whites is attributable, at least partly, to differences in age, body weight, choice of estrogen or estrogen metabolite, and degree of "westernization" among the Asian samples. In a study with greater control for potential confounders (Bernstein et al., 1990), luteal-phase estradiol levels were ~20% higher in Los Angeles whites than in women in Shanghai. Progesterone levels and cycle length in ovulatory cycles did not differ significantly. Adjusting for weight accounted for only 26% of the difference in estradiol.

Even greater differences have been reported for salivary progesterone in a set of samples, assayed in the same laboratory, from agricultural populations in Poland, Bolivia, Nepal and the Democratic Republic of the Congo compared to Boston women (Ellison et al., 1993b). However, once the comparison is restricted to women aged 25–35 years observed during seasons not characterized by extreme energetic stress, the variation among the populations is markedly less (see Fig. 10). In addition, because the published summary indices cannot be adjusted for the inadvertent inclusion of anovulatory cycles nor for selection of those more likely to be subfecund because of selection bias and/or sexually transmitted diseases (see discussion in section on "Biometry of Ovarian Functioning"), the range of true values among these populations may not be as great as it appears (Vitzthum et al., 2000a).

Variation also has been observed within ethnically heterogeneous populations. Among northern California women, aged 18–39 years, Asians had lower estrogen levels compared to whites but the concentration in Hispanics was about 12% higher (Windham et al., 2002). Progesterone metabolites did not vary with ethnicity in this population. Another study in Los Angeles reported that African-American women had 25% higher luteal estradiol and 36% higher progesterone levels, and Latina women had 15% higher luteal estradiol and 18% higher progesterone levels, than non-Latina Whites (Haiman et al., 2002). Matched samples from the Nurses' Health Study II observed elevated estradiol levels in both African Americans and Asian Americans compared to Caucasians, but no variation in progesterone by ethnicity (Pinheiro et al., 2005).

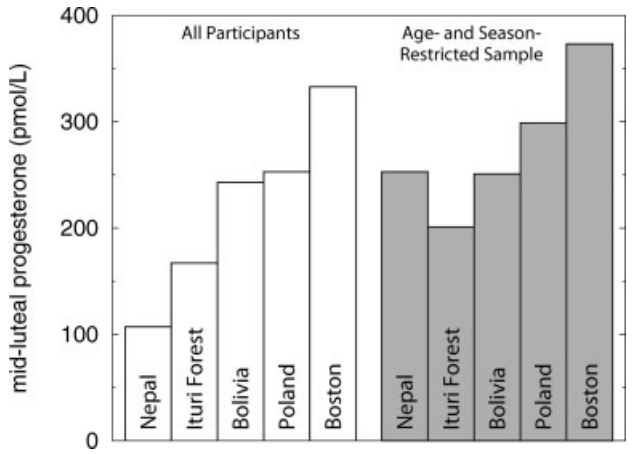

Fig. 10. Comparison of mid-luteal progesterone levels in five samples assayed following the same protocol in the same laboratory. The left panel shows the comparison for all participants in each sample, suggesting large interpopulational differences in progesterone levels. The right panel shows the effect of selecting a comparable subsample (ages 25–35 years, energetically least-stressed season) from each sample: when free of age- and season-confounding, the actual interpopulational differences are seen to be much smaller. (Data from Vitzthum et al., 2000a.)

Less is known of populational variation in gonadotrophins. In !Kung San (van der Walt et al., 1978) and Bolivians (Vitzthum et al., 2002, 2007a,b), ovarian steroids were low relative to urban South African Negroes and Chicago women, respectively, but gonadotrophin levels were similar. These patterns suggest that the HPO axis was not impaired in !Kung San or Bolivians and that their lower ovarian steroid levels were adequate for successful reproductive functioning.

FACTORS INFLUENCING OVARIAN CYCLE VARIABILITY

> . . . the reproductive system [is] eminently susceptible to changes in the conditions of life. Charles Darwin, 1859.

Within individuals, cycle length, ovulatory frequency, and hormone levels vary temporally with age, pregnancy, lactation, psychosocial stress, energy intake, and activity level. Factors less central to reproductive ecology but which can disrupt ovarian cycling include travel (especially to harsh locales), smoking, alcohol, and illness (Creff, 1982; MacMahon et al., 1982b; Michnovicz et al., 1988; Steinkampf, 1990; Westhoff et al., 1996; Liu et al., 2004; Jean et al., 2005). Because these factors can confound analyses of cycle variables, potential study subjects should be screened and, excluded if necessary, or the factors should be controlled for statistically. Once temporally varying confounders are excluded, the determinants of inter-individual variation are almost entirely unknown, although dietary practices and developmental conditions are thought to be influential, and genetic variation may be important.

Factors generating temporal (within-woman) variation

Pregnancy Loss. Because lactation can suppress the HPO axis (McNeilly, 2001), breastfeeding women are typically excluded from studies of "normal" ovarian cycling (although this selection bias may exclude women of higher fecundity). But because most pregnancies are lost shortly after conception (Vitzthum, 2008a), it is much more difficult to exclude segments from pregnant women who are unaware of having conceived. Assuming a modest fecundability of 0.20 and a modest risk of early pregnancy loss (EPL) of 50%, 100 non-contracepting study participants would have 20 conceptions/month of which half (10% of the sample) would be lost without detection. In any study not monitoring for conceptions, at least some of the reported variability in segment length is due to unrecognized EPL. In Bolivian women, segments in which EPL had occurred were ~7 days longer than the sample of non-conception cycles that had also not followed a loss (36.4 versus 29.1) (Supporting Information Table S3). Non-conception cycles following EPL were also significantly longer by 3–4 days than those not following a loss (Vitzthum et al., 2000b).

Energetics. Although the precise physiological pathways are not well understood, ovarian functioning in humans and other primates can vary with changes in energetic variables (e.g., body weight, body fat mass, and energy balance) (Prior, 1985a,b, 1987; Ellison, 1990; Rosetta, 1993; Cumming et al., 1994; Cameron, 1996; Warren, 1997; Loucks and Thuma, 2003; Wade and Jones, 2003; Goodman and Warren, 2005). Escalating energy deficits over time are associated with a progressive series of responses beginning with suppression of gonadotrophin secretion, followed by declines in ovarian steroids, advancing to anovulation, and culminating in amenorrhea (de Souza, 2003). Even modest levels of physical activity are associated with longer cycles and shorter menses in studies of U.S. women (Ellison and Lager, 1986; Cooper et al., 1996; Sternfeld et al., 2002; also Harlow and Matanoski (1991) in 17–19-year-olds). However, in a sample of ovulatory cycles, an activity-associated difference was observed only in those women <35 years old and only in the follicular phase (2 days longer) but not in total cycle length (Liu et al., 2004).

Anthropologists' studies documented changes in ovarian functioning synchronous with more energetically stressful periods. van der Walt et al. (1978) reported low ovarian steroid levels in !Kung San and suggested that these might be a mechanism to restrict conception to seasons of better nutrition. Notably, the number of births was highest about 9 months after San women had reached their peak body weight. Leslie and Fry (1989) linked the extreme birth seasonality in nomadic Turkana pastoralists to fluctuations in rainfall that drove varying availability of foodstuffs (see Fig. 11). Studies of the Lese, subsistence farmers in the Ituri Forest, reported declines in both body weight and the frequency of ovulatory cycles over a 4-month period (Ellison et al., 1989), and periods of low food production and lower body weight correlated with lower progesterone levels and reduced conception frequency (Bailey et al., 1992). Nepalese women who lost weight between winter and the more arduous monsoon season also had a significant drop in mid-luteal progesterone (Panter-Brick et al., 1993). Polish agriculturalists had lower progesterone levels during the months of greatest physical labor compared to levels at the end of the harvesting season (anovulation rates were not reported) (Jasienska and Ellison, 1998). In rural Bolivian agropastoralists, ovulation frequency was lowest during the physically demanding

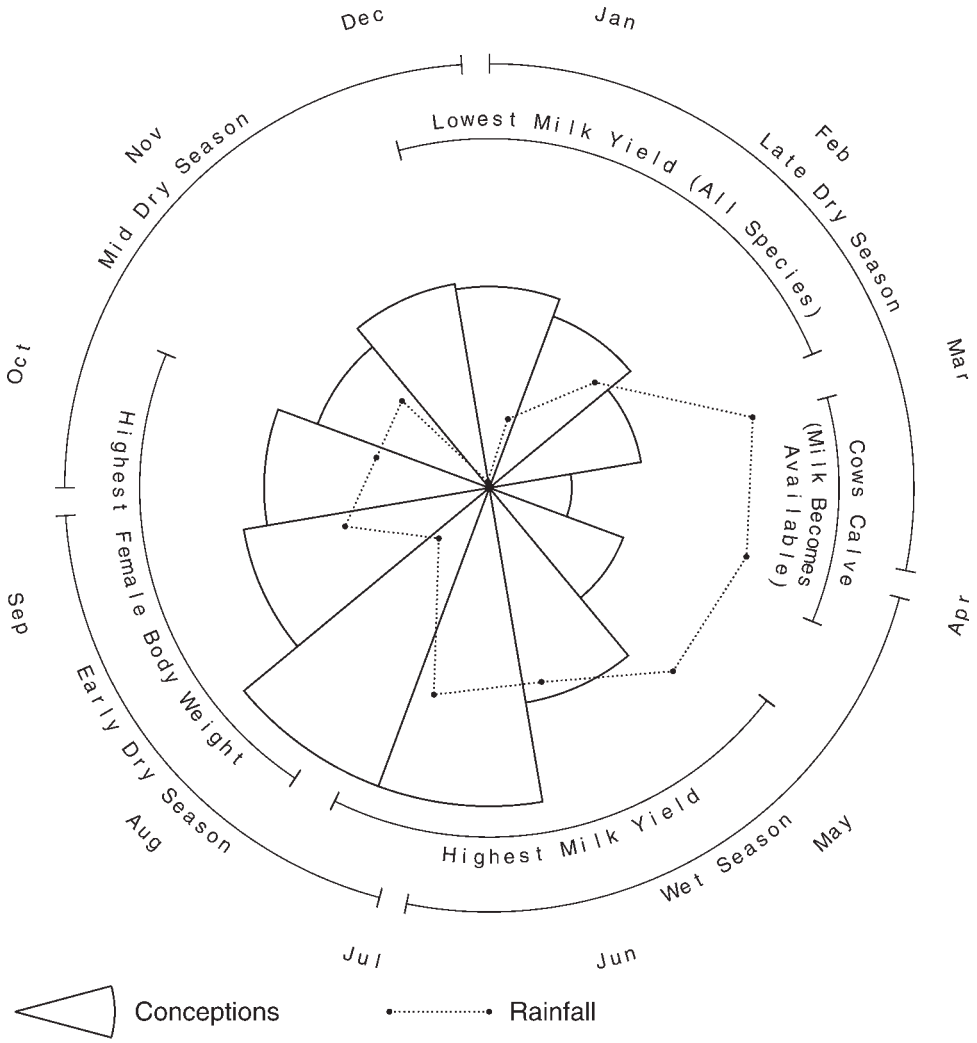

Fig. 11. Seasonality in conceptions leading to live births in nomadic Turkana pastoralists (sectors) and in rainfall (points connected by dashed lines). The highest proportion of conceptions (radius of sectors) occurred during and shortly after the period of highest animal milk yield, as the women were gaining body weight. (Conceptions extrapolated from birth dates; figure adapted from Leslie and Fry, 1989).

planting and harvesting seasons (see Fig. 12) (Vitzthum et al., 2009a).

These changes are similar to those documented among exercising and/or dieting women in wealthier countries. But a consistent progressive relationship between stressors and changes in ovarian functioning is less evident among women who have lived in demanding circumstances their entire lives. In Nepalese women, despite "moderately heavy" energy expenditure in the winter and "very heavy" in the monsoon, only those who lost weight between these periods had a significant decline in progesterone (Panter-Brick et al., 1993). In Lese women, those who lost $\geq$2 kg during 4 months averaged lower progesterone levels during this period than those who lost less or gained weight (Ellison et al., 1989). But ovulatory frequency did not significantly differ between these two subsamples, even though the proportion of ovulatory cycles per month was progressively lower in the population over the 4 months. Differences among Polish women in progesterone levels during the physically demanding summer months were best explained by variation in energy expenditure independent of any change in weight (Jasienska and Ellison, 1998). Why was this effect of demanding physical labor not observed in the Nepalese women? In Bolivian women, the risk for EPL, like that for anovulation, was greater in the physically arduous seasons (see Fig. 12) (Vitzthum et al., 2009a). What role might unrecognized EPL have played in the patterns of ovarian functioning observed in other non-industrialized populations?

Seasonality in segment lengths may also occur independent of energetic stress. In Indian women, segments were shorter in the late monsoon and longest in the early spring (Datta, 1960; Williams, 2006). Analyses of 38,194 woman years from Minnesota (Treloar et al., 1967) suggested segments were $\sim$5 h longer in December than in July (Sundararaj et al., 1978).[1] The authors noted that such a small difference may have neither practical nor biological significance, especially in light of the far greater individual variability.

[1]Some citations of this work have misreported the difference as about 50 h (2 days).

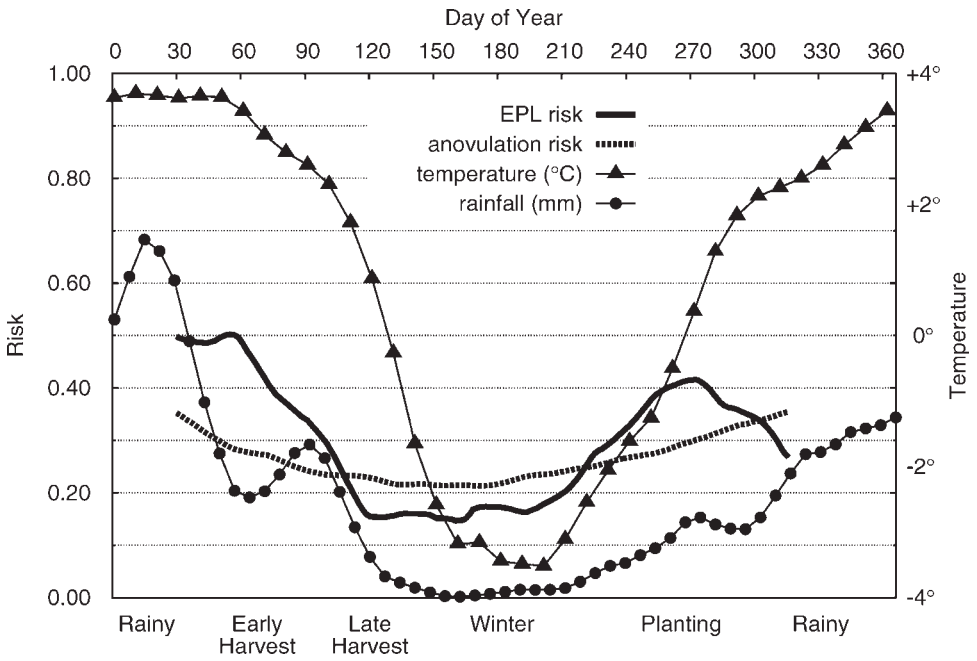

Fig. 12. Seasonality of EPL and anovulation risks (left-hand scale) in rural Bolivians. Daily rainfall (far right-hand scale) and minimum-temperature (near right-hand scale), as functions of time (top scale, day of year). Agricultural activities (bottom scale) are positioned relative to day of year. The data were smoothed using triangular moving-average windows of duration ±60 days for the EPL and anovulation risks and ±30 days for the climate data. Climate data are for the weather station (La Paz) closest to the study region, for the same year as the study (NOAA, 2008). Risk of EPL and anovulation are elevated during the most energetically demanding periods. (Reproduced from Vitzthum et al., 2009a).

Psychosocial factors. Experimental studies in monkeys (Williams, 2003) and both clinical and observational studies in humans (Sanders and Reinisch, 1992; Marcus et al., 2001; Nepomnaschy et al., 2007) have reported changes in ovarian functioning associated with psychosocial stressors. One putative mechanism involves stimulation of the adrenal cortex and production of corticosteroids, thought to disrupt the HPO-axis (Ferin, 1999; Puder et al., 2000). A prospective study of hormonal changes in rural Guatemalan women (Nepomnaschy et al., 2004, 2009) found rises in urinary cortisol to be significantly associated with self-reports of personal problems and to be accompanied by increases in gonadotrophin and progestin levels during the follicular phase, and decreases in mid-luteal progestin levels.

Although there are many reports hypothesizing a link, Ellison et al. (2007) argued that "The evidence for a suppressive effect of psychological stress on female fecundity independent of other causes has ... always been equivocal and plagued with methodological difficulties." Among the problems of many studies, they included failure to account for covariates, especially energetic stress; reliance on anecdotal evidence; inadequate study designs; small sample sizes; reversal of causality direction; and poor operationalization of "stress." In their study of Harvard students, the authors took pains to avoid these problems. They found that, compared with a control sample, ovarian steroid levels were not affected in those students scoring high on the Spielberger State-Trait Anxiety Inventory shortly before taking a demanding exam (the MCAT) (Ellison et al., 2007). But cortisol levels also did not differ between the MCAT and control groups, suggesting that the perceived stress was not accompanied by adrenal activation, which (if the mechanism proposed above is correct) would be necessary for ovarian functioning to be affected by a putative psychosocial stress.

It is possible that the effects of psychosocial stressors explain reports that Danish women from lower social groups were 2.7 times more likely to have high cycle variability (Münster et al., 1992), that the risk of anovulation is 37% in unmarried 20–29-year-old New Zealand women of European ancestry living alone but only 1% in married same-aged women (Metcalf and Mackensie, 1980; Metcalf, 1983), and that in India less education was associated with longer cycles (Jeyaseelan and Rao, 1993). There is no direct evidence to support this suggestion. But further work on whether psychosocial factors could have a significant impact on human ovarian functioning will need to develop a study design that accounts for all potential confounders, adequately measures ovarian functioning, includes stressors that can reasonably be expected to activate an adrenal response, and adequately measures adrenal activity.

Factors generating inter-individual variation

Energetics. In general, increasing BMI is associated with increasing and more variable segment length (Symons et al., 1997; Rowland et al., 2002; Williams, 2006), but the lowest BMI may also be associated with longer, more variable cycles (Cooper et al., 1996; Symons et al., 1997; Williams, 2006). These observations suggest a non-linear relationship between BMI and cycle length. Although increasing body fat was associated with shorter segments in a study of Austrian women (Kirchengast, 1994), much of the data were recalled rather than prospective. High ponderal index [(body weight in

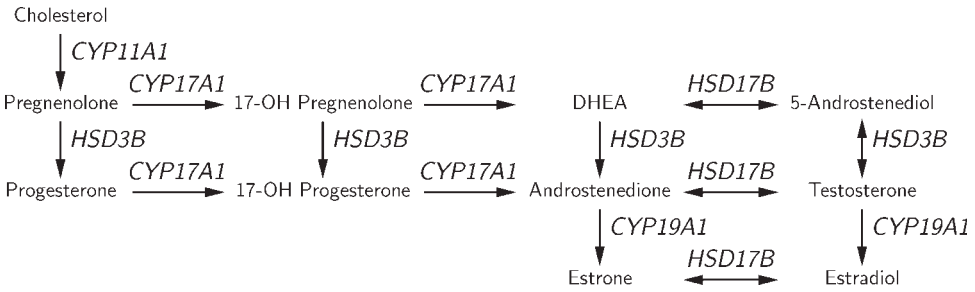

Fig. 13. Simplified schematic of steroid biosynthesis and the loci (in italics) coding for the enzymes acting in these pathways. 17-OH pregnenolone = 17α-hydroxypregnenolone; 17-OH progesterone = 17α-hydroxyprogesterone; DHEA = dehydroepiandrosterone. (Adapted from Olson et al., 2007.)

kg)/(body length in m)^3] was associated with less variable segments in a WHO study (Belsey et al., 1988), but because the women were from 10 (some non-industrialized) countries, there may have been a poor representation of higher weights in the sample. Neither segment nor follicular phase length varied with BMI in analyses restricted to ovulatory cycles (Liu et al., 2004); perhaps extremes in BMI are associated with anovulation (not detectable in these analyses) as well as increases in segment length.

In South India, segments averaged 1 day longer in rural than in urban women, a consequence of the much longer cycles in the youngest cohort of rural women (see Fig. 6). The authors attributed this difference to participation in agricultural labor (Jeyaseelan and Rao, 1993). In a subsequent path analysis combining urban and rural samples, physically laborious occupations were directly linked to longer segments (Jeyaseelan and Rao, 1995). Episode duration was positively correlated with height and lean body mass in U.S. women 29–31 years old (Cooper et al., 1996). In Bolivian women, episodes lengthened with fatness (Miller et al., 2002), but there was no relation to current age, age at menarche or first birth, segment length (either previous or subsequent), or lactation status (Vitzthum et al., 2001). In ovulatory cycles from U.S. women, progesterone levels were lower in those of greater weight or BMI, but estradiol levels were not related to either variable (Westhoff et al., 1996; Windham et al., 2002).

In sum, it appears that an individual's typical energy status has less of an effect on ovarian functioning than does energy balance (i.e., changes in energy status). The few reported associations between cycle attributes and anthropometrics are inconsistent, and may be confounded by unaccounted differences in activity levels and/or drinking and smoking habits, and/or unrecognized conceptions that were lost before detection.

Dietary composition. Despite vast differences in diets, most populations have similar cycle lengths (Supporting Information Tables S3, S4; Fig. 6, 7). There was no association between dietary variables and cycle length in Japanese (Nagata et al., 2006). Animal fat and protein intake is 5-fold greater in Mongolians than Bolivians, but they had comparable cycle and phase lengths (Jurado et al., 2009). Compared with Canadian non-vegetarians, vegetarians had similar cycle and follicular-phase lengths but longer luteal phases (Barr et al., 1994). Cycle and follicular-phase lengths increased in South Africans given a meat supplement, but no changes occurred with a soy protein supplement (Hill et al., 1986). Follicular phases lengthened with lowered fat intake in a clinical intervention (Reichman et al., 1992). These findings run counter to the absence of diet-related patterns in Japanese, suggesting differing effects of lifelong and intervention diets.

The putative role of dietary fat in ovarian steroid variation has received much attention because of interest in the etiology of breast cancer. The risk of breast cancer varies with hormone levels in both pre- and post-menopausal women (Key et al., 2002; Micheli et al., 2004; Kaaks et al., 2005). Dietary fat has been hypothesized to raise ovarian steroid levels because mammary tumors in lab rodents are linked to fat consumption (Tannenbaum and Silverstone, 1953), fat consumption and the risk of breast cancer is correlated cross-nationally (Armstrong and Doll, 1975), and steroids are derived from cholesterol (see Fig. 13), which is high in some animal foods. However, prospective studies have thus far failed to find unequivocal support for a link between breast cancer incidence and relatively recent dietary consumption patterns in peri-/post-menopausal women (Willett, 1987; Duncan, 2004; Holmes and Willett, 2004; Mannisto et al., 2005).

A handful of studies compared hormone levels in samples with markedly different adult diets or monitored hormones while manipulating subjects' dietary intakes (Hagerty et al., 1988; Bagga et al., 1995; Lu et al., 2001; Gann et al., 2003; Maskarinec et al., 2004). The results from these studies are inconsistent, however, several factors may have unavoidably confounded the analyses. First, co-variation among nutrients made it difficult to attribute changes in hormone levels to any one nutrient. Second, the fat intake usually varied narrowly (30–40% of total calories), which may not have yielded a detectable change in hormone levels. The one study of an intervention diet with only 10% fat did observe significant reductions in estradiol and estrone (Bagga et al., 1995). Third, participants may not have reported their diets accurately and/or failed to follow consistently the dietary modifications required by the study protocol. Collectively, these studies provide, at best, only limited evidence of a role for dietary fat.

Dietary patterns during maturation may be more important than those during adulthood (Micozzi, 1985, 1987; Willett, 1987; de Waard and Trichopoulos, 1988; Vitzthum, 1990, 2001b). Evidence for this includes a greater risk for breast cancer among women who had rapid childhood growth (Ahlgren et al., 2004) and a lower risk among Norwegian women whose puberty occurred during the World War II famine (Tretli and Gaars, 1996). Women aged 26–46 years (whose current

diets might differ less from their adolescent diets than would those of post-menopausal women) had higher breast cancer risk with greater animal fat intake (Cho et al., 2003). In a study of U.S. adolescent girls (Dorgan et al., 2003), those on a lower-fat/lower-calorie diet were found to have lower ovarian steroid levels compared to a control group, although it was not possible to separate the effects of energy from those of fat intake.

A recent study of Mongolian herders supports the role of life-long intake of dietary fat as a key determinant of ovarian steroid levels (Vitzthum et al., 2008). These Mongolians have a caloric intake as low as Bolivian agropastoralists (and hence might be expected to have comparably low ovarian steroid levels if these are mainly determined by energetic factors) but a fat intake (~40% of total calories) as high as Germans. As predicted by the dietary fat hypothesis, the Mongolian women have progesterone levels at least as high as those of German women despite the relatively lower caloric intake in the Mongolians.

Developmental conditions. Beginning with Boas' (1911) pioneering studies of immigrants and their U.S.-born children, anthropologists have investigated the role of conditions experienced during development in shaping adult form and functioning. For example, the Human Adaptability Project (Weiner, 1964; Lasker, 1969; Baker, 1978) produced a large body of empirical evidence amply demonstrating the significance of developmental experiences in generating human variation and unequivocally refuting "biological uniformitarianism" (Leslie and Little, 2003). Reflecting this legacy, anthropologists have proposed that pre-adult conditions have shaped adult reproductive functioning (Purifoy, 1981; Vitzthum and Smith, 1989; Vitzthum, 1990, 1992b, 1997, 2001b; Ellison, 1990, 1994, 1996a,b; Chisholm, 1993, 1999; Chisholm et al., 2005).

Because of the logistical difficulties of testing this hypothesis in a long-lived species, one approach has been to evaluate correlations among relevant population-level indices, but such analyses risk the ecological fallacy. For example, it has been proposed that more arduous conditions during development underlie lower ovarian steroid levels in adulthood (Vitzthum and Smith, 1989; Ellison, 1990). Under the assumption that U.S. "white" women grew up in generally favorable environments, this hypothesis is consistent with lower progesterone levels in non-industrialized populations compared with U.S. women (Ellison et al., 1989; Panter-Brick et al., 1993; Jasienska and Ellison, 1998; Vitzthum et al., 2000a, 2002). On the other hand, the relatively lower steroid levels in whites compared with other U.S. ethnic groups (Haiman et al., 2002, Windham et al., 2002; Pinheiro et al., 2005), and the high ovarian steroid levels observed in Mongolian nomadic herders (Vitzthum et al., 2008) do not support this hypothesis. Resolving such inconsistencies requires greater control of confounders and/or individual-level analyses.

Another approach for evaluating developmental hypotheses is to test for correlations between indices of environmental quality and ovarian cycle variables. Adult height ("the biological standard of living" [Komlos, 1994]) has been well studied (Lasker, 1969; Bogin, 1999) and is a commonly used barometer of environmental quality and population health (WHO, 1995). Because height is largely determined by environmental factors (e.g., food, disease) during the first 2 postnatal years (WHO, 1995; Bogin, 1999; Cole, 2003), it is an established indicator of childhood conditions. In economically heterogeneous urban Bolivians, mean luteal progesterone level in ovulatory cycles was correlated with height ($r = 0.35$, $P = 0.015$). A somewhat stronger correlation ($r = 0.40$, $P = 0.005$) was also observed between overall progesterone level and overall body size (a principal component factor loading mainly on height). Ovulatory cycles from poorer urban Bolivians had lower salivary progesterone and serum estradiol levels than those from same-aged better-off women (see Fig. 4; Vitzthum et al., 2002, 2007a,b), a difference attributed to the quality of the environments experienced by these women during childhood.

Reported associations between age at menarche, known to vary with environmental quality (Bogin, 1999), and adult steroid levels are inconsistent. Controlling for several confounders, Shanghai women had lower estradiol levels and reported an age at menarche 2 years later than Los Angeles "white" women (Bernstein et al., 1990). However, individual-level analyses of these same samples found no significant relationship between age at menarche and estrogen levels (Bernstein et al., 1991). Comparing samples from Boston, rural Poland, highland rural Bolivia, Ituri forest, and highland rural Nepal, Ellison (1996b:Fig. 2) suggested a negative correlation between population mean menarcheal age (from Eveleth and Tanner, 1990) and mean mid-luteal progesterone level. But in seasons of relative abundance, the Nepal and Bolivian samples have similar mid-luteal progesterone levels (see Fig. 10) even though the age at menarche in Nepal is 3 years later (Vitzthum, 2001a). Jasienska and Thune (2001) reported a correlation between sample mean progesterone levels and either national mean total energy intake or national breast cancer incidence, but these correlations vanish when comparing hormone levels during the energetically less stressed seasons (also see Harvie and Howell [2001]; Lewis [2001]). Again, cross-populational comparisons are at risk for the ecological fallacy.

Reports of associations between menarcheal age and an individual's cycle attributes are also inconsistent. U.S. agricultural workers whose recalled menarche was <12 years of age were more likely to have short cycles, and those recalling menarcheal age ≥15 years had longer and more irregular cycles (Rowland et al., 2002). In Finnish girls, menarcheal age and duration of adolescent subfecundity (i.e., age-associated risk of anovulation) was positively correlated (Apter and Vihko, 1983; Vihko and Apter, 1984) and, in a follow-up study in adulthood, age at menarche and follicular-phase (but not luteal phase) estradiol levels were negatively correlated (Apter et al., 1989). But two much larger studies found no evidence of such associations (MacMahon et al., 1982a; Foster et al., 1986). Progesterone, but not estrogen, was lower in ovulatory cycles from New Yorkers with an earlier menarcheal age (Westhoff et al., 1996). But estrogen metabolites in ovulatory cycles were lower in Californians with age at menarche ≥14 years (Windham et al., 2002). However, follicular progesterone was lower in those with menarche *either* ≤ 11 or ≥14 years of age, and menarcheal age was not related to any luteal-progesterone index. Particularly revealing, even when matched for chronological and gynecological age (time since menarche), British girls had higher levels of progesterone than Thai girls (Danutra et al., 1989). Clearly, whatever factors shape menarcheal age and/or ovarian

steroid levels, these two aspects of ovarian functioning can vary independently to some degree.

Migrant study designs have also been used to understand the effects of developmental conditions on adult steroid levels, but the findings have been inconclusive. Falk et al. (2002) compared hormone levels in Asian women living in California and Hawaii, sorted by birthplace and by "westernization" based on migration history. Even though birthplace and estrogen levels were not related, in pre-menopausal women, the least westernized had the lowest estrogen levels, and western-born women had lower androgen levels than Asian-born. In post-menopausal women, androgens were highest among the least westernized and declined with greater westernization. But none of these patterns were significant at $P < 0.05$ (except that western-born post-menopausal women had lower dehydroepiandrosterone [DHEA]). Small sample sizes and only one blood sample to characterize an entire cycle's hormone levels may have obscured genuine differences among the migrant samples. Pollard et al. (2009) reported no differences in serum estradiol levels (estimated from a single sample drawn some time during Days 9–11 of the cycle) between adult migrants from Pakistan, British-born British Pakistani women, and British-born women of European ancestry.

Núñez-de la Mora et al. (2007b) compared progesterone levels in British women of European descent ("whites"), non-migrant residents in Sylhet, Bangladesh, and three samples of U.K. women of Bangladeshi descent (immigrated as adults, immigrated as children, born in the U.K.); participants were 19–39 years old. Their analyses suggested that non-migrant and adult-migrant Bangladeshi women had progesterone levels about half those of U.K. whites, and that child-migrant and U.K.-born Bangladeshi had progesterone levels more similar to U.K. whites than to the other Bangladeshi samples. However, although migrant study designs (e.g., Boas, 1911) can be powerful, serious limitations in design and statistical analyses undermine this study's conclusions (Thornburg, 2007; Vitzthum, 2007).

The multiple linear regression model that Núñez-de la Mora et al. (2007b) fitted to their data assumed that age-associated variation of progesterone levels is a steady exponential growth (or steady exponential decay) at a rate that is constant across the samples and across the age range of each sample. As discussed earlier, the true age-associated variation in progesterone is probably more complicated than the steady monotonic rise (or fall) assumed in the authors' model (i.e., it may rise, peak (or plateau) and then fall). The mean ages of the five samples ranged from 24.4 to 31.8 years (Núñez-de la Mora et al., 2008), and their standard deviations differed by >50%. Hence, there may be very substantial age-induced biases in the inter-group comparison of hormone levels estimated from the authors' regression model (Thornburg, 2007).

In addition, estimates of progesterone levels in the five samples are likely biased downward to varying degrees because of the unintended inclusion of anovulatory cycles and/or selection bias because of the cross-sectional study design (Vitzthum, 2007). Peak progesterone in the U.K. white sample is ~75 pg/ml, only ~60% as high as that in Chicagoans assayed by the same method in the same laboratory (Lu et al., 1997, 1999; Gann et al., 2001; Vitzthum et al., 2002). In non-migrant and adult-migrant Bangladeshi, luteal progesterone barely rises above follicular progesterone, resembling the distinctive profile of anovulatory cycles (Vitzthum et al., 2002) (see Fig. 4). Also, although described as "well-nourished" women (anthropometrics were not given), progesterone levels in these two samples are markedly lower than those in ovulatory cycles of very poor, chronically undernourished Bolivians (also assayed in the same laboratory [Vitzthum et al., 2002]), again suggesting that these two Bangladeshi samples include anovulatory cycles.

Inferring from what has been learned of the consequences of pre-natal (in utero) environments on post-natal health (e.g., Rinaudo and Lamb, 2008), it may be that developmental conditions starting early in gestation play some role in adult ovarian functioning, but this has yet to be demonstrated in humans. One study has reported that among Polish women engaged in only low physical activity, mean estradiol levels did not vary with ponderal index at birth (Jasienska et al., 2006b), suggesting that prenatal energetic conditions do not appear to influence the unstressed levels of adult ovarian steroids. Likewise, decades-long follow-up on the effects of the Dutch famine during 1944–1945 found no impact of in utero famine exposure on subsequent fertility in adulthood (Elias et al., 2005).

Genetic and epigenetic variation. The production of progestagens, androgens and estrogens, and the loci (in italics) coding for the enzymes acting in these pathways, are depicted in Figure 13. Of the few investigations of hypothesized links between variants in these loci and variation in hormone levels in healthy pre-menopausal women, most have not yielded any clear support for a relationship, perhaps because of serious limitations in study designs and analyses. Virtually all of these studies (discussed later) relied on a single measurement of a hormone to represent its varying levels during the entire ovarian cycle (see Fig. 3). In addition, with only one measurement, anovulatory cycles could not be identified and excluded from analyses. In some studies, there was little or no control for the day of the cycle on which the sample was taken, or for a woman's age or other potential confounders. As a consequence, the variance for a given hormone level in these study samples was typically very high, and the statistical power of the studies was low. Despite these problems, there are some data which suggest that genotypic variation may contribute to individual and populational differences in ovarian steroid levels.

The first step in the production of steroid hormones is the conversion of cholesterol to pregnenolone through the activity of cytochrome P450 11A1 (aka P450scc), coded by *CYP11A1* (Olson et al., 2007). Of the numerous known polymorphisms, only the pentanucleotide [TTTTA]*n* repeat (D15S520) has been examined for its relation to steroid levels; those few studies of this variant in healthy pre-menopausal women failed to observe any statistically significant hormone/genotype associations (Diamanti-Kandarakis et al., 2000; Daneshmand et al., 2002; Gaasenbeek et al., 2004). However, Garcia-Closas et al. (2002) reported 53% higher mean progesterone in those carrying the [TTTTA]4 repeat versus those who did not ($p = 0.17$). The lack of statistical significance was because of the very high variance in the sample of progesterone measurements, likely attributable to the study limitations discussed above. This study also failed to find significant variation in estradiol levels across genotypes, but the mean differences in estradiol

were much less striking than those for progesterone. Frequencies of [TTTTA]*n* variants differ among populations (Olson et al., 2007): $n = 4$ is the most common in northern Europeans (frequency ≈ 0.6), and $n = 6$ is the most common among Afro-Caribbeans, South Asians and Chinese (frequency $\approx$ 0.5–0.6). Thus, if [TTTTA]4 does generate higher progesterone levels than other alleles, this *CYP11A1* polymorphism may explain, in part, the higher progesterone levels observed in U.S. white women versus those observed in Bolivians, Nepalese and African women (see Fig. 10), but this hypothesis has not been tested.

CYP17A1 codes the enzyme, cytochrome 450c17α (see Fig. 13). A SNP (rs743572) that substitutes cytosine (A2 allele) for thymine (A1 allele) varies in frequency across populations: A2 homozygosity is 43% in U.S. Latinos, 30–35% in persons of East Asian descent, 20–24% in Japanese, and 10–20% in "whites" (Feigelson et al., 1999; Lai et al., 2001). In premenopausal women, Feigelson et al. (1998) reported higher progesterone levels in A1A2 and A2A2 compared with A1A1. Garcia-Closas et al. (2002) and Hong et al. (2004) failed to find such an association. Hong et al. (2004) observed a significant [$p = 0.007$] increase in dehydroepiandrosterone-sulfate with the A2 allele; Garcia-Closas et al. (2002) and Kahsar-Miller et al. (2004) did not. Of eight studies in premenopausal women, three reported that the A2 allele was associated with increased estradiol levels (Feigelson et al., 1998; Small et al., 2005 [but only in women with BMI $\leq$ 25]; Jasienska et al., 2006a) and five did not (Marszalek et al., 2001; Garcia-Closas et al., 2002; Hong et al., 2004; Travis et al., 2004; Lurie et al., 2005). However, seven of these studies relied on one sample to represent hormone levels over the entire cycle; the one study with high sampling density used an inappropriate statistical approach (Vitzthum and Thornburg, 2008).

CYP19A1 codes for aromatase, the rate-limiting catalyst for conversions of androstenedione to estrone in adipose tissue and testosterone to estradiol in ovarian granulosa cells. Although the gene is very large (114,452 base pairs), only two variants have been studied in premenopausal women: a [TTTA]*n* repeat (n = 7–13, 7 being the most common) and a [TCT] insertion/deletion (rs11575899). Repeat number was not associated with estrogen or androgen levels (Haiman et al., 2000; Garcia-Closas et al., 2002), but mean progesterone was 27% higher in those with one or more [TTTA]7 versus those with none ($p = 0.22$) (Garcia-Closas et al., 2002). Androgens were significantly lower in Swedes homozygous for the [TCT] insertion than in those with at least one deletion; insertion homozygotes had 26% higher (but not statistically significant) estrogen levels and a significantly higher estrogen/free testosterone ratio (Baghaei et al., 2003).

HSD3B1 and *HSD3B2*, which code 3β-hydroxysteroid dehydrogenases, share 93% homology but are active in different tissues. *HSD17B1* and *HSD17B2* code for 17β-hydroxysteroid dehydrogenase 1 and 2 which, respectively, reduces estrone to estradiol and oxidizes estradiol to estrone. Allelic variation is known to exist, but there are no genotype/hormone association studies in pre-menopausal women for these four loci (Olson et al., 2007).

Although there is no unequivocal evidence of genetic contributions to variation in ovarian steroid levels, the large differences in progesterone levels associated with *CYP11A1* and *CYP19A1* genotypes, and the differences in estradiol levels linked to *CYP17A1* alleles, argue for further study of these and the other loci involved in the biosynthesis of steroids. It is essential that future hormone/genotype association studies measure hormone levels with greater precision and accuracy, control for potential confounders, and use appropriate statistical methods.

Nonetheless, no matter how well such studies are executed, it is evident that genetic polymorphisms alone cannot fully explain variation in ovarian steroid levels. Reports that hormone levels vary substantially with socioeconomic status in the same population (Vitzthum et al., 2002) or with migration status (Falk et al., 2002) are strong evidence that gene-environment interactions (epigenetics) contribute to differences in hormone levels among women and populations. Such patterns are not readily attributable to typically small intergenerational changes in allele frequencies but could arise from gene-environment interactions that alter gene expression.

One biochemical mechanism intricately linked to gene expression is epigenetic modification of chromatin, that is, heritable changes external to the DNA nucleotide sequence (Jablonka and Lamb, 2002; Egger et al., 2004). These modifications, including methylation of deoxycytosine and modifications of histones, are responsible for altered gene expression patterns that allow for cell- and tissue-specific phenotypes (Jablonka and Lamb, 2002; Morange, 2002; Li, 2002). Epigenetics are thought to play a role in most diseases, as clearly demonstrated by developmental disease discordancy in monozygotic twins and the delayed (adult) onset of most heritable diseases (Bird, 2007).

Methylation patterns determined in utero are known to be susceptible to alteration by maternal nutrient intake. For example, *IGF2* is a maternally imprinted gene coding for insulin-like growth factor 2, which regulates fetal growth and development. Sixty years after conception, individuals conceived during the Dutch Hunger Winter (1944–45) had lower methylation at *IGF2* than siblings conceived at another time (Heijmans et al., 2008). Likewise, human populational differences in dietary patterns may influence adult steroid levels by modifying methylation patterns at the loci involved in steroid biosynthesis. There is growing evidence that epigenetic mechanisms help to regulate ovarian steroidogenesis (LaVoie, 2005; LaVoie and King, 2009). For example, DNA methylation affects expression in rodents of *CYP17A1* (Missaghian et al., 2009). The role of epigenetic mechanisms in generating variation in human ovarian steroid levels is entirely unknown, but these newest findings suggest that the contribution of epigenetic variants could be at least as significant as that of genetic polymorphisms.

LIFE HISTORY EXPLANATIONS FOR OVARIAN CYCLE VARIABILITY

> Individual adaptability ... is itself perhaps the chief object of selection. Sewall Wright 1931.

The origins and reproductive significance of individual and interpopulational variation in ovarian cycle attributes are, for the most part, riddles wrapped in an enigma. The keys to these puzzles can be found in LHT and in a better grasp of the ontogenetic mechanisms by which a developing organism integrates aspects of its habitat into the shaping of its adult form and function-

ing such that it responds adaptively to the challenges presented throughout life. Very little is known of these mechanisms, but fascinating research on epigenetic modifications holds enormous promise for understanding environment-gene dynamics and the processes of adaptation (Jaenisch and Bird, 2003; Fraga et al., 2005; Heijmans et al., 2008).

LHT makes it abundantly clear, despite current ignorance of molecular mechanisms, that life history phenotypes, including indicators of ovarian functioning, are the outcome of physiological and behavioral mechanisms that modulate reproductive investment in response to locally specific physical, biotic, and social conditions. Variation in ovarian functioning is only explicable in the context of a specific population and its habitat. There is no evolutionary reason for the reproductive functioning of women born and living in arduous conditions to be analogous to that of athletes, dieters, or even the lower end of the "normal range" of HPO functioning in wealthier populations (Vitzthum and Smith, 1989; Vitzthum, 1990, 1992b, 1997, 2001b, 2008b).

Current theory and evidence argue that the locally specific mortality schedule is a powerful factor driving life history strategies in a population and generating interpopulational variation in the biological and behavioral mechanisms by which these strategies are realized (Promislow and Harvey, 1990, 1991; Charnov, 2001). A recent study of 40 systems of prey exploited by humans dramatically demonstrated the substantial rapidity and magnitude of changes in life history traits as a consequence of increased mortality of reproductive-aged adults (Darimont et al., 2009). As predicted by LHT, reproduction in prey populations shifted to earlier ages and/or smaller sizes and reproductive investment increased; the average change in life history traits was 25%.

Human populations have also been found to exhibit life history strategies consistent with the hypothesis that increased adult morbidity and mortality schedules reduce the age at first reproduction (Chisholm, 1993, 1999; Chisholm et al., 2005; Geronimus et al., 1999; Geronimus, 2004). Other work also demonstrates that the forces driving the expression of life history traits in other organisms are operating in humans. Data from 17 natural-fertility populations supports an offspring quantity-quality trade-off in nonindustrial societies (Walker et al., 2008). Across populations, offspring size at 5 years old (a measure of parental investment) varied inversely with the energy-corrected fertility rate (i.e., those with smaller offspring had more offspring). Integrating growth, fertility and mortality data, Migliano et al. (2007) explained the extremely short stature of the Aeta and Batak as a trade-off between time invested in growth versus time invested in reproduction. In an elegant analysis, Strassmann and Gillespie (2002) were the first to demonstrate the trade-off between human female fertility and offspring survivorship.

Much more work is needed to generate satisfactory proximate and evolutionary explanations of variation in ovarian functioning. Nonetheless, currently available data do permit an initial evaluation of the predictions made by different models of human reproductive functioning.

Ovarian cycle length: more than opportunities

In the PDNF framework, cycle length is a potentially important fecundability factor because it determines the number of ovulations per month of exposure. This mechanical view is logical but fails to consider the biology underlying cycle length and its link to cycle quality. On the basis of the available data (Supporting Information Table S3), Wood and Weinstein's (1988, p 108) expectation that "well-nourished, healthy contemporary Western women would be near the lower extreme for this parameter" is not borne out (e.g., cycle lengths are equal in Bolivian and U.S. women of the same age).

There are few data on the relationship between cycle length and fecundity and/or fertility, and the reported findings may be confounded by undetected pregnancy losses. Two prospective studies reported a $\cap$-shaped relationship between fecundity and segment length. Danish women whose first observed cycle was 30–31 days had a higher rate of conception (number of conceptions/number of observed cycles) than those with longer or shorter cycles (Kolstad et al., 1999). Also, women whose first observed cycle equaled their own reported "usual cycle length" (interpreted as low cycle variability) had a higher conception rate than those whose usual and observed cycle lengths differed. If the difference was $\geq$10 days, the rate of conception was $<$50% of those with low variability. The authors concluded that low cycle variability was an even stronger predictor of conception than cycle length. U.S. women (Small et al., 2006) were more likely to conceive following cycles of 30–31 days than following cycles of longer or shorter duration, and conceptions following cycles shorter or longer than 30–31 days were more likely to end in pregnancy loss. However, the 95% confidence interval of the odds ratio in most of the analyses in this study encompassed 1.0 (i.e., were non-significant). Analyses of retrospective questionnaire data (Denmark: Jensen et al., 1999; U.S.: Rowland et al., 2002) reported a significantly lower probability of conception in women who had longer or more irregular cycles. In the U.S. sample, having long cycles was associated with a doubling in the adjusted odds of having a fetal loss. While these findings are provocative, caution is always warranted with recalled data.

Cycles in breastfeeding menstruating Bolivian women were 2 days longer than in those not currently breastfeeding (Supporting Information Table S3), but this increase was not associated with a reduction in fecundity (Vitzthum et al., 2001). In fact, the rate of conceptions was nearly twice as high among the lactating cycling women than among those women who were not currently breastfeeding, and their risk of pregnancy loss was comparable. These observations are consistent with the expectation that there is a higher proportion of more fecund women among the sample of currently lactating than non-lactating cycling women (see earlier discussion of selection bias). Also, it appears that a small lengthening of the cycle is not itself indicative of lower fecundity.

Tests of evolutionary models of reproductive functioning

Conceptions at low progesterone levels. Energetics models have extrapolated from the association between lower ovarian steroid levels and subfecundity *within populations* to argue that variations in steroid levels *across populations* are necessarily associated with variation in fecundity. Project REPA generated the data necessary to test this hypothesis. Serial collection of saliva and urine samples afforded correlation of steroid levels with specific conceptions and their outcomes (Vitzthum

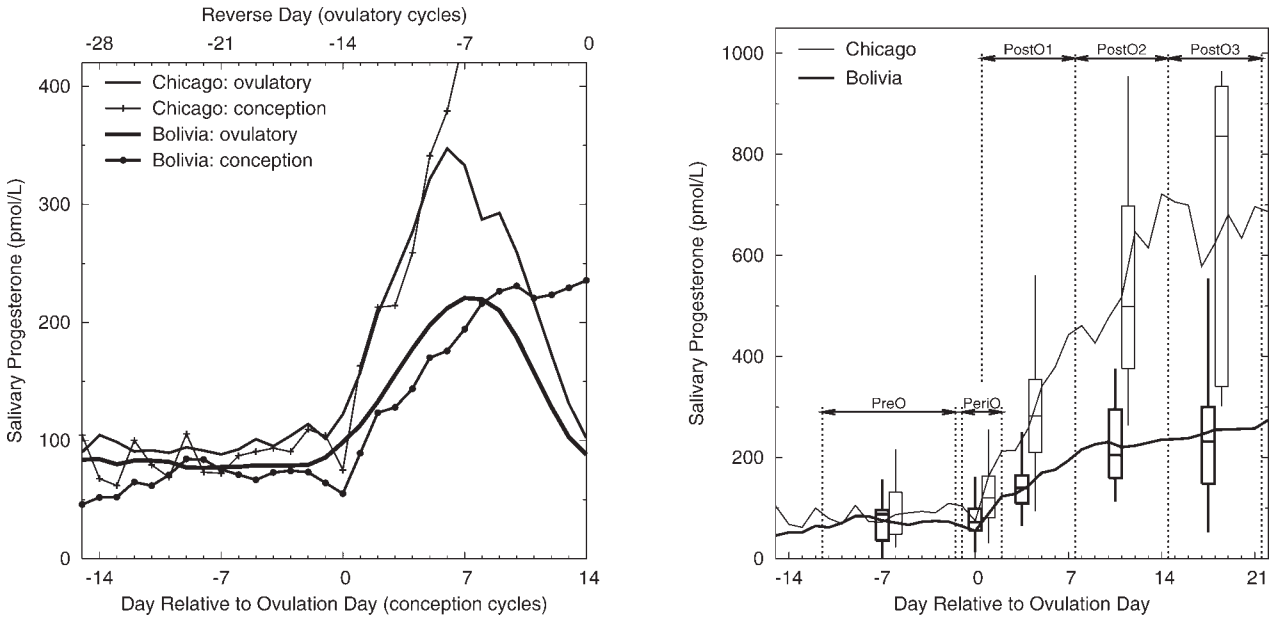

Fig. 14. Left plot: Salivary progesterone profiles in ovulatory non-conception and conception cycles in women from Chicago and rural Bolivia (cycle days 1–28). Ovulatory cycles are aligned on the first day of the subsequent cycle (days numbered backward); conception cycles are aligned on the putative day of ovulation (day 0). Progesterone levels in ovulatory cycles are significantly lower in Bolivian women than in women from Chicago throughout the ovarian cycle; in each sample, conception and ovulatory cycles have comparable progesterone levels. Right plot: Salivary progesterone levels in conception cycles through 21 days post-conception. Box plots display median, quartiles, and range of progesterone indices corresponding to the range of days delimited by vertical dashed lines to the respective left and right of box plot. Progesterone levels do not significantly differ in women from Bolivia and Chicago during the follicular phase but are significantly different during and subsequent to ovulation and through implantation. PreO = preovulatory, PeriO = periovulatory, PostO = postovulatory. (Reproduced from Vitzthum VJ, Spielvogel H, Thornburg J. 2004. Interpopulational differences in progesterone levels during conception and implantation in humans. Proceedings of the National Academy of Sciences USA 101:1443–1448. © 2004 by the National Academy of Sciences).

et al., 2004). In these rural Bolivians, progesterone levels in conceptions that were carried to full term were about 70% of those observed in a comparative sample of conception cycles from Chicagoans (see Fig. 14). Progesterone levels continued to be relatively lower throughout these pregnancies, and the live births were of normal weight (i.e., >2.5 kg). Furthermore, progesterone levels in ovulatory cycles from the same Bolivian women were not statistically different from those in the conception cycles. Consistent with the FRM, these findings argue that relatively lower progesterone levels are functionally adequate in this and perhaps in other populations. In addition, the fertility levels of these Bolivians do not suggest lower fecundability nor unduly prolonged interbirth intervals. Between the ages of 20 and 30 years, these women averaged four live births, each of which was breastfed on demand for 1–2 years and was associated with at least 1 year of post-partum amenorrhea in addition to 40 weeks of gestation. Clearly, these women have high fecundity despite their relatively low progesterone levels.

There are no other comparable studies of hormone levels at conception in women living in arduous conditions. At the population level there are some findings consistent with those from Project REPA, but these are subject to the caveat regarding the ecological fallacy. For example, most studies have reported ovarian steroid levels in Asian women to be $\leq$80% of the levels observed in "white" women in the U.S. and the U.K. (Dickinson et al., 1974; MacMahon et al., 1974; Trichopoulos et al., 1984; Bernstein et al., 1990; Key et al., 1990; Shimizu et al., 1990; Wang et al., 1991), yet none of the endocrinologists or epidemiologists conducting these studies suggested there was any difference in fecundity between women of Asian and European ethnicity nor could I locate any reports that such a difference might exist. In addition, Sylhet, Bangladesh has high fertility (Islam et al., 2004) yet its residents were reported to have progesterone levels <50% those of U.K. "white" women (Núñez-de la Mora, 2007b). However, because of selection bias and inadequate control for confounders, progesterone levels in Sylhet are likely to be much higher than reported (Thornburg, 2007; Vitzthum, 2007).

Acute versus chronic energetic stressors. In studies of women in industrialized countries, acute energetic stress is associated with reductions in ovarian steroids and a suite of other disruptions in the ovarian cycle including changes in the pulsatility and levels of FSH and LH, in durations of cycle and phases, and in the risk of anovulation. Hence, energetics models would predict that several characteristics indicative of subfecundity should be evident in those populations with low ovarian steroid levels. In contrast, the FRM argues that the effects of acute and chronic stressors are not comparable, and that women in chronically demanding habitats (which likely bear a closer resemblance to ancestral habitats than do modern industrialized settings), do not exhibit the suite of changes typically seen in women experiencing acute stress.

Data from Project REPA and other studies afford the opportunity to test these predictions. Progesterone levels

in the ovulatory cycles of rural Bolivian women (who consume about 1600–1800 kcal/day depending on socioeconomic status and season) are about 70% those of Chicago women (assayed in the same laboratory). Nonetheless, average cycle length in rural Bolivians is about 29 days and the variation is no greater than in other populations (Supporting Information Table S3). Ovulation frequency in a sample of better-off urban Bolivians is 88%, comparable to 91% observed in a sample of Chicagoans and to reports from industrialized populations (Supporting Information Table S6). Perhaps most importantly, gonadotrophin levels in the urban Bolivians are also similar to those observed in samples from industrialized countries, even though both salivary progesterone and serum estradiol levels are lower (Vitzthum et al., 2007a,b). This finding indicates that the relatively lower ovarian steroid levels in these Bolivian women are adequate for the regulation of the HPO axis; in other words, the central neuroendocrine regulator of reproductive functioning in these women is apparently not impaired. In sum, the data support the FRM.

Acclimatization to stressors. Energetics models predict that ovarian suppression persists as long as the energetic stress that prompted it continues. In contrast, the FRM argues that an organism can adjust to an initially stressful condition through the physiological processes known as acclimatization; i.e., after a period of time there will be a return to homeostasis and normal ovarian functioning. Acclimatization to environmental stressors is well documented in the physiology literature (e.g., the adjustments that occur when life-long sea-level residents travel to and then remain at high altitude). Selection favors mechanisms that return individuals to normal functioning, even if a stressor continues. In the simplest comparison, those who can adjust to the prevailing conditions and reproduce have an undeniable selective advantage over those who are unable to do so and die while waiting for conditions to get better. In the parlance of LHT, the trade-off between RV_p and RV_n changes with time because residual reproductive value (loosely, the number of opportunities left to reproduce) declines as one approaches the end of one's reproductive life.

This prediction of the FRM is supported by experimental studies in animals (e.g., Barker-Gibb and Clarke, 1996), but there is only a single study to address this question in humans. Langenberg et al. (2009) collected daily urine samples for nine weeks during in-season training and off-season recovery in 17 competitive athletes. On the basis of hormonal profiles, they proposed that these athletes became acclimated to training during the season and did not experience disruption of reproductive function, possibly because of various counter-regulatory mechanisms.

The role of energetics in women's reproductive functioning

Collectively, the findings from anthropological, epidemiological, clinical, and laboratory studies are consistent with the hypothesis that short-term perturbations in women's reproductive functioning are potentially adaptive in that reductions in reproductive effort co-occur with energetically stressful conditions that could have a negative impact on a woman's health status and also on fetal growth and development, and ultimately on infant survivorship and Darwinian fitness. Even if such responses are not adaptive, it is clear that such changes in ovarian functioning do occur when faced by energetic stressors. But more study is needed to learn why there are substantial differences among women in their responsiveness to these challenges.

A relatively much smaller body of data, consistent with the FRM and LHT more generally, suggests that the response to chronic energetic stress differs from that to acute energetic stress (Vitzthum, 1990, 1992b, 1997, 2001). In habitats characterized by limited food resources and demanding physical activity (which has likely been the norm throughout human history until very recently), a number of life history strategies other than reducing offspring number may be engaged including smaller maternal body size, smaller offspring size, and initiating reproduction earlier (Stearns, 1992). It should not be assumed that such strategies are undesirable. For example, smaller infant size does not carry the same risk of mortality in every population. The distribution of birth weight in Mexican–American babies is shifted to the left (i.e., is lower) than that of U.S. white babies, but Mexican–American babies have better overall survival (Wilcox, 2001). Of course, energetic resources are important (as are other resources; see Chisholm (1993), Chisholm et al. (2005), and Geronimus et al. (1999)), but there are many ways to meet these challenges. LHT does not yet have the tools to predict which combination has been favored by selection in a specific population (Stearns, 1992).

Energy is a necessary, but not sufficient, resource for life itself. But energetic factors are not proximate determinants—they influence human reproduction only by modifying one or more PDNF. Nor is any energetic factor an ultimate explanation of reproductive functioning. Selection does not operate to conserve energy nor to maintain energy balance. To the contrary, evolution involves expending resources on offspring. "Optimal" LHSs, defined only by multi-generational fitness, need not be energetically efficient. They merely need to outpace—within the bounds of phylogeny, genetics and physics—any alternative allocation strategy possible in the local habitat.

CLOSING REMARKS

> We seldom really know the things we think we know. Mark Twain, 1909.

Reproductive ecologists have established a foundation for developing evolutionary explanations of temporal, individual, and populational variation in women's ovarian functioning. Yet the rapid growth of this knowledge belies how much remains unknown. Although some studies have no doubt been missed (please alert me to these), a good-faith effort was made to bring together most of the relevant available data for this review. Doing so reveals a few clear patterns and highlights avenues for future research.

It is inescapable that marked variation—between cycles, women, and populations—is the norm rather than an aberration. But most of these differences remain unexplained and, in fact, the full extent of variation in human ovarian functioning is likely not yet documented. Ovarian steroid levels vary greatly within and across populations, but no consistent pattern is yet apparent. The possibility that genetic differences and/or epigenetic

TABLE 5. Factors generating cycle variation

	Sample		Segment				
	(US unless noted otherwise)	Source	Length	Variability	Menses	Follicular phase	Luteal phase
Increasing age to 40 years old	Several	See text	Shorter	Less	Shorter?	Shorter	Shorter?
Asian vs. whites	20–44 years; n = 309; ovulatory cycles	Liu et al. (2004)	Longer			Longer in <35 years	NS
Smoking	21–40 years; 3941 agriculture workers	Rowland et al. (2002)	Shorter	More			
	20–44 years; n = 309; ovulatory cycles	Liu et al. (2004)	NS			Shorter in ≥35 years	NS
Alcohol	29–31 years; n = 766	Cooper et al. (1996)	Shorter	Less			
	20–44 years; n = 309; ovulatory cycles	Liu et al. (2004)	Shorter			Shorter in ≥35 years	NS
Physically active	29–31 years; n = 766	Cooper et al. (1996)	Longer	More	Shorter		
	20–44 years; n = 309; ovulatory cycles	Liu et al. (2004)	NS			Longer in <35 years	NS
Physically active occupation	South India; <15 to >40 years; n = 2566	Jeyaseelan and Rao (1995)	Longer				
Increasing body fat	Austria; 20–62 years; n = 327	Kirchengast (1997)	Shorter				
Increasing height	Idem	Ibid.			Longer		
Increasing BMI	24–45; n = 436	Symons et al. (1997)	Longer	More			
BMI: lowest decile	Idem	Ibid.	Longer				
Increasing BMI	21–40 years; 3941 agriculture workers	Rowland et al. (2002)	Longer	More			
BMI	20–44 years; n = 309; ovulatory cycles	Liu et al. (2004)	NS			NS	NS
BMI: very high or very low	India; 24–36 years; n = 200	Williams (2006)	NS	More			
BMI: lowest quartile	29–31 years; n = 766	Cooper et al. (1996)	Longer	More	Longer		
Taller or leaner	Idem	Ibid.			longer		
Higher ponderal	10 nations; mean age = 29 years; n = 164	Belsey et al. (1988)		Less			
Increasing body fat	Bolivia; 20–38 years; n = 191	Miller et al. (2002)			Longer		
Lower social status	Denmark; 15–44 years; n = 1301	Münster et al. (1992)		More			
Less education	South India; <15 to >40 years; n = 2566	Jeyaseelan and Rao (1993)	Longer				
Rural (vs. urban)	Idem	Ibid.	Longer	More			
High altitude (hypoxia)	Bolivia; 20–38 years; n = 191	Vitzthum et al. (2000b)	NS	NS	NS		
Breastfeeding	Idem	Ibid.	Longer		NS		
Menarche <12 years	21–40 years; 3941 agriculture workers	Rowland et al. (2002)	Shorter				
Menarche ≥15 years	Idem	Ibid.	Longer	More			

NS, non-significant.

mechanisms are important remains an open question (Jablonka and Lamb, 2002; Sharp et al., 2004; LaVoie, 2005; LaVoie and King, 2009; Small et al., 2005; Jasienska et al., 2006a; Olson et al., 2007; Vitzthum and Thornburg, 2008; Missaghian et al., 2009).

The mean (or median) cycle length across populations falls between 27 and 31 days except for the Papua New Guinea sample at 36 days (Johnson et al., 1987). In the few relevant studies, cycle length decreased with age but then increased during peri-menopause. Within a population, the follicular phase accounts for most of the variation in cycle length. Phase lengths appear to vary little across populations, but there are few data from non-industrialized countries. Women 20–40 years old usually have lower risks of anovulation than younger and older women. Some pre-menopausal New Zealand and poor Bolivian women show high risks for anovulation. Menses duration varies approximately two-fold across the world, for unknown reasons.

Several factors are associated with greater variability or changes in segment length (Table 5), but the findings across studies are disparate. There is little agreement on the relationship between cycle or phase lengths and hormonal variation (this has not been studied in non-indus-

trialized populations). These different findings may be attributable, in part, to participants' ages, using retrospective data, lack of control for potential confounders, inclusion of anovulatory cycles, excluding cycles that are outside a specified range (which may eliminate significant variation), and using a single sample to represent a cycle's hormone level. Some studies have reported significant variation in ovarian steroids from 20 to 40 years of age, but others have not. Apparent age-associated variation often vanishes when only ovulatory cycles are considered. From the perspective of LHT, there is no reason to expect identical patterns of age-variation across populations, but the data are inadequate for assessing this question.

Behavioral studies would benefit from a greater appreciation of the variability in hormonal patterns. It is untenable to assume an idealized hormonal profile or day of ovulation (or that it even occurs). Efforts to correlate variation in a behavioral, cognitive, or physiological trait with assumed changes in the ovarian cycle are rightly open to criticism. Even statistically significant correlation can arise from some confounder rather than from the purported association with an assumed hormonal status. As well, ignoring cyclical hormonal variation is no more warranted than assuming it. Few studies of human variation and adaptation have specifically attended to the potential influence of cyclical hormone changes on outcome variables.

Sample selection, collection, and analyses must be explicitly described, with sufficient detail (including descriptive statistics of sample characteristics) to allow comparisons by others. Selection bias is also a concern. For example, in a natural fertility population, cross-sectional studies of non-pregnant, non-lactating women may be excluding the most fecund women (those most likely to be pregnant or lactating, and hence unavailable for recruitment). This effect may be quite large. Lactating menstruating Bolivians (who would typically be excluded from cross-sectional studies) conceived at about twice the rate of non-lactating menstruating women (Vitzthum et al., 2000b) and had 18% higher mean peak progesterone than those who had been non-lactating for $\geq$180 days (Thornburg and Vitzthum, 2009).

There are also many subtleties in analyzing hormonal data. Ovulatory and anovulatory cycles are best separated before estimating hormonal indices; in some studies where this has not been done, there's no knowing if apparent changes in hormone indices can be explained wholly or partly by differing anovulation risk. Multiple cycles from the same woman are *not* statistically independent, so if, for example, they are treated as separate data points in a *t*-test, the computed significance level is meaningless. Multi-level models (West et al., 2007) or bootstrap methods (Efron and Gong, 1983; Efron and Tibshirani, 1986) may be more appropriate.

The PDNF model highlights the dependency of fertility on factors other than ovarian functioning. Wood's framework is a valuable tool for delineating the specific biological and behavioral pathways by which varying environmental conditions influence fertility. The statistical analysis of fertility determinants is not the ultimate theoretical goal. Rather, Wood stressed that a "focus on the proximate determinants [is] merely a necessary first step toward assessing the effects of more remote influences ...; [it] can be thought of as an accounting frame within which to specify the precise mechanisms whereby remote influences act upon the reproductive process" (1990).

The modulation of reproductive effort in humans extends, of course, beyond conception. Ovarian functioning continues to play a critical role in adjusting these investments, including those necessary for the maintenance of early pregnancy (Csapo et al., 1972; Sunder and Lenton, 2000; Norwitz et al., 2001; Baird et al., 2003; Vitzthum, 2008a). In fact, a prospective study of nearly 500 Bangladeshi women observed little decline in fecundity with age but dramatic increases in EPL (Holman, 1996; Holman et al., 2000; Holman and Wood, 2001). These findings suggest that the role of the HPO-axis in regulating reproductive effort may be as important after fertilization as before. The few weeks following conception and implantation present a low cost opportunity to curtail investment if maternal evaluation of offspring quality and available resources find either to be inadequate (Haig, 1990, 1993, 1999; Stearns, 1987; Nepomnaschy et al., 2006; Vitzthum, 2008a). The approximately two-fold seasonal variations of EPL risk in Bolivian (see Fig. 12) (Vitzthum et al., 2009a) and North Carolinian women (Weinberg et al., 1994) support this hypothesis: seasonal variation would *not* be expected if EPL were overwhelmingly attributable to genetic defects of the conceptus (as had been hypothesized by Bishop, 1964). Determining the mechanisms that regulate pregnancy termination if environmental conditions and/or maternal status are less favorable than usual is an exciting area for further investigation.

LHT is a foundation for developing explanantory models and generating testable hypotheses regarding women's modulation of reproductive effort. Both theory and present evidence argue that the reproductive functioning of women born and living in arduous conditions is not analogous to that of athletes, dieters or even the lower end of the "normal" range of HPO functioning in women accustomed to richer environments. The reproductive system is not designed, as Malthus had supposed, to keep chugging along unless prevented by incapacity, self-restraint, or some exogenous factor. Rather, the biological mechanisms have been shaped by natural selection to function in a manner appropriate to context. The temporary suspension of reproductive investment is no more a failure of adaptation than the "freezing" (motionless) response of an animal faced by a predator is a failure of locomotory adaptations. Rather, even though it may reasonably be argued that legs are made for walking, by allowing the organism to be still in appropriate circumstances, the locomotory system is performing in a manner that increases the animal's fitness. The legs are functioning adaptively, even if they are not in motion. Likewise, adaptive reproductive functioning in the human female can include not conceiving. For each individual, the ontogenetic interplay of genotype and environment gives rise to behavioral and physiological mechanisms that modulate reproductive investment in response to locally specific physical, biotic, and social conditions. From this vantage point, we can test whether curtailed investment in reproduction is selectively advantageous, even if termination is subsequent to conception and implantation. Contrary to the widespread assumption that humans have low fecundity and an inefficient reproductive system, we may actually have very high fecundity and a reproductive system that has evolved to be flexible, ruthlessly efficient and, most importantly, strategic. Only additional data

will be able to help us in deciding which characterization is more accurate.

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