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New Paradigms for the Female Reproductive System

Menstrual Cycling and Breast Cancer: An Evolutionary Perspective

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ABSTRACT

This article attempts to bridge the disciplinary gap between evolutionary biology and clinical studies of women's health. The resulting dialogue is predicted to have useful implications for research aimed at the prevention of women's reproductive cancers. The specific focus is on the relationship between breast cancer and exposure to ovarian hormones during normal menstrual cycling. The clinician's view of normal cycling is radically different from that uncovered by evolutionary studies of noncontracepting populations. This point is illustrated by data on the Dogon of Mali, a traditional West African population with a mean of 8.6 ± 0.3 live births per woman. The Dogon data include hormonal profiles (urinary estrone-3-glucuronide and pregnanediol-3-glucuronide) of 93 women (sampled twice weekly for 10 weeks) and a census of women's visits to menstrual huts (n = 736 days). Dogon women menstruated regularly only if they were sterile. Otherwise, women aged 20–34 years had a median of only two menses each over the 2-year study period. The median number of menses per lifetime was approximately 100, about a third as many as experienced by an American woman who had three live births. These results contribute to a growing body of evidence that women's bodies were designed by natural selection to spend most of the time in lactational amenorrhea and add support to the view that contraceptives can be made safer if they forego the hormonal swings associated with menstruation. This conclusion is further reinforced by evidence that menstrual bleeding serves no adaptive purpose.

INTRODUCTION

BREAST CANCER WILL AFFLICT approximately one in eight North American women.[1] Less than 2% of all breast cancers are caused by heritable mutations.[2] A likely contributor to the remaining 98% of cases is a drastic change in life history patterns that has skyrocketed women's exposure to the endogenous steroid hormones estrogen and progesterone.[3,4] Compared with noncontracepting foragers and traditional agriculturalists, women in industrialized nations experience earlier menarche, lower parity, later first birth, and nursing of shorter intensity and duration.[4] Epidemiologic evidence links each of these changes to an increased risk for breast cancer.[5–7] Part of the underlying mechanism appears to be an increased proportion of the life span spent in menstrual cycling as opposed to lactational amenorrhea.[3,4,8] During menstrual cycling, the ovarian

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hormones stimulate cell proliferation in breast epithelium, enhancing the risk for the random genetic errors that lead to malignancy.[8–10]

Epidemiologic and clinical studies of menstruation have focused almost exclusively on contracepting populations, but reproductive patterns in these populations are radically different from the patterns that prevailed over the majority of human evolutionary history.[3,4] I examine menstruation in the absence of contraception to obtain a baseline against which the evolutionarily novel patterns of clinical populations can be compared.

FIG. 1. Dogon menstrual hut. In the background are granaries in the village of Sangui.

MENSTRUATION IN THE ABSENCE OF CONTRACEPTION

Menstruation in the absence of contraception has been studied among the Gainj of Papua, New Guinea,[11] the Lese of Zaire,[12] and the Dogon of Mali.[13] The Gainj study was pioneering but was based on a small sample (n = 23 cycles). The Lese sample was larger (n = 89 cycles in 1984 and 178 cycles in 1987) and has been a valuable source of information on the relationship between energy balance and ovarian function.[14,15] With the exception of a preliminary report,[12] the Lese data have not been analyzed for the purpose of characterizing menstrual patterns over the life course. The Dogon study included a total of 477 cycles, and the prevalence of primary sterility in the study village was <1%.[13,16] This low incidence of sterility made it possible to observe menstrual patterns in the absence of the confounding effect of sexually transmitted diseases (STDs). In populations with a high incidence of sterility, many women display the menstrual profiles associated with women using contraceptives: repeated menses without pregnancy.[13,16]

The Dogon live along a sandstone cliff, called the Bandiagara escarpment, and are a natural fertility population with a total fertility rate of 8.6 ± 0.3 live births per woman.[17] They are particularly amenable to the study of menstruation because strict taboos require menstruating women to sleep at a menstrual hut (Fig. 1). The function of these taboos is to force women to advertise their reproductive status.[17,18] When a woman visits a menstrual hut, all members of her husband's patrilineage learn that she is cycling rather than pregnant or in amenorrhea, which means that she is potentially fecundable. Information about the timing of conceptions is used in paternity assessments. By censusing the women present at the menstrual huts in the study village on each of 736 consecutive days, it was possible to detect menstruation without interviews and thereby to avoid a potential source of reporting bias.[17,18]

How accurate is menstrual hut visitation as an indication of menstruation? The explorer Samuel Hearne described menstrual taboos in the Hudson Bay area in the 18th century.[19] He concluded that cheating is rampant.

> There are certain periods at which they never permit the women to abide in the same tent with their husbands. At such times they are obliged to make a small hovel for themselves at some distance from the other tents. . . . It is also a piece of policy with the women, upon any difference with their husbands, to make that an excuse for a temporary separation. . . . This custom is so generally prevalent among the women, that I have frequently known some of the sulky dames [to] leave their husbands and tent for four or five days at a time, and repeat the farce twice or thrice in a month, while the poor men have never suspected the deceit.[19]

To determine whether or not menstrual hut visitation is a reliable indication of menstruation among the Dogon, urine samples were obtained from 93 women twice weekly for 10 weeks. After storage in liquid nitrogen and transport to a laboratory, the samples were assayed for pregnanediol-3-glucuronide (PdG), a metabolite of progesterone, and estrone-3-glucuronide (E1G), a metabolite of estrogen, using ELISA methods as described elsewhere.[18,20] A comparison of the timing of the women's visits to the menstrual huts

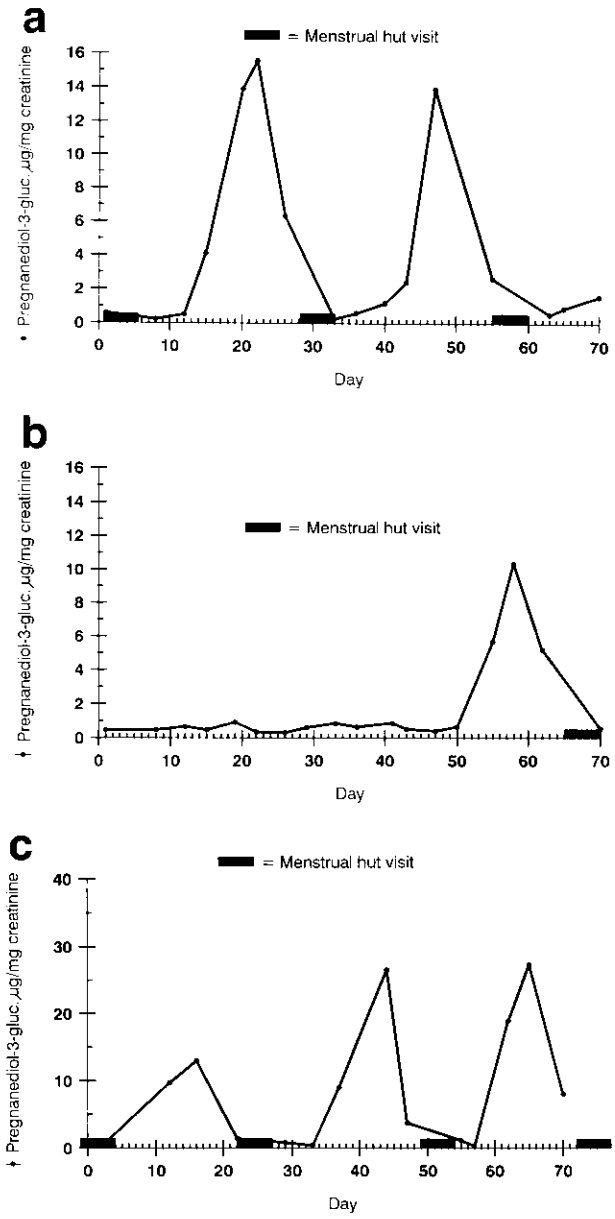

FIG. 2. Hormone profiles for three Dogon women (**a,b,c**) and the timing of their visits to a menstrual hut. Note that they went to the hut only after pregnanediol withdrawal when they were, in fact, menstruating. (From Strassmann.[18])

with their hormone profiles indicated that women went to the huts during 86% of all menses (Fig. 2). Women did not go to the huts in the absence of bleeding (except for one visit by a pregnant woman who appears to have been spotting).[18] Prospective monitoring of 25 pregnancies indicated that all 25 births occurred approximately 9 months after the mother's last visit to the menstrual huts.[17] These results confirmed the overall reliability of menstrual hut visitation as an indication of menstruation.

According to the menstrual hut census, 67 women had a total of 553 menses and 58 women had a total of 477 uncensored cycles (i.e., complete cycles, untruncated by the beginning or end of the study). In this 2-year study, most of the cycles that still were ongoing at the end of the study were actually conception cycles, as indicated by a prolonged absence from the menstrual hut followed by a documented birth. These conception cycles were excluded from the calculation of cycle length. The median of the women's median cycle lengths was 30 days (lower and upper 95% confidence limits were 30.0 and 32.0 days, $n = 58$ women, 477 cycles).[13] Exclusion of cycles longer than 46 days ($n = 73$) or shorter than 17 days ($n = 4$), which were statistical outliers,[21] brings the median of the women's median cycle lengths down to 28.5 days (lower and upper 95% confidence limits were 27.5 and 29.0 days, $n = 54$ women, 400 cycles).[13] Estimates of cycle length for any population reflect the age structure of the sample (here the age range was 15–53 years, mean age ± standard deviation was 30.9 ± 9.7 years), but median cycle length among the Dogon was biologically indistinguishable from that reported for Western populations.[22–24] The absence of contraception had no detectable influence on median cycle length.

How many menses did women typically experience before the advent of contraception? Existing conjectures on this topic are widely divergent and range from about 35 to 160 menses per lifetime.[4,25] Neither of these estimates, however, is based on empirical data on menstruation. The median number of menses for Dogon women over the life span was 94. This value was calculated from the median number of menstrual hut visits by women at each age from menarche (median age 16 years) to menopause (median age 50 years). As Dogon women were absent from the menstrual hut during 14% of all menses, a total of 94 menses per life time may be an underestimate. After correction for the absences from the menstrual hut, the estimated median number of menses per lifetime was 109.[13]

The best evidence on the number of lifetime menses in contracepting populations derives from longitudinal studies in the United States ($n = 2702$ women)[23] and Switzerland ($n = 691$ women).[24] For example, an American physician who had three live births experienced a total of

355 menstrual cycles.[23] She had a little over three times as many menses as noncontracepting Dogon women. In view of the link between the number of menstrual cycles and breast cancer risk, this comparison may help to explain the breast cancer epidemic in the United States and other developed countries.[3,4,8] Data on the incidence of breast cancer among the Dogon are unavailable, but in urban West Africans (whose menstrual patterns are similar to those of the Dogon), the incidence of breast neoplasm is only 1/12 that of North American women.[26]

In the absence of contraception, how is menstruation patterned over female life histories? As previously predicted,[25] menstruation had an approximately U-shaped relationship with age between menarche and menopause (Fig. 3). After excluding women who never menstruated because of pregnancy and amenorrhea, women aged 15–19 years had a mean of 11 menses during the 2-year study period, women aged 20–34 had 4 menses, and women 35 years and older had 13 menses ($n = 50$). Menstruation was a rare event for women during the primary childbearing years (20–34 years) (Fig. 4). Over the 2-year study period, the mean proportion of time spent in menstrual cycling for women of this age group was only 0.15 ± 0.07. The mean proportion of time occupied by postpartum amenorrhea was

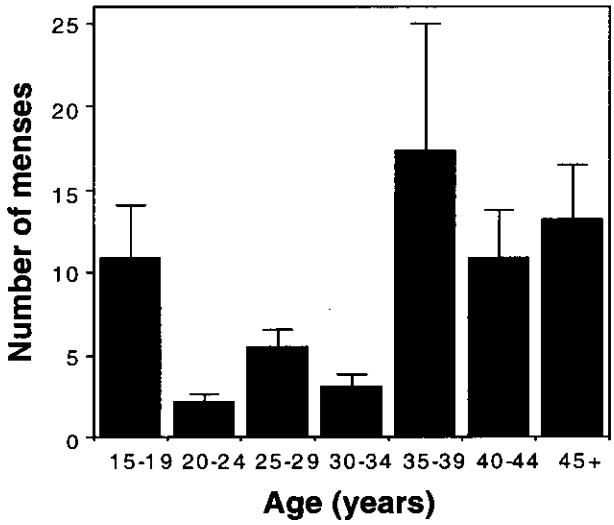

FIG. 3. Mean number of menses per woman per 2 years (the duration of the study). Women who never menstruated during the study are excluded. Error bars are standard errors of the mean. $n = 50$ women. (From Strassmann.[13])

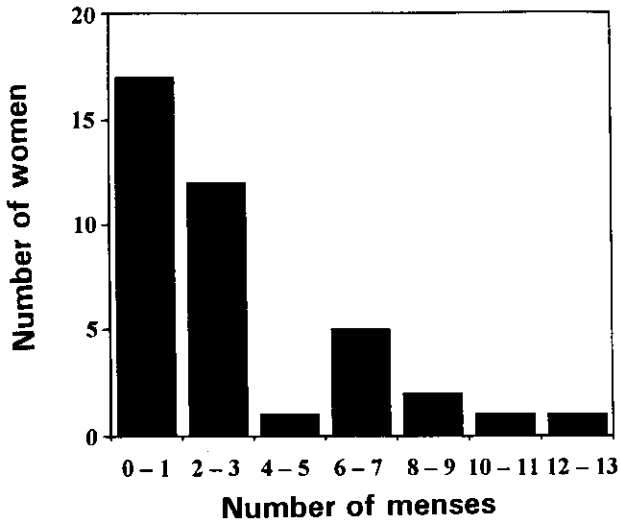

FIG. 4. Number of menses for women aged 20–34 years during the 2-year study. $n = 39$. This figure includes data for women who never menstruated during the study. (From Strassmann.[17])

nearly twice that of pregnancy (0.56 ± 0.07 versus 0.29 ± 0.05) (Fig. 5). The reproductive profile of 122 women over the 24 months of the study is shown in Figure 6. On a given day, a mean of 25% of the women were cycling, 16% were pregnant, 29% were in lactational amenorrhea, and 31% were postmenopausal.[13]

Based on survival analysis, fecundability—or the monthly probability of conception—reached a peak value of 0.19 at age 26–29 years.[16] The

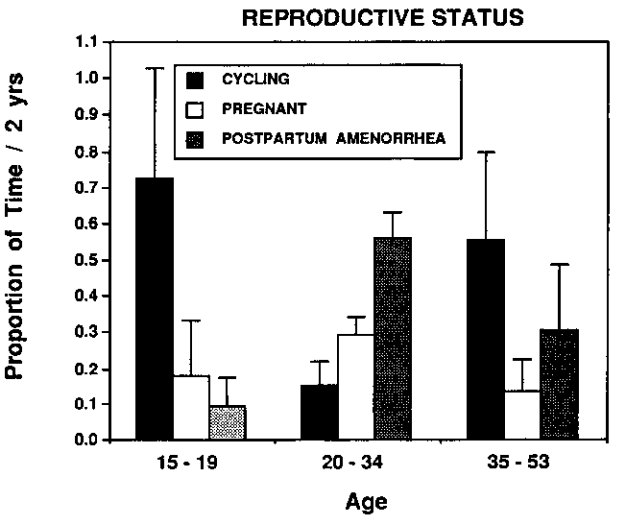

FIG. 5. Variation in reproductive status with age between menarche and menopause. $n = 66$. Bars are means; extensions show 95% confidence limits. (From Strassmann.[17])

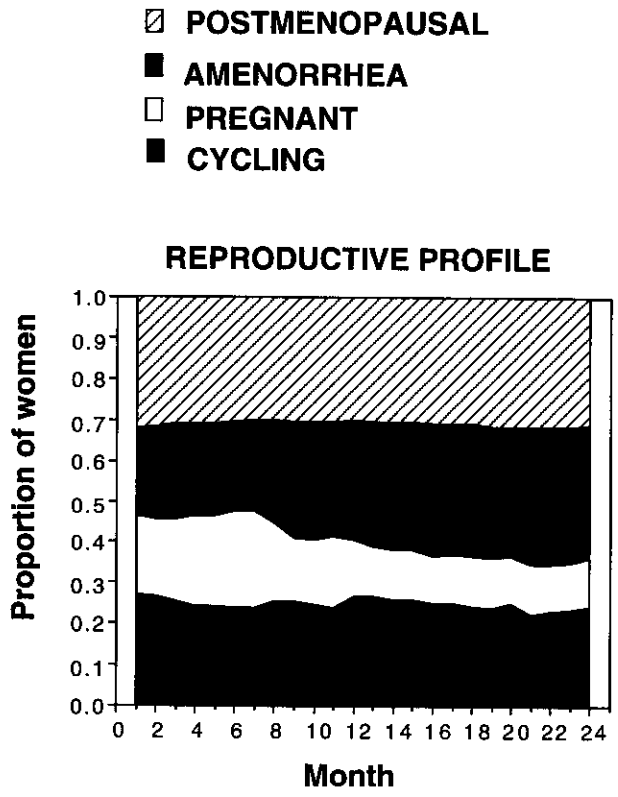

FIG. 6. Reproductive profile for the women (n = 122) of the study village over 24 months. (From Strassmann.[13])

younger and older women who did most of the menstruating had much lower fecundability (Fig. 7). They kept on menstruating because they failed to get pregnant. Other studies corroborate the overall pattern shown here.[27]

Regular menses were a sign of sterility, not fecundity. The most fecund women conceived on one of their first postpartum cycles, whereas the less fecund women continued to cycle regularly. In the age cohort 20–34 years, the Western pattern of repeated cycling was displayed only by two women who were sterile. They had 23 and 29 menses each during the 2 years of the menstrual hut census, whereas all their age-mates had a median of only 2 menses.[13,17]

MEDICAL IMPLICATIONS

In summary, women's reproductive profiles in modern industrial societies are very different from those of noncontracepting populations.[3,4,13,25] Over human evolutionary history, the majority of our ancestors probably had reproductive profiles that were much more similar to those of the Dogon than to those of the women in most clinical studies.[13] One of the medical implications is that physicians need to reassess what is normal. Amenorrhea in young women is often treated as if it were a pathologic state, yet as first noted by Short, women's bodies were designed by natural selection to spend most of the time in lactational amenorrhea.[3] According to the epidemiologic evidence, if a woman spends more time in amenorrhea and less time in menstrual cycling, she lowers her risk for reproductive cancers.[3,4,8] Even comparatively short breaks from menstrual cycling seem to reduce cancer risk, so it may be worth asking whether or not amenorrhea should be treated in women not trying to conceive.

Another suggestion is that contraceptives need not be designed to make a woman go through hormonal withdrawal and menstruation every month.[3,4,8–10] They were designed this way on the erroneous assumption that regular menses are normal. Instead, contraceptives should be designed so as to provide the greatest overall benefits to women's health. The combination oral contraceptives (COCs) used by millions of women today are associated with a substantial reduction in the risk of ovarian and endometrial cancers.[9,28] However, because of synthetic estrogen and progestogen, both of which are breast mitogens, COCs fail to protect against breast cancer.[9,28] Medroxyprogesterone acetate (MPA) (marketed under the trade name Depo-Provera or Farlutal 500 AD) is an injectable contraceptive that suppresses ovulation and menstruation for up to 1

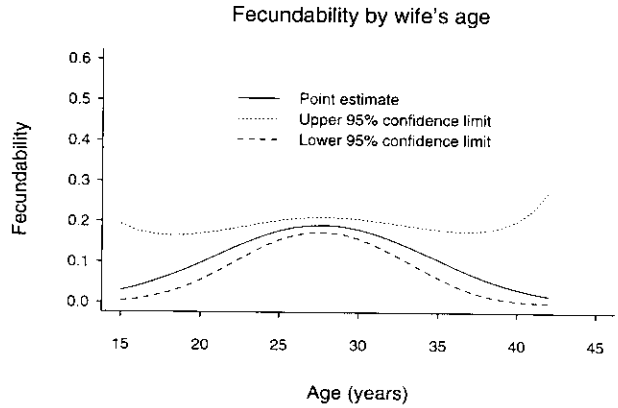

FIG. 7. Fecundability by wife's age (n = 50). (From Strassmann and Warner.[16])

year, depending on dosage and individual response.[29] Because of substantial amounts of synthetic progestogen, MPA also does not reduce breast cancer risk.[9]

An alternative contraceptive is under development that is aimed at protecting against all forms of reproductive cancer in women.[8–10] This contraceptive would employ an agonist of gonadotropin-releasing hormone (GnRHA) to reversibly suppress ovarian function and add-back sex steroids at doses below those of COCs. Menstrual bleeding would be reduced to three or four times per year. The dose of add-back steroids would need to be high enough to prevent the adverse effects of hypoestrogenemia, which is associated with osteoporosis, heart disease, and Alzheimer's disease in postmenopausal women.[30–32] The dose of estrogen used in postmenopausal estrogen replacement therapy appears to be high enough to meet this criterion yet is still low enough to reduce breast cancer risk below that of current COCs.[8–10] Use of this new contraceptive for 5 years has been predicted to reduce lifelong breast cancer risk by 31%, and 15 years of use might cut risk by as much as 70%.[8–10]

THE EVOLUTION OF MENSTRUATION

A second, related topic is: Why did menstruation evolve in the first place? Menstrual complaints, including premenstrual syndrome, amenorrhea, and dysmenorrhea, are among the most frequent reasons for visits to the gynecologist. Medical research on these gynecologic problems has illuminated many of the proximate mechanisms that trigger menstruation but has largely ignored the functional significance of menstruation. The study of the adaptive significance of a trait, such as menstruation, is often dismissed as teleologic, but this concern can be misplaced. What would happen if an eye surgeon did not know that the eye is designed for seeing or if a heart surgeon did not know that the heart is designed for pumping blood? Although the selective background for menstruation is more obscure than that for the eye or the heart, it would be imprudent to conclude that it can be safely dismissed. Gynecologists routinely intervene to suppress or induce the menses. This gets the body's machinery working the way the physician thinks it should. But would not these interventions be better informed if we knew why women menstruate in the first place?

That is the question recently posed by evolutionary biologists and other researchers interested in the origins of menstruation. Research on this question has just begun, and I highlight this field as one of the areas in which further investigation is needed. Such research demands an interdisciplinary effort between evolutionary biology and gynecology. Profet, one of the instigators of this inquiry, suggested that menstruation evolved to rid the uterus of sperm-borne pathogens.[33] She argued that contraceptives that suppress the menses may lead to uterine infection. However, rather than squelching infection, menstrual blood is exacerbatory because of amino acids, proteins, and sugars that provide an excellent culture medium for bacteria.[34,35] Existing reviews have found the hypothesized hygienic function for menstruation to be incompatible with the evidence.[36–39]

An alternative approach argues that there are really two phenomena to be explained: (1) the cyclicity of the endometrium, which is the lining of the uterus, and (2) vaginal bleeding.[38,39] During each cycle, the endometrium proliferates, developing a high secretory capacity and a micronetwork of vascular support. If implantation and pregnancy do not occur, the endometrium regresses. Anatomists have established that the cyclic growth and retreat of the endometrium through reabsorption are found throughout the mammals.[40–42] Vaginal bleeding is found only in humans, apes, Old World monkeys, and shrews.[38]

Current unerstanding of the evolutionary relationships among the primates and the variation in the degree of menstrual bleeding is shown in Figure 8. All primates have endometrial regression, but only certain Old World species, such as chimpanzees (*Pan troglodytes*) and humans, have copious bleeding.[38] Even in humans, about two thirds of the endometrial tissue is reabsorbed rather than shed.[42–44]

A hypothesized function of endometrial cyclicity is energy economy, whereas vaginal bleeding is proposed to be a side effect that arises when there is too much blood for efficient reabsorption.[38,39] In all mammalian species, the endometrium can only sustain implantation by the embryo during a fraction of the cycle. This fraction coincides with the period when an embryo might actually be available to implant. In hu-

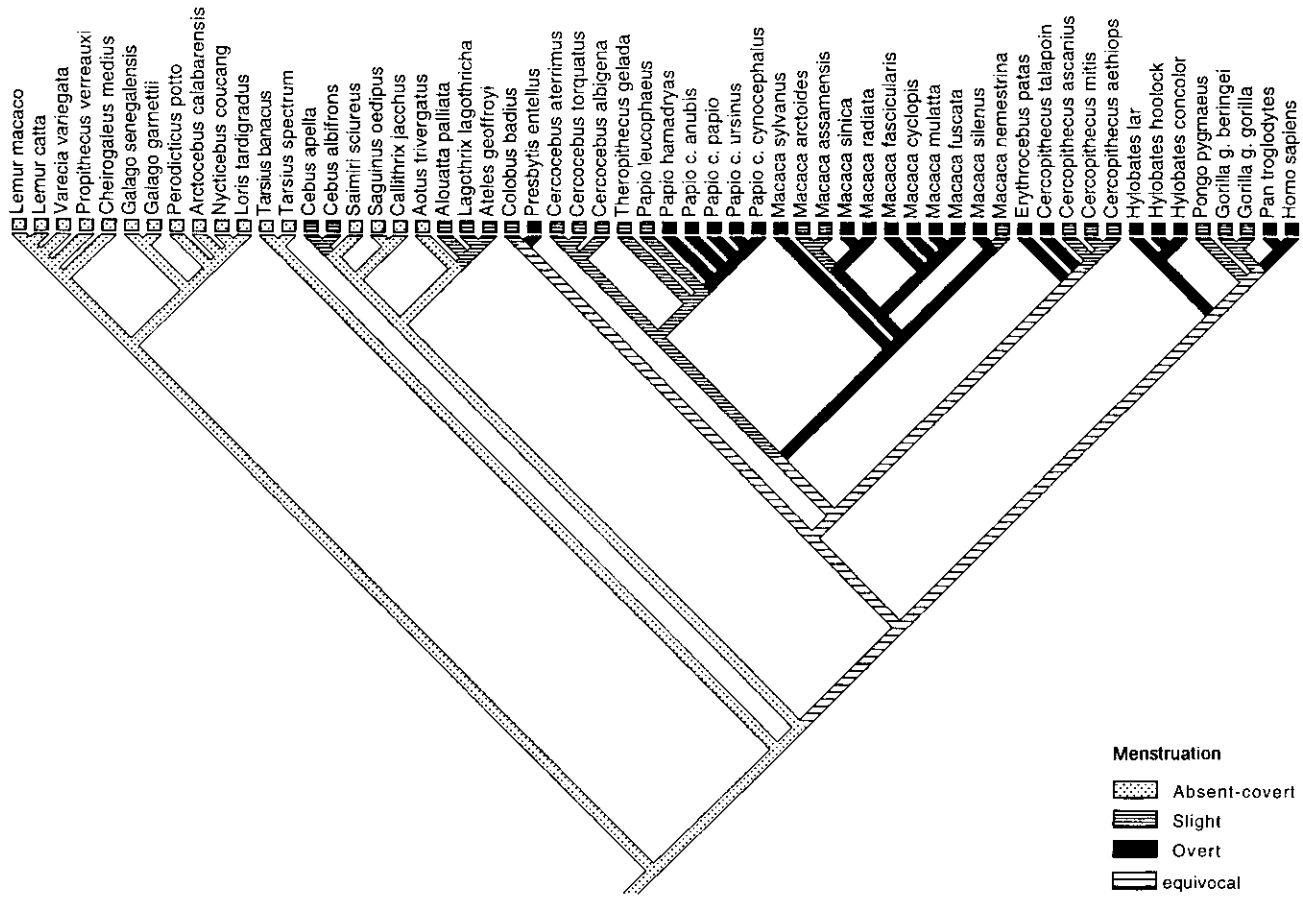

FIG. 8. Phylogeny of the primates showing the distribution of menstrual copiousness in extant taxa and the inferred ancestral states in each lineage. Absent or covert menstruation, blood is fully reabsorbed. Slight menstruation, blood is externally detectable. Overt menstruation, blood is externally obvious. Prosimians have absent or covert bleeding, New World monkeys have covert or slight menstruation, and Old World monkeys, apes, and humans have slight or overt bleeding. (From Strassmann.[38])

mans, the window of opportunity for implantation is less than 3 days.[43] Without an embryo, implantation cannot occur. Hence, selection to extend this window should be nonexistent. Given that the endometrium is only useful for a short time, is it more costly to sustain this tissue when it is not needed or to regenerate it in each cycle?

One way to estimate the cost of tissue maintenance is to measure oxygen consumption. In intact endometrial strips, oxygen consumption increased over the course of the menstrual cycle until ovulation or implantation.[45] The endometrium consumed about sevenfold less energy (per milligram protein per hour) in the regressed state just after menstruation.[45] Thus, the endometrium consumed the most energy while it was ready for implantation and the least energy after it had been torn down, with a gradient in between while it was being built back up. This means that it is energetically cheaper to regrow the endometrium each cycle than to maintain it continuously.[38,39]

According to this argument, endometrial regression is part of a broader tendency, displayed throughout the vertebrates, for tissues to spare energy by regressing when not in use. This flexibility has been shown to permit energy savings not only in the endometrium but also in the oviducts, gonads, and other reproductive tissues of a variety of vertebrates outside the breeding season.[38,39] Energy-sparing fluctuations in organ size have also been found in the small intestine, kidneys, liver, stomach, lungs, and heart in a variety of organisms.[46] The most spectacular example involves the Burmese python (*Python molurus*), a sit-and-wait predator. Within 2 days of consuming a large piece of meat, intestinal mucosal mass in this species doubled, and metabolic

rate and intestinal absorption increased sevenfold.[47] The python does not incur the cost of maintaining a functional gut when it has nothing to digest. Reptilian oviducts are homologous to the endometrium in mammals, and like the endometrium, they regress when not in use.[38,48]

The costs of preparing for implantation are not paid in the endometrium alone. The ovarian hormones estradiol and progesterone coordinate the activity of all tissues involved in reproduction. The cyclic action of the ovarian steroids on target tissues produces cycles in the metabolic rate of the entire body. In women, metabolic rate is about 7% lower, on average, during the follicular phase than it is during the luteal phase of the menstrual cycle.[49,50] Women compensate by an increase in food intake of up to 35%.[51] The energy savings of the follicular phase is about 50 megajoules (MJ) over four cycles, or about 6 days' worth of food. A woman who foregoes the luteal phase for 12 months during amenorrhea spares about 130 MJ, the energy equivalent of half a month's food supply.[38,39]

What about the nutritional cost of blood loss during menstrual bleeding? The protein loss is less than 0.5% of the required protein intake over one cycle. Relative to fecal protein loss, this is trivial.[37–39,52] Iron loss became a problem only in the evolutionarily novel circumstance of repeated cycling.[38,39]

To date, little is known about the causes of the variation in the extent of menstrual bleeding between species. Some of the candidate causes include placental structure, the extent of tissue differentiation before implantation, endometrial thickness, depth of shedding, and uterine volume/body mass ratios.[38,39,53–57] More research is needed in all these areas if we are to understand why women menstruate more copiously than females in other species. In a given woman, the degree of bleeding is predicted by her height, parity, and the birth weight of her infants.[58] These variables influence uterine size and vascularity, which in turn influence degree of bleeding.[58]

In summary, endometrial regression appears to be a carryover from our premammalian ancestors. They developed the energy-sparing practice of dispensing with reproductive tissues when they were not needed.[38,39] Vaginal bleeding itself is not adaptive but instead is probably a by-product of endometrial regression.[38,39] When pregnancy is not the objective, the waxing and waning of endometrial cycles is unnecessary. In the hope of stimulating further research, this article outlines a few of the implications for contraceptive design and women's health.

ACKNOWLEDGMENTS

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