

Reproductive Control in Wild Baboons Measured by Fecal Steroids¹

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ABSTRACT

Measurements of reproductive hormones (progesterone and estrogens) excreted in feces were used to discriminate between 25 conceptive and 76 nonconceptive (including undetected early abortion) cycles of free-ranging yellow baboons at Mikumi National Park, Tanzania. Conceptive cycles had significantly higher luteal-phase progesterone and estrogen concentrations than nonconceptive cycles as early as Day 4 postovulation. However, mean early luteal-phase progesterone concentrations in conceptive cycles were lower when conception occurred during ecologically optimal vs. suboptimal times, and among females of high compared to low dominance rank. Mean estrogen concentrations in conceptive cycles showed the opposite dominance rank pattern: mean luteal-phase estrogen concentrations were higher in conceptive cycles of high-compared to low-ranking females. None of these relations existed for nonconceptive cycles. These data suggest that successful implantation is facilitated by relatively high early luteal-phase progesterone and estrogen concentrations. However, long-term environmental cues predicting the probability of offspring survival appear to influence the amount of progesterone required for successful implantation; progesterone concentrations necessary to facilitate successful implantation are higher during suboptimal seasons or among females of low dominance rank—cues that also suggest that offspring survival conditions are relatively poor. This may act as a reproductive filter, restricting conception to females whose immediate condition (e.g., low social stress and good physical health) enables them to compensate physiologically and behaviorally for effects associated with these relatively harsh offspring survival conditions.

INTRODUCTION

This paper addresses whether reproductive failure (i.e., fertilization, implantation, or early pregnancy failure) is an important means by which wild female baboons optimize their timing of reproduction at Mikumi National Park, Tanzania [1, 2]. As with most mammals, timing has a strong impact on baboon reproductive success [3]. Baboons give birth year-round at Mikumi but have a distinct birth peak in the early dry season. These early dry season births are conceived during the previous early wet season (given their 180-day gestation). Survival is relatively high for offspring born during the early dry season birth peak because these young undergo the critical transition toward weaning during the subsequent wet season when weaning foods and water are most available and predation risk to developing young is relatively low [3]. This contrasts with the situation of

infants born during the early wet season (conceived during the early dry season); they enter their transition toward weaning during the subsequent dry season—the least favorable time for weaning survival [3]. Conception rate (number of confirmed conceptions per number of estrous females) was doubled during the early wet vs. dry season as evidenced by 9 yr of data preceding the present study.

Reproductive impacts of competition between females and their developing young also depends on the timing of births. As the size of the birth peak increases, so do competitive pressures and the probability of mortality among members of the birth cohort [3, 4]. Female-female attack coalitions and associated reproductive suppression accordingly increase with estrous and pregnancy synchrony (reflecting the size of the forthcoming birth peak). Occasionally, infants born at the onset of the birth peak may even be killed by pregnant females [4]. These circumstances make conditions for offspring survival substantially more variable for low-vs. high-ranking females. Perhaps as a result, low-ranking females show significantly more variability in conception rates (Table 1). However, when they do conceive, low-ranking females experience significantly lower rates of mid- to late-gestation spontaneous abortion than do high-ranking females [5, 6].

Fecal steroid measures of estrogens and progesterone (estradiol and progesterone [P_4] metabolites, respectively) are used to examine endocrine mechanisms of reproductive control among free-ranging female yellow baboons (*Papio cynocephalus*). Comparisons of fecal estrogen and progesterone profiles are made between conceptive and nonconceptive (including undetected early abortion) cycles, as a function of season of the year and female dominance rank, in two separate troops. Data suggest that the season- and rank-related reproductive patterns mentioned above are partly a physiological response to the integration of long- and short-term environmental cues predicting conditions for offspring survival. Physiological mechanisms increase the amount of luteal-phase P_4 concentrations required to establish and sustain implantation when long-term cues predict that offspring survival conditions will be relatively poor (dry season or low dominance rank). This tends to restrict conception under these conditions to females whose immediate, short-term conditions are sufficiently good (e.g., low social stress, good physical health) to compensate for these long-term constraints on offspring survival.

Fecal steroid technology has grown considerably in recent years [7–11]. Laboratory studies on baboons have demonstrated a close correspondence between serum and fecal steroid measures and have also shown how to control for effects of diet, urine contamination, and bacterial degradation on fecal steroid measures [7, 8, 11]. This, coupled with the ease of collection, enabled fecal steroid technology to accurately reflect the reproductive condition of free-ranging baboons in the present study.

Accepted March 26, 1996.

Received November 7, 1995.

¹Supported by grants from the H.F. Guggenheim Foundation, the National Geographic Society, the Smithsonian Institution, and the National Institute of Mental Health (MH48563RO1).

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TABLE 1. Number of cycles to conception (CTC; mean \pm SEM) across dominance-rank quartiles of female baboons in Mikumi, over a 9-yr period prior to this study (sample sizes shown in parentheses).

Reproductive event	Dominance-rank quartile			
	High	Mid-high	Mid-low	Low
CTC*	3.6 \pm 0.35 (30)	3.7 \pm 0.42 (27)	4.2 \pm 0.63 (25)	4.6 \pm 0.70 (18)

* Rank differences were not significant. However, as indicated by the SEMs, CTCs were significantly more variable among the low- vs. high-ranking quartiles of females ($p < 0.05$; Bartlett test). In fact, this high variability largely explains why the association between rank and CTC failed to reach significance.

MATERIALS AND METHODS

Animals and Sampling Protocol

Fresh fecal samples were collected between 1990 and 1992 from each of 30 individually recognizable adult female baboons of proven fertility, in two separate troops. These troops have been followed almost daily since 1974 and are fully habituated to human observers [12]. While field logistics at times prohibited sampling at the desired frequencies, we attempted to sample females 1–2 times per week when they were in the early follicular phase of their 32-day menstrual cycle; sampling attempts were increased to 2–3 times per week during the period of peak sex-skin tumescence (swelling, indicative of estrus), until the next menses or until conception was visually confirmed (see below). Sampling then occurred weekly for the remainder of pregnancy. Immediately after defecation, approximately 10 g of feces was removed from the entire well-mixed fecal sample and placed in a vial containing 25 ml 95% ethanol and 0.2% sodium azide. The ethanol/sodium azide mixture prevents bacterial enzyme degradation of steroids as well as impacts of urinary contamination [11]. Samples were stored frozen within 8 h after collection until shipped to the United States for processing.

Every attempt was made to include only ovulatory cycles in this study, on the basis of a transient rise in luteal-phase progesterone concentrations. Ovulation was assumed to have occurred 2 days before onset of detumescence [13, 14]. For purposes of this study, conceptive cycles were defined as those ending with a birth. These cycles also showed a pinkening of the perineum that becomes visible between 30 and 50 days of pregnancy [15]. Some cycles classified as nonconceptive undoubtedly represented undetected early abortions. No mid- to late-gestation abortions were observed during the period of sample collections. Luteal-phase fecal progesterone and estrogen concentrations [8] were compared across conceptive and nonconceptive cycles. Mean luteal-phase progesterone and estrogen concentrations per female were subsequently examined as a function of season of year and dominance rank.

Progesterone and Estrogen Extractions and RIAs

Fecal samples were dried in a centrifugal evaporator (Savant, Farmingdale, NY), enabling all fecal hormone concentrations to be expressed per gram dry weight. Expressing steroid concentrations per gram dry weight controls for most dietary, and hence seasonally, related changes in steroid excretion [7]. Dried samples were extracted using the method described by Wasser et al. [8], and RIAs for progesterone were performed according to the methods described by Wasser et al. [8]. The monoclonal P₄ antibody used to quantify fecal

progesterone was chosen for its high cross-reactivity with the pregnanones that predominate in baboon feces [8]. That antibody cross-reacts 100% with P₄, 96% with 5 α -pregnane-3 β -ol-20-one, 36% with 5 α -pregnane-3 α -ol-20-one, 15% with 5 β -pregnane-3 β -ol-one, 15% with 17 β -hydroxyprogesterone, 13% with pregnenolone, 7% with 5 β -pregnane-3 α -ol-20-one, 5% with 5 β -pregnane-3 α -ol-17 α -diol, 20 α -one, and < 1% with pregnanediol-3-glucuronide, androstenedione, testosterone, estradiol, estrone, estriol, 21-hydroxyprogesterone, 20 α -hydroxyprogesterone, and cortisol [8]. The 17 β -estradiol antibody used to analyze fecal estradiol cross-reacts 100% with 17 β -estradiol, 77% with 6-keto-estradiol, 2% with estrone and 17 α -hydroxyprogesterone, 0.8% with estriol and ethinylestradiol, 0.6% with 5-androstene-3 β -17 β -diol, < 0.01% with cortisol and cholesterol, and 0.00% with testosterone [16]. RIAs for combined estrogens (estradiol and estrone) were performed using the RSL ¹²⁵I total estrogen kit (ICN Biomedicals, Inc., Costa Mesa, CA). The total estrogen assay cross-reacts 100% with both 17 β -estradiol and estrone (the two predominant estradiol metabolites in baboon feces [8]), 9% with estriol, 7% with 17 α -estradiol, and < 0.01% with all other steroids tested, including sulfate and glucuronide conjugates. All of these assays cross-reacted < 0.1% with the androgens. Coefficients of variation for extraction and assay of two separate internal controls (pooled fecal samples containing high concentrations of estrogens and progesterone, and low concentrations of progesterone and estrogens, respectively) were 9.5% for progesterone, 12% for estradiol, and 10% for combined estrogens (eight extractions and assays each). Intraassay coefficients of variation were < 5% for each of these assays.

Statistical Analyses

Mean hormone concentrations across females were aligned by the onset of the luteal phase, with Day 0 defined as 2 days before the onset of detumescence (see above). ANOVA was used on transformed data (taking the square root of the dependent measure to achieve homoscedasticity [17]) to assess the significance of overall mean differences in luteal-phase estrogen and progesterone concentrations between conceptive and nonconceptive cycles. Student's *t*-tests were used on log-transformed (normalized [17]) data to determine the day in which these overall differences first reached significance. Multifactor ANOVA was used to assess the significance of season- and dominance rank-related differences in mean luteal-phase fecal estrogen and progesterone concentrations (Days 4–11 postovulation) of conceptive and nonconceptive cycles. The dependent variable consisted of the mean progesterone or estrogen concentration per female (with an average of 3 samples per mean) for Days 4–11 postovulation of an individual cycle. Each female contributed an average of 3.15 nonconceptive cycles to the overall analyses (median = 3, range = 1–8), with females of rank quartiles 1, 2, and 4 each contributing an average of 2.3 nonconceptive cycles and rank quartile 3 females contributing an average of 4.6 nonconceptive cycles (rank quartile 1 = high; 4 = low). Only 4 females contributed more than one conceptive cycle to the analyses; 2 of these were rank quartile 1 and the others were rank quartiles 3 and 4. Female dominance rank was determined annually, on the basis of the outcome of aggressive interactions systematically recorded during the study period. A female's dominance rank is typically retained throughout life in Old World primates such as the baboon [18]. A *p* value of less than 0.05 was considered significant.

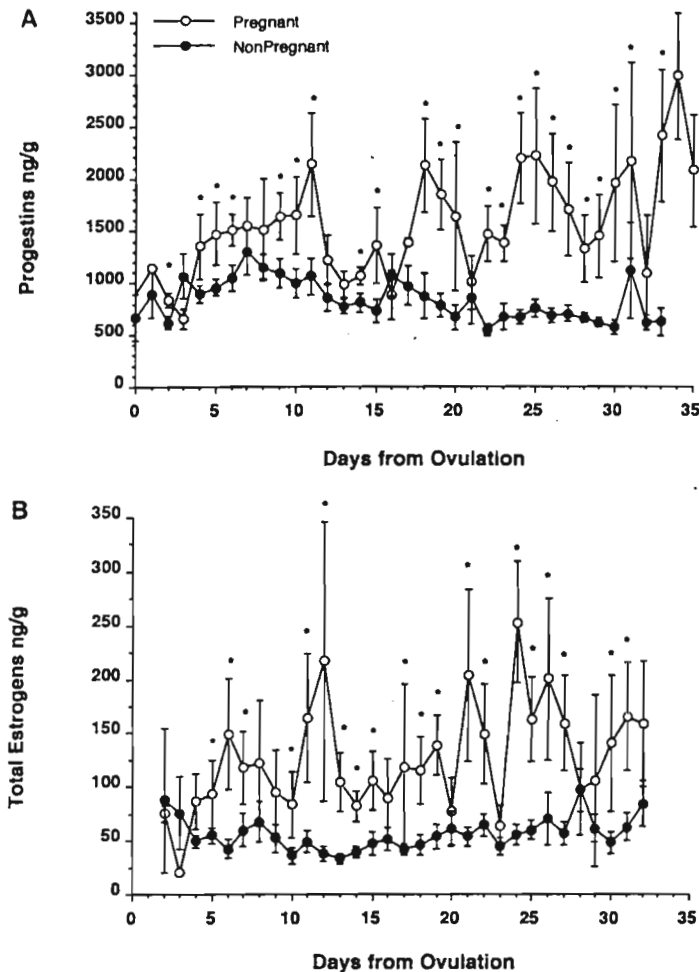


FIG. 1. Luteal-phase (A) progesterin and (B) estrogen concentrations excreted in feces of fertile female baboons during ovulatory nonconceptive (solid circles; 555 samples) and conceptive (open circles; 206 samples) cycles. Ovulation was confirmed by a transient rise in luteal-phase progesterin concentrations. Several females had cycles represented in both conceptive and nonconceptive data. Significance was determined through use of ANOVA and a Student's *t*-test. * = $p < 0.05$. Overall luteal-phase concentrations of fecal progesterins ($p < 0.0001$, Days 4–11 or 4–30 post-ovulation, ANOVA) and estrogens ($p < 0.0001$ for Days 4–11 or 4–30) were significantly higher in conceptive cycles than in nonconceptive cycles, first reaching significance by postovulation Day 4 for progesterins ($p < 0.03$; Student's *t*-test) and postovulation Day 5 ($p < 0.03$) for estrogens.

RESULTS

Overall Differences Between Conceptive and Nonconceptive Cycles

Fecal steroid measures accurately reflected reproductive condition. Both conceptive and nonconceptive cycles showed a transient rise in fecal progesterins over the luteal phase, but differed with respect to the magnitude and duration of this rise (Fig. 1A). Overall luteal-phase concentrations of fecal progesterins were significantly higher in conceptive cycles than in nonconceptive cycles ($p < 0.0001$, Days 4–11 pooled, or 4–30 pooled, postovulation; ANOVA), first reaching significance by Day 4 postovulation ($p < 0.03$; Student's *t*-test). Luteal-phase progesterin concentrations peaked by Day 7 postovulation in nonconceptive cycles vs. Day 11 in conceptive cycles. Progesterin concentrations in the conceptive cycles fell to levels virtually indistinguishable from those of nonconceptive cycles between Days 12 and 17 postovulation, after which time signifi-

cantly higher conceptive concentrations compared to those of nonconceptive cycles were sustained. Progesterin concentrations briefly declined in conceptive cycles around post-ovulation Day 32; there was then a progressive rise with stabilization at around Day 40 of gestation.

The fecal estrogen (estradiol and estrone combined) profile was similar to, but perhaps even more distinctive than, that of the progesterins. Overall luteal-phase estrogen concentrations were significantly higher in conceptive than in nonconceptive cycles ($p < 0.0001$ for Days 4–11 or 4–30, ANOVA; Fig. 1B). Conceptive estrogen concentrations became significantly greater than nonconceptive concentrations on postovulation Day 5 ($p < 0.03$), with high levels sustained throughout pregnancy. These early pregnancy differences were primarily due to changes in fecal estrone (a major metabolite of estradiol in baboon feces [8]), since fecal estradiol measures alone (not shown) did not reflect these early luteal-phase changes.

A random collection of fecal samples were examined for progesterin and estradiol (but not total estrogen) concentrations over the last 7 days (Day -7 to 0) of the follicular phase. Mean concentrations did not differ significantly ($p > 0.05$, *t*-test) between conceptive and nonconceptive cycles. (Mean progesterins = 435.7 ± 23 ng/g; mean estradiol = 45.8 ± 4.8 ng/g; $N = 26$.)

Season- and Dominance Rank-Related Differences during the Luteal Phase

Mean luteal-phase differences (Days 4–11 postovulation) in fecal concentrations of progesterins and estrogens were analyzed by season and female dominance rank for conceptive vs. nonconceptive cycles. Postovulation Day 4 corresponded to the day in which fecal progesterin and estrogen concentrations in conceptive cycles became significantly different from those in nonconceptive cycles (Fig. 1). Given the 36-h time lag between steroid secretion in blood and excretion in feces [7, 8], fecal hormones on post-ovulation Day 11 reflect hormone secretions in serum around the time of implantation (postovulation Day 9 [14]).

Conception (i.e., conception vs. nonconception; $p < 0.0001$) and season ($p < 0.05$) each had significant main effects on mean fecal progesterin concentrations. The interaction between season and conception was also significant ($p < 0.05$, ANOVA); the influence of season on luteal progesterin concentrations was largely confined to conceptive vs. nonconceptive cycles. In conceptive cycles, luteal-phase fecal progesterin concentrations were highest in the early dry season and lowest in the early wet season (Fig. 2A). A significant main effect of conception on mean total estrogen concentrations also was found ($p < 0.0001$). However, total estrogen concentrations were not significantly different across seasons for either conceptive or nonconceptive cycles (Fig. 2B).

Dominance rank had a significant main effect on mean luteal-phase progesterin concentrations ($p < 0.04$, ANOVA). Luteal-phase progesterin concentrations were significantly lower in high-ranking than in low-ranking females during conceptive cycles, but did not appear to differ by rank during nonconceptive cycles (Fig. 3A). Mean luteal-phase estrogen concentrations also were significantly associated with dominance rank ($p < 0.02$) and with the interaction between conception and dominance ($p < 0.03$, ANOVA). However, the dominance-related fecal estrogen pattern was opposite to the pattern for progesterins. Fecal estrogens were significantly greater in high-ranking compared to low-rank-

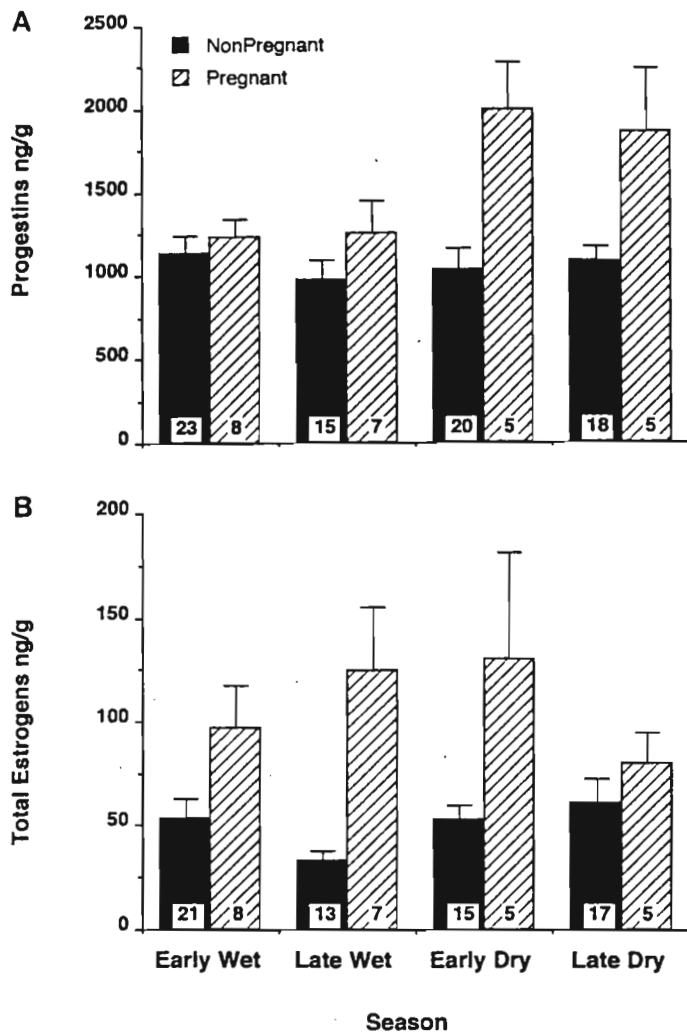


FIG. 2. Mean luteal-phase (postovulation Days 4–11) fecal (A) progesterin and (B) estrogen concentrations of conceptive and nonconceptive cycles across seasons of the year. Early wet = December-February; Late Wet = March-May; Early Dry = June-August; Late Dry = September-November. Given a 180-day gestation, newly pregnant females represented in each season gave birth 6 mo (2 seasons) later. Sample sizes shown in bars reflect the number of cycles in which adequate fecal sampling occurred during postovulation Days 4–11 and do not necessarily correspond to the total number of cycles that occurred. Season had a significant main effect on fecal progesterin ($p < 0.05$) but not estrogen ($p > 0.05$) concentrations; the interaction between season and conception was also significant for progesterin ($p < 0.05$, ANOVA). No seasonal effects were found in non-conceptive cycles.

ing females during conceptive cycles, but again did not differ by rank during nonconceptive cycles (Fig. 3B) [6].

The combined effect of dominance rank and season on mean luteal-phase progesterin and estrogen concentrations, across conceptive and nonconceptive cycles, also was examined. However, sample sizes permitted only two divisions for rank or season (high vs. low rank and wet vs. dry season, respectively). The basic rank and season patterns were largely retained in these comparisons (Fig. 4, A and B). The main effect of dominance on luteal progesterin concentrations as described above remained significant ($p < 0.05$). The described main effect of season on luteal progesterin concentrations approached significance ($p < 0.08$), and the interaction between season and conception remained significant ($p < 0.05$). Thus, among conceptive cycles, the lowest progesterin concentrations occurred in high-ranking females dur-

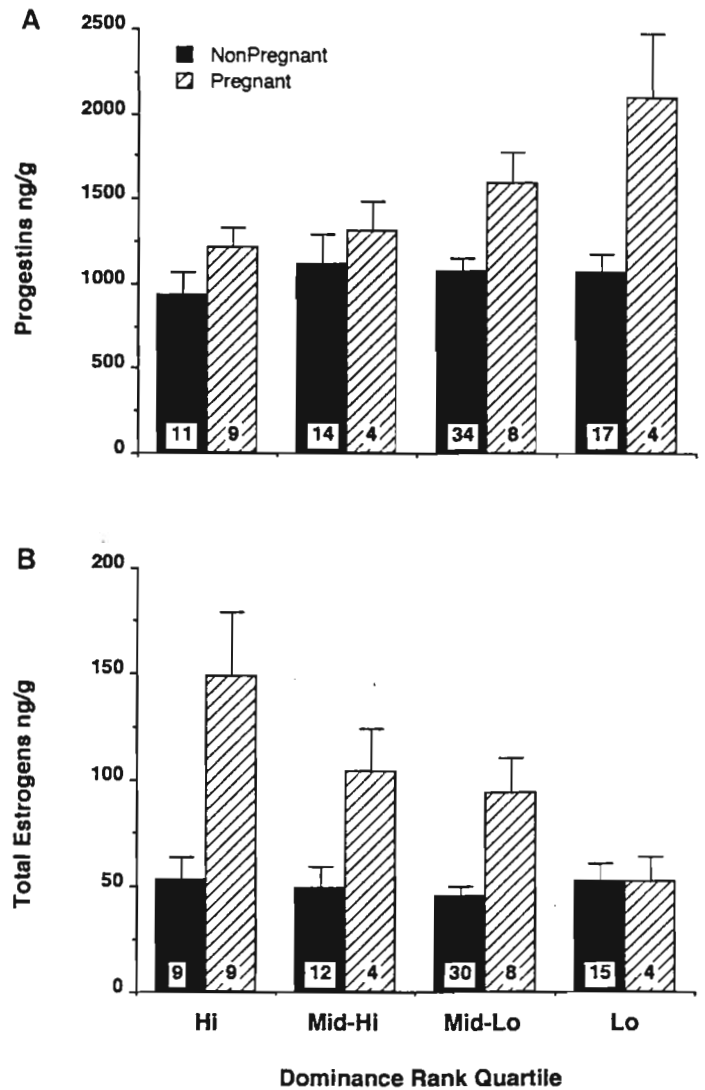


FIG. 3. Mean luteal-phase (postovulation Days 4–11) (A) progesterin and (B) estrogen concentrations of conceptive and nonconceptive cycles as a function of female dominance rank. Rank was quantified on the basis of the outcome of bouts of aggression systematically recorded during the study period. Female dominance rank tends to be stable throughout life in the baboon. Sample size is shown in bars, as in Figure 2. Progesterin ($p < 0.04$, ANOVA) and estrogens ($p < 0.02$) were significantly associated with dominance rank. The interaction between dominance rank and conception was also significant for estrogens ($p < 0.03$). No dominance effects were found in nonconceptive cycles. (Reprinted with permission from *Nature* [9].)

ing the wet season, and the highest occurred in low-ranking females during the dry season. Intermediate progesterin concentrations occurred among conceptive cycles of high-ranking females in the dry season and of low-ranking females in the wet season (Fig. 4A).

Dominance rank also continued to have the described main effect on luteal estrogen concentrations ($p < 0.01$), as did the interaction between dominance and conception ($p < 0.02$). The effect of season on luteal estrogens was not significant. Thus, among conceptive cycles, estrogen concentrations remained greatest in high-vs. low-ranking females, regardless of season (Fig. 4B).

DISCUSSION

The timing and duration of changes in fecal steroid concentrations among pregnant and nonpregnant females (Fig.

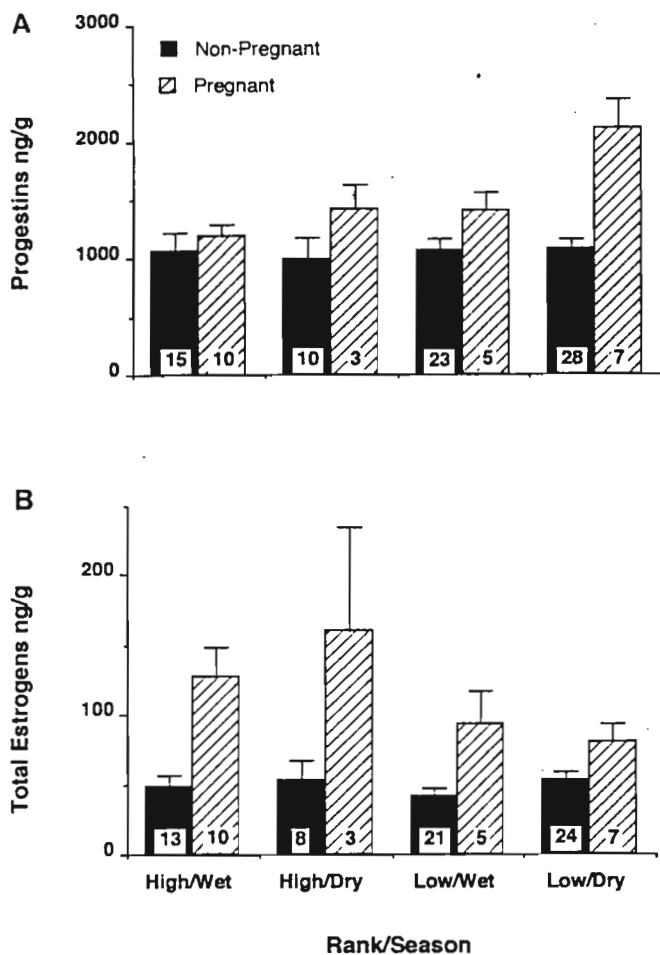


FIG. 4. Mean luteal-phase (postovulation Days 4–11) (A) progesterin and (B) estrogen concentrations of conceptive and nonconceptive cycles as a function of female dominance rank (high or low) and season (wet or dry). Sample size is shown in bars, as in Figure 2. Progesterins were significantly associated with dominance rank ($p < 0.05$, ANOVA), approached significance with season ($p < 0.08$), and were significantly associated with the interaction between season and conception ($p < 0.05$). Estrogens were significantly associated with dominance rank ($p < 0.01$, ANOVA) and the interaction between dominance and conception ($p < 0.02$), but not with season. No dominance or season effects were found in nonconceptive cycles.

1, A and B) corresponded to serum data for the baboon [19–21]. Hodges et al. [20] reported a decline in serum P_4 during conceptive cycles following Day 9 postovulation—around the time of implantation [13, 14]. The decline following Day 11 in feces (Fig. 1) corresponds to the Day 9 decline in serum, given the ~36-h time lag between excretion of estradiol and P_4 metabolites in feces and their secretion in serum [7, 8]. The rise in fecal progesterins that occurred around Day 18 in conceptive cycles is consistent with that found by Day 16 in baboon serum, and corresponds to an elevation in chorionic gonadotropin (CG) during that same period [21]. The dip at Day 32 (Fig. 1) is also consistent with serum measures in baboons, corresponding to the shift in primary P_4 production from the CL to the placenta [20]. These comparisons suggest that fecal steroid concentrations accurately reflect reproductive function in free-ranging baboons, distinguishing conceptive from “nonconceptive” cycles by the midluteal phase. The nonconceptive cycles did show a small, but notable, rise in progesterins around Day 16. This rise is likely the contribution of cycles that are labeled “nonconceptive” but that

actually aborted very early in conception; the small, variable Day 16 progesterin rise occurred around the same time as the progesterin rise in the conceptive cycles (Fig. 1A).

The differences in early luteal-phase progesterin and estrogen concentrations between conceptive and nonconceptive cycles (Figs. 1 and 2) parallel those found in other species (e.g., [22]), including humans [23, 24]. Stewart et al. [23] and Lenton et al. [24] compared serum P_4 and estradiol concentrations in conceptive cycles that went to term with those of nonconceptive cycles in normal untreated women of proven fertility. Estradiol concentrations were significantly higher during conceptive vs. nonconceptive cycles beginning 6 days after the LH peak and continuing through the end of the menstrual cycle. Progesterone showed a similar trend, which reached significance by Day 7. However, as also suggested for the data in Figure 1, these early luteal-phase differences were absent in comparisons between nonconceptive and conceptive cycles (based on hCG) that terminated in spontaneous abortion [23]. None of the studies mentioned [22–24] found follicular-phase differences in P_4 or estradiol concentrations between conceptive and nonconceptive cycles.

The data in Figure 1, and findings of other studies [22–26], suggest that successful implantation is facilitated by relatively high early luteal-phase fecal progesterin and estrogen concentrations. However, the seasonal and dominance rank effects reported in Figures 2A and 3A suggest that the luteal-phase P_4 concentration threshold for successful implantation increased in response to long-term environmental cues predicting a reduced probability of survival among offspring that might be conceived under these circumstances (i.e., offspring conceived in the dry season or to females of low dominance rank [3]). If it is assumed that luteal-phase P_4 concentrations decline in response to acute physical or social stressors [25, 27], this elevated P_4 concentration threshold for successful implantation effectively acts as a reproductive filter [2, 28], reducing the probability of conception in females most negatively impacted by these harsh conditions (e.g., females mating during the dry season that are also in poor physical condition, or low-ranking females experiencing relatively high rates of social harassment around the time of conception).

Infants conceived during the early wet season are born 6 mo later, during the early dry season birth peak, at Mikumi. These infants enter their critical transition toward weaning [29] during the most favorable time for weaning survival—the early wet season, when weaning foods and water are becoming most available and predation risk is relatively low [3, 30]. By contrast, infants conceived during the early dry season are born during the early wet season. They enter their transition toward weaning during the subsequent dry season—the least favorable time for weaning survival. Conception rates during the optimal early wet season are twice those during the suboptimal early dry season, presumably because relatively high luteal-phase progesterin concentrations are necessary to establish and maintain implantation during the early dry vs. wet season (Fig. 2A). These differences could not have resulted from diet-induced, seasonal changes in steroid excretion (vs. secretion), since 1) changes in estrogen concentrations across seasons were not significant and were inconsistent between conceptive and nonconceptive cycles (Fig. 2, A and B), and 2) expressing samples per gram dry weight controls for most diet-related changes in steroid excretion [7].

Analyses based on female dominance rank showed a similar result. The threshold of luteal-phase P_4 necessary

for successful implantation appeared to be elevated in low-ranking vs. high-ranking females (Fig. 3A). Consistent with this, conception rates were substantially more variable among low-ranking females (Table 1), who also experience greater variation in offspring survival conditions [3, 4]. This apparently tighter reproductive filtering among low-ranking females may also partly explain their reduced rate of mid- to late-gestation spontaneous abortion. Fifteen percent of conceptions spontaneously aborted in the highest-ranked quartile of females, compared to only three percent in the lowest-ranked quartile, over a 9-yr period at Mikumi [6]; see also below).

One way in which female baboons may be responding to these long-term predictors of harsh offspring survival conditions is through season- or rank-related changes in P_4 receptor (PR) densities. Thus, PR densities during the luteal phase may tend to be relatively low in the dry season and in low-ranking females.

The relatively higher fecal estrogen concentrations found in high-vs. low-ranking females (Fig. 3B) are consistent with the receptor density hypothesis. Estrogen increases PR and estrogen receptor (ER) densities in the epithelial layer of the endometrium of Old World primates, where implantation takes place; P_4 has the opposite effect on these receptor densities [31–33]. Three to four days of P_4 treatment in the absence of estrogen causes the epithelial surface on which the embryo implants to lose 100% of its PRs (R. Brenner, personal communication). This decline is significantly less rapid in the presence of estrogen [32]. More importantly, PR and ER densities in the endometrium decreased significantly from Days 2–6 postovulation in conceptive and nonconceptive cycles; but absolute PR and ER densities were significantly higher in conceptive vs. nonconceptive cycles on Days 4–6 [33]. These combined data suggest that the higher estrogen concentrations observed in the early luteal phase of dominant female baboons (Fig. 3B) may be moderating the P_4 -induced decline in PR (and ER) densities over the early luteal phase, making successful implantation easier to achieve with less P_4 present (Fig. 3A). Subordinate females would experience the opposite; lower luteal-phase estradiol (Fig. 3B) would require more P_4 (Fig. 3A) for successful implantation. The greater rate of mid- to late-gestation spontaneous abortion in high-vs. low-ranking females [5, 6] is also consistent with the above. Since very little, if any, steroid regulation of PR densities occurs in the deeper stroma and myometrium layers that maintain pregnancy [31–33], the relatively low amount of P_4 required for high-ranking females to establish implantation may not always be sufficient for them to maintain it [6].

Estrogen appears to play a less important role in the presumed seasonally related changes in PR densities, perhaps because estrogen concentrations are more closely tied to social conditions (e.g., [34]). On the other hand, other secretagogues shown to increase PR densities, such as insulin, insulin-like growth factor, epidermal growth factor, and cAMP [22, 32], are likely to play an analogous role in the observed season-related P_4 patterns, given the strong positive association of these secretagogues with nutrition [35].

Implications for Reproductive Medicine

Soules [25] speculates that insufficient luteal-phase P_4 levels, termed luteal-phase deficiency (LPD), is one of the most common abnormalities of the menstrual cycle in women. Low luteal-phase P_4 levels retard maturation of the

endometrium, resulting in failure of nidation. Most instances of LPD in women occur sporadically; e.g., they are present in 1 or 2 cycles that are followed by normal cycles. But when persistent, LPD constitutes up to 10% of infertility and 25% of habitual abortion cases in women [25]. LPD has also been implicated as an important cause of reduced fertility in captive lowland gorillas [36]. The present study suggests that LPD-like mechanisms, in combination with changes in PR densities, may have been naturally selected because they prevented reproduction at sub-optimal times. LPD appears to be multicausal, but a key element is abnormally rapid or slow pulse frequency of LH secretion in the early follicular phase, driven by modulation of the hypothalamic GnRH pulse generator [25, 26, 37]. These alterations in gonadotropin secretion are thought to result from sustained exposure to psychosocial or physical (e.g., strenuous exercise) stressors [25]. It would be interesting to know whether impacts of these alterations on reproduction vary in response to long-term predictors of social status and/or environmental conditions promoting reproductive seasonality in humans [38]. Thus, long-term environmental predictors may adjust PR densities, determining the degree to which fertility will be reduced by relatively short-term, stress-mediated alterations in reproductive physiology such as LPD.

If LPD-like mechanisms did evolve to promote reproductive control, environmental change may well have a clinical role in the diagnosis and treatment of LPD in women [28, 39]. At a more mechanistic level, diagnosis of LPD might be improved by inclusion of measures (such as estradiol) that affect PR densities, as opposed to reliance simply on assessment of P_4 levels or P_4 effect (endometrial biopsy) [25]. Moreover, LPD treatment by luteal-phase P_4 supplementation also might prove more effective if coupled with agents (e.g., estrogens) that reduce the likelihood of P_4 down-regulating its own receptors too rapidly to ensure successful implantation.

ACKNOWLEDGMENTS

Sincere thanks go to Steve Monfort, Nicole Presley, Dave Wildt, and Janine Brown. Dave Battaglia, Robert Brenner, Vic Fujimoto, Nancy Klein, Don Moore, Tom Hahn, Michael Romero, Gene Sackett, Michael Soules, and Richard Stouffer provided valuable comments on the manuscript. Lisa Stratton, Sonia Kleindorfer, JoAnne Docktor, Sabine Schmid, Chris Holmes, Laurie Neville, Dinah Wilson, Mary Liebman, Charles Kidungho, and William Marwa provided sample collections. Permission to work in Mikumi was provided by the Serengeti Wildlife Research Institute, The Tanzania Commission for Science and Technology, and the Tanzania National Parks.

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