Comparative Medicine
Copyright 2006
by the American Association for Laboratory Animal Science

406018-7

Vol 56, No 4
August 2006
Pages 291-299

The Effects of Aging on Hormone and Reproductive Cycles in Female Chimpanzees (*Pan troglodytes*)

Elaine N Videan,[1,*] Jo Fritz,[1] Christopher B Heward,[2] and James Murphy[1]

In contrast to those for human females, observational cycle data available for chimpanzees suggest that menstrual cycling, and thus reproductive potential, continues until near death. This study documents age-related changes in estrous cycling and hormone profiles in 14 female chimpanzees (*Pan troglodytes*) ranging in age from 31 to 50 y. Estrous data were analyzed from daily cycle charts, averaging 13.3 y of cycle data per subject, after omission of gestational and postpartum amenorrhea. Concentrations of total luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E_2), and other hormones were assayed in serum samples taken biannually. Sample collection times were chosen to avoid the ovulatory LH and FSH peaks of the female's cycle and yielded a mean of 19.6 serum samples over an average of 14.4 y per subject. Analysis of cycle charts revealed a negative relationship between age and the percentage of cycle days at maximal tumescence. There also were positive relationships between age and the length of the estrous cycle and age and the percentage of cycle days at complete detumescence. Analysis of hormonal data revealed curvilinear relationships between age and both LH and FSH. These cycle and hormonal changes mirror those in perimenopausal and menopausal women. Our data provide evidence of perimenopause (at 30 to 35 y) and menopause (at 35 to 40 y) in the chimpanzee.

Abbreviations: E_2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PFA, Primate Foundation of Arizona

Research into the aging process mandates an integrative approach because it relates to all areas of biomedical scientific study.[7] The nonhuman primate is an appropriate model for studying the aging process in humans because of its close phylogenetic relationship.[8] In particular, various species of primates have been used as models for studying the evolution of female menopause in humans.[2,15] Studies of the aging process in wild and captive chimpanzees have primarily focused on behavioral correlates of aging and neurobiology.[4,7,14,19,20] Defining 'old age' as around 31 y to death, Goodall[14] documented a gradual decrease in activity levels and a more difficult time climbing trees. However, little mention is made of reproductive cycling in aged females.

Reproductive senescence in the human female is characterized by cessation of menstrual cycling and ovarian steroid hormone production in approximately the fifth decade of life, with death not occurring for more than 20 y thereafter.[21] Perimenopause in humans is defined as the period of menstrual irregularity preceding menopause and lasting 2 to 8 y.[21] Perimenopause also is marked by endocrine changes, including a gradual increase in both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations. Menstrual cycling-based definitions of menopause have been widely used, but this practice has led to inaccurate determinations of menopausal status in some women.[10] Endocrinologic definitions, which may be more accurate than cycling-based approaches, define the onset of menopause as the point at which FSH levels exceed 20 IU/l[3,10] or 30 IU/l.[21] Exact thresholds for LH have not been determined, but LH levels typically have more than doubled by the menopausal transition.[21] Regardless, data addressing the effects of age on reproductive cycling in chimpanzees are in sharp contrast to those for women.

Most chimpanzees in captivity cycle (based on anogenital swelling) until death, which may occur in the fourth or fifth decade of life, although cycle lengths increased with age in some animals.[16] Births are negatively correlated with age in the wild[28] and in captivity,[25,31] although anogenital swelling continues in some animals until death. Longitudinal studies on wild chimpanzees can only estimate ages of the senior members of the troops, but they do address the question of behavioral correlates of aging related to female cycling.[14,20,28] Hiraiwa-Hasegawa and colleagues[19] described 2 female chimpanzees who were estimated to be older than 40 y and who continued to cycle but did not become pregnant. Goodall[14] noted 1 chimpanzee older than 40 y who did not cycle for almost 3 y prior to her death. Ghiglieri[13] reported 2 old females who never cycled during his 2-y study of the chimpanzees of Kibale Forest. Finally, Nishida and colleagues[28] reported 5 females who ceased cycling and could have been postreproductive. Reproductive endocrinology has been conducted on both wild[35] and captive[33,34] female chimpanzees; however, no study to date has examined hormone profiles in female chimpanzees as a function of aging.

Permanent cessation of reproductive cycling has not been noted in the chimpanzee, according to some authors.[7,16] They argue that this phenomenon may be due to death at a younger age than for humans.[7] Only 2 studies in captive chimpanzee have examined the relationship between age and menstrual cycling.[15,16] Although better able to identify ages of the subjects and track sexual cycling than those of wild animals, these studies lacked detailed hormonal analyses, and no attempts to reexamine the question of menopause in captive chimpanzees have been made. A closer examination of anogenital swelling patterns in captive chimpanzees may be more indicative of changes in cycling than are duration and frequency. Refining the analysis of cycling data by observing

Received: 20 Feb 2006. Revision requested: 2 May 2006. Accepted: 7 May 2006.
[1]Primate Foundation of Arizona, Mesa, Arizona; [2]Kronos Science Laboratories, Phoenix, Arizona.
[*]Corresponding author. Email: evpfa@qwest.net

the subtle changes rather than the more overt changes may lead to a better understanding of the cycle pattern in female chimpanzees. In addition, long-term hormonal analyses can give us a better picture of how aging affects female chimpanzee endocrinology and reproduction. Finally, the possibility of reproductive senescence (menopause) in captive chimpanzees has important implications for long-term breeding programs. Failure to recognize reproductive senescence in aging captive female chimpanzee populations may result in gross overestimation of their reproductive capacity.

The purpose of this study was to document longitudinal age-related changes in estrous cycling and hormone profiles in female chimpanzees to provide a comparative viewpoint to human female reproductive senescence. Estrous cycling and hormonal changes associated with increased age were examined. Cycle frequency, cycle duration, subtle changes of anogenital swelling patterns, and hormone profiles with correlations to age may provide new information on the process of aging in the female, captive chimpanzee. Increased information will, in turn, provide answers to the perplexing question of why cessation of menses has rarely been noted in chimpanzees (contrary the situation for women) as well as provide valuable information for the management and breeding strategy of captive chimpanzees.

Materials and Methods

Animals. Subjects included 14 female chimpanzees (*Pan troglodytes*) housed at the Primate Foundation of Arizona (PFA), a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International, in social groups of 3 to 6 animals. Subjects ranged in age from 31 to 50 y at time of study or natural death. Until the enactment in 1997 of the National Center for Research Resources breeding moratorium, all subjects were housed in breeding configurations. Table 1 provides reproductive and life history information for all subjects. No breeding has taken place in this colony since 1997, and all subjects are currently housed in either single-sex configurations or with a single vasectomized male. All subjects are defined as 'clean' according to criteria from the National Center for Research Resources. No subject has been exposed to hepatitis C or human immunodeficiency virus, and all are free from hepatitis A and B antigens. Likewise, no subjects were on infectious studies over the course of the sample collection period. Housing and care met and exceeded all current national and US Department of Agriculture guidelines. Chimpanzees were housed in either indoor-only or indoor–outdoor enclosures. All cages were furnished with elevated benches, vertical and horizontal poles, and firehose ropes. Chimpanzees also were provided with paper or straw bedding, manipulatable enrichment items, and forage–browse material on a daily basis. The data collection protocol was reviewed and approved by the PFA Institutional Animal Care and Use Committee.

Estrous cycling data. Sexual cycling data were collected from preexisting records on file at PFA collected by 4 observers with a minimum of 85% interobserver reliability, according to the index of concordance. Cycling data was analyzed from a mean of 19.8 (± 3.1) y of age to present on each subject, creating a longitudinal dataset for each of the 14 subjects. Total available data averaged 13.3 (± 4.6) y of cycle data per subject, after omission of periods of gestational and postpartum amenorrhea, resulting in a total of 186.4 y of cycle data. Sexual cycling data recorded included length of cycle, length of peak estrous (maximal tumescence), and length of complete detumescence. Menses and length of menses were not included in the analysis, because menses is difficult to note in chimpanzees.[6,17] Bleeding is often slight, and female chimpanzees are often fastidious and clean themselves as they bleed, such that menses is not visible.[17] Cycle length was defined as the number of days from the onset of maximal tumescence in one cycle to the onset of maximal tumescence in the next consecutive cycle. Maximal tumescence was defined as very taut skin with no wrinkles or sags. Complete detumescence was defined as no swelling and flaccid skin with many wrinkles.[17] Both length of time at maximal tumescence and complete detumescence were converted to a percentage by dividing by the number of days in each complete cycle.

Table 1. Breeding and life-history information for female chimpanzees, ranked according to current age or age at natural death

Subject	Age (y)	Parity
1031	31	3
1025	35	5
1010	35	1
1012	35	0
2721	35	4
1034	35	5
1006	36	6
1061	37	2
1015	37	4
1026	37	5
1022	37	3
1060	44	5
1016	48	6
1009	50	0

Hormonal profiles. A hormonal profile, including total luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E_2) was prepared from each sample at Kronos Science Laboratories by use of standard human clinical reference laboratory assays. Serum samples have been taken biannually for all PFA-housed animals from 1987 to present (or time of death). The samples used in this study were chosen to avoid the ovulatory LH and FSH peaks of the female chimpanzee's cycle (4 d before to 2 d after onset of detumescence). This selection resulted in a mean of 19.6 (± 6.0) serum samples over an average of 14.4 (± 2.9) y for each subject, thus yielding a longitudinal dataset for each of the 14 subjects and resulting in a total of 275 serum samples.

Data analysis. Because multiple samples were taken from each subject, resulting in 14 longitudinal data subsets, a mixed effects regression model controlling for subject was used to model the relationship between estrous cycle characteristics and age.[9] Cycle length, percentage of time at maximal tumescence, and percentage of time at complete detumescence were modeled separately against age using mixed effects regression models controlling for subject. The mixed effects regression model is an extension of the multiple regression model, allowing and controlling for repeated measures and unbalanced designs. The mixed effects model accounts for potential correlations within subjects across time and adjusts the sample size accordingly. In addition, because multiple serum samples were taken from each subject, total LH (mIU/ml), FSH (mIU/ml), and E_2 (pg/ml) were modeled against age by use of mixed effects regression models controlling for subject.[9] A threshold FSH value (14 mIU/ml) was estimated in light of endocrinologic definitions of menopause and perimenopause in

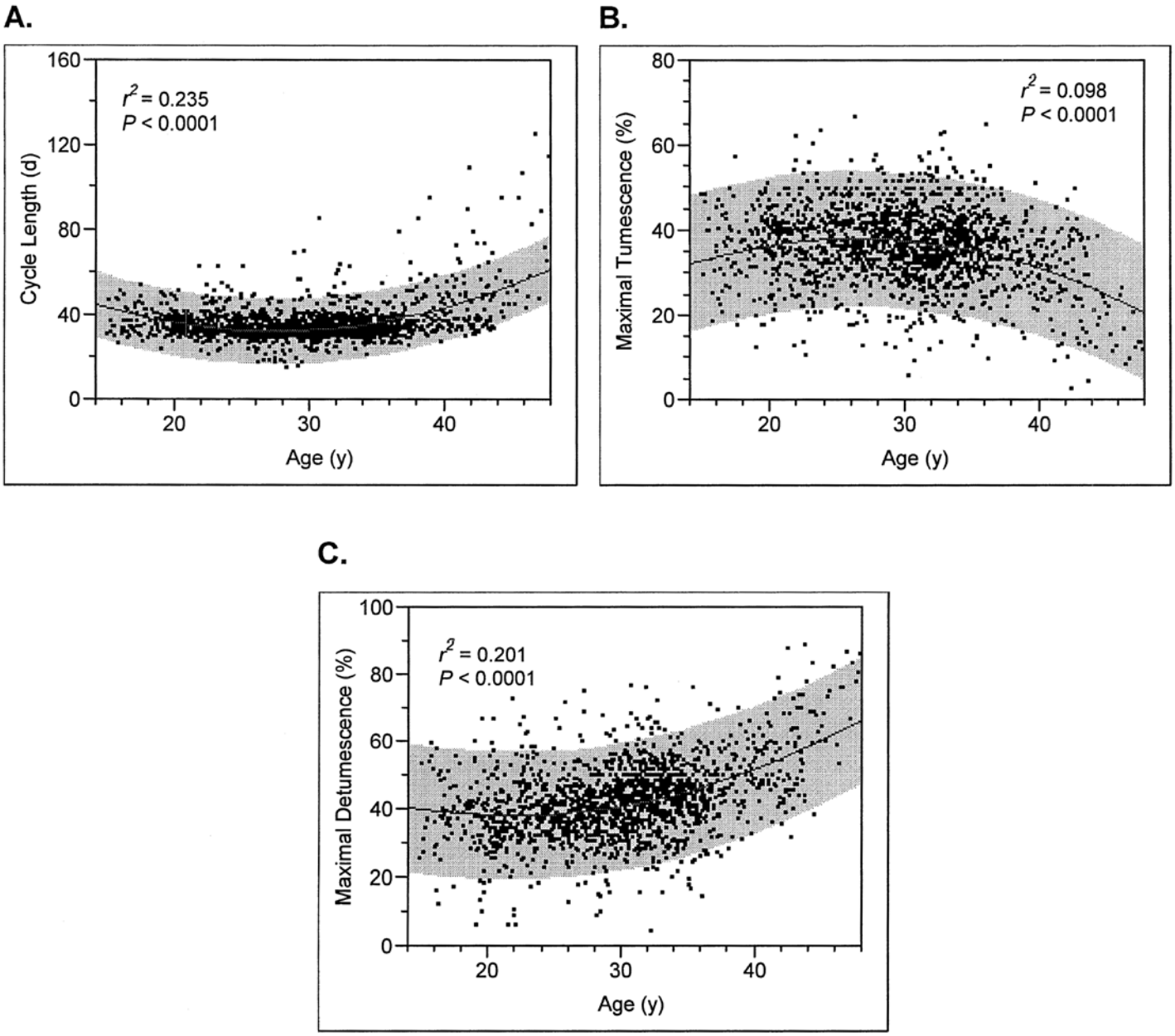

Figure 1. Relationship of (A) cycle length, (B) percentage maximal tumescence, and (C) percentage maximal detumescence to age (y) in female chimpanzees (n = 14). Regression lines, confidence intervals, and statistics were calculated by use of a mixed model (see text for details).

human females.[3,10,21] Further, longitudinal hormonal and estrous cycling data were analyzed separately for 3 female chimpanzees older than 40 y (nos. 1009, 1016, and 1060) in a second set of mixed effects regression models, again controlling for subject. For all tests, the threshold for statistical significance was set at 0.01, and all analyses were run using JMP 6.0 (SAS Institute, Cary, NC).

Results

Perimenopause. Analysis of cycle charts revealed a positive curvilinear relationship between age and cycle length ($F = 26.364$, $P < 0.001$, Figure 1). Interpretation of the graph indicates that cycle length remained fairly stable between ages 20 and 35 y but began increasing thereafter. There was a negative curvilinear relationship between age and percentage of cycle days at maximal tumescence ($F = 14.088$, $P < 0.001$) and a positive curvilinear relationship between age and percentage of cycle days at complete detumescence ($F = 10.500$, $P < 0.001$, Figure 1). The percentage of cycle at maximal tumescence began decreasing exponentially and the percentage of cycle at maximal detumescence began increasing exponentially between ages 30 and 35 y.

Analysis of hormonal data revealed a bell-shaped curvilinear relationship between age and LH ($F = 18.270$, $P < 0.001$), with LH peaking around age 30 to 35 y (Figure 2). Mean adult (15–29 y) values for LH ranged from 6 to 10 mIU/ml (Figure 2). A histogram displaying mean LH values across 5-y age blocks shows a similar curvilinear pattern (Figure 3). There was also a positive curvilinear relationship between age and FSH ($F = 5.628$, $P = 0.004$), but the data were highly variable, and the fit was poor ($r^2 = 0.04$, Figure 2). A histogram of mean FSH values across 5-y age blocks reveals

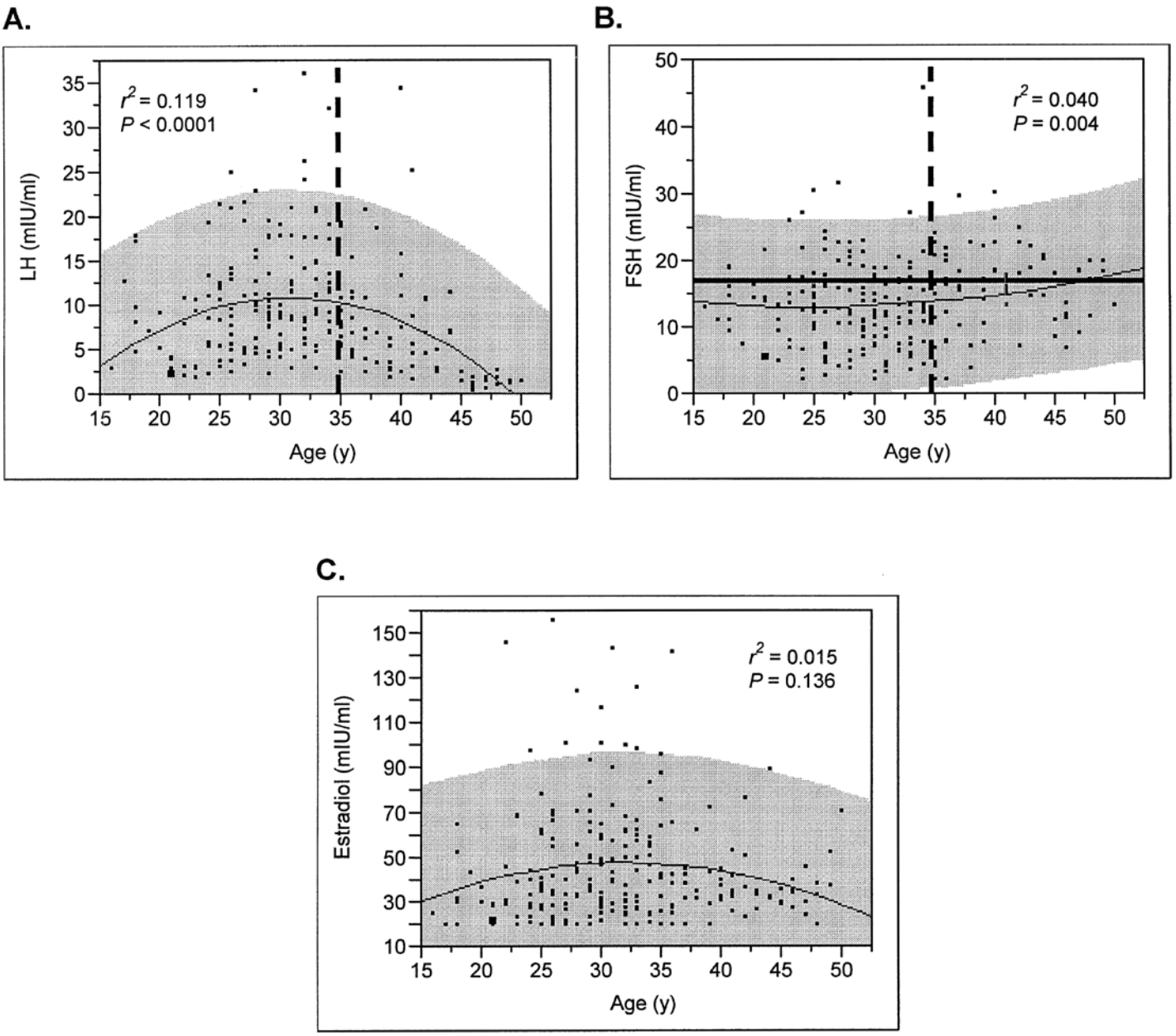

Figure 2. Relationship of (A) total luteinizing hormone (LH, mIU/ml), (B) follicle-stimulating hormone (FSH, mIU/ml), and (C) estradiol (E_2, pg/ml) to age (y) in female chimpanzees (n = 14). Regression lines, confidence intervals, and statistics were calculated by use of a mixed model. The solid horizontal line indicates the estimated threshold above which female chimpanzees would be classified as menopausal (see text for details). The vertical dashed lines on the LH (A) and FSH (B) graphs represent the hypothesized menopausal age of 35 y.

steady levels until approximately the mid-30s, when a gradual increase in hormone levels occurs (Figure 3). In addition, the majority of the points fall below the FSH threshold level until about age 35 y (Figure 2). Analysis revealed that estradiol tended to decrease with age, but this pattern was not significant, and data were highly variable (F = 2.010, $P = 0.136$, Figure 2).

Menopause. The number of cycles per year in the 3 oldest females decreased dramatically from approximately 10 per year (cycle length, 37 to 40 d) before the age of 30 y to 4 to 5 per year (cycle length, 60 to 70 d) beginning around the age of 43 y (F = 13.146, $P < 0.0001$, Figure 4), particularly in 2 of the subjects (nos. 1016 and 1009). The percentage of cycle days at maximal tumescence decreased (F = 6.645, $P = 0.002$), and the percentage of days at maximal detumescence increased (F = 8.474, $P = 0.0002$), particularly steeply after age 35 y (Figure 4). In addition, 2 of the females aged 49 y (no. 1016) and 50 y (no. 1009) experienced extremely long, erratic cycles at ages 44 and 46 y, respectively, and ceased having cycles associated with anogenital swelling at 46 and 48 y, respectively.

The hormonal data from these 3 aged females revealed significant bell-shaped curves (FSH: F = 5.217, $P = 0.008$; LH: F = 8.693, $P = 0.0004$) similar to those seen in the other older females, with an FSH peak around 40 y of age and an LH peak around 35 to 40 y of age (Figure 5). All 3 females achieved FSH levels above

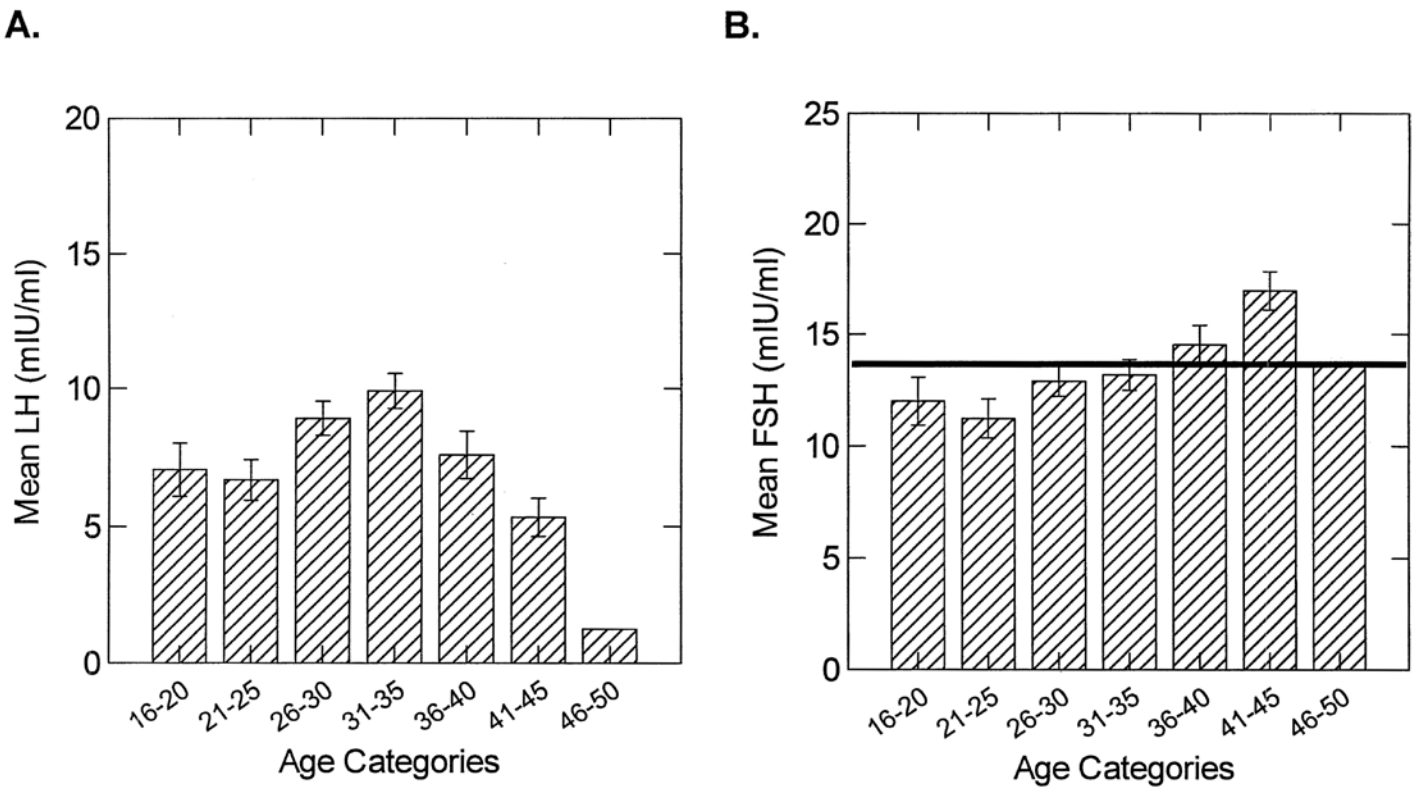

Figure 3. Mean (± standard error) concentrations of (A) luteinizing hormone (LH, mIU/ml) and (B) follicle-stimulating hormone (FSH, mIU/ml) across 5-y age categories in female chimpanzees (n = 14). The solid horizontal line indicates the estimated threshold above which female chimpanzees would be classified as menopausal (see text for details).

the hypothesized menopausal thresholds between ages 35 and 40 y (Figure 5). Two of the females had LH levels 2 to 3 times the adult (>30 y) mean as early as their late 30s. In addition, LH decreased dramatically after age 40 y; in 2 of the females (nos. 1016 and 1009) these levels approached 0 mIU/ml by age 45 y. Finally, E_2 showed different relationships for the 3 oldest females, but there was a high degree of scatter, and none of these regression lines were significant (Figure 5).

Discussion

In human females, perimenopause is marked by a decrease in the frequency of menstrual cycles and an increase in cycle irregularity.[26,30] Similarly in chimpanzees, we observed a decrease in cycle frequency, observable due to the overall increase in cycle length (Figure 1). Cycle length increased from approximately 35 d (10 to 11 cycles per year) between ages 15 and 30 y to an average of 40 to 50 d (7 to 9 cycles per year) at approximately age 35 y. This finding is similar to the previous examination of estrous cycles in aging female chimpanzees.[16] Closer examination of the relationship between age and cycle length in the present study also indicated an increase in cycle variability, beginning at approximately age 30 y. Similar to what has been observed in women, cycle length in female chimpanzees ranged 21 to 55 d during ages 15 to 25 y but grew to a range of 21 to 85 d beginning between ages 30 and 35 y (Figure 1).[26] Perimenopause in women also is characterized by a shortening of the length of the follicular phase of the cycle.[26] In female chimpanzees the decreased length of the follicular phase (maximal tumescence) began between ages 30 and 35 y. This change was preceded slightly by an increase in the length of maximal detumescence, which began closer to 30 y of age (Figure 1). The increasing length of detumescence could be interpreted as an increase in the luteal phase of the cycle. However, the increase in maximal detumescence is more likely an indication of increasing periods of amenorrhea, another hallmark of perimenopause in humans.[30] Therefore, the estrous cycle changes we report support an onset of perimenopause in chimpanzees between 30 and 35 y of age.

In addition to changes in menstrual cycles, perimenopausal women exhibit increasing levels of both FSH and LH.[21,30] In chimpanzees we observed similar patterns of increasing FSH beginning around age 35 y (Figure 2). There was a high degree of scatter, but similarly collected human samples from a much larger population (n = 2030) also yield a high degree of scatter in FSH as females approach menopause (Figure 6, reproduced with permission[18]). The increases we observed were gradual increases in FSH, whereas LH levels increased more dramatically beginning at age 25 y. This pattern resulted in pronounced spikes in LH, reaching 2 to 3 times the normal range (5 to 10 mIU/ml). These spikes in LH were not likely related to a typical LH ovulatory spike, because the sample times for this study were chosen to avoid the ovulatory window. Therefore, the steady increase in FSH and spikes in LH mirror changes seen in gonadotropins during human perimenopause[21,30] and further support cycle data that indicate perimenopause in chimpanzees begins after shortly after the age of 30 y. What remains unknown is how these changes in hormone levels affect menstruation and reproductive potential. As noted earlier, menses is often difficult to observe in chimpanzees because of the small amounts of blood and fastidious nature

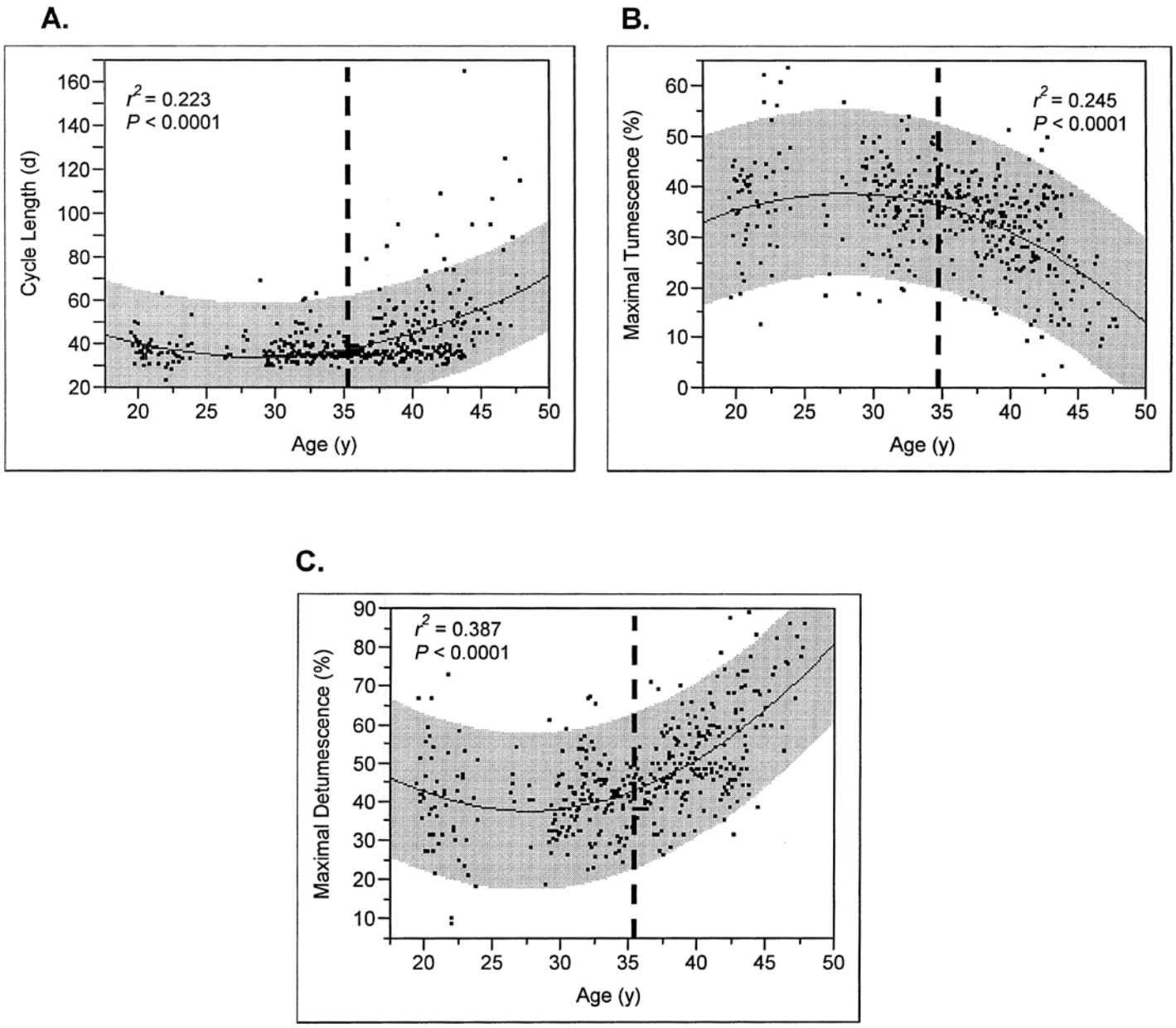

Figure 4. Relationship of (A) cycle length, (B) percentage maximal tumescence, and (C) percentage maximal detumescence to age (y) in female chimpanzees older than 40 y (n = 3). Regression lines, confidence intervals, and statistics calculated by use of a mixed model (see text for details). The vertical dashed lines represent the hypothesized menopausal age of 35 y.

of female chimpanzees.[6,17] We also were not able to test reproductive potential through follicular counts. However the elevated LH levels suggest that reproductive potential is markedly reduced beginning at approximately 30 to 35 y. Our findings support previously reported data from wild[28] and captive[25,31] chimpanzee populations that indicate birth rates significantly decline with age, particularly after 30 to 35 y.

Research on changes in estrogens during perimenopause in humans has revealed conflicting reports. Early research found a steady decrease in estrogen during the perimenopausal transition,[32] and some more recent studies have supported those earlier findings.[29] However, other studies have observed either an increase in estrogen[22] or little change at all.[24] Studies of estrogen levels during perimenopause in women are further complicated by decreases in dehydroepiandrosterone sulfate, an adrenal hormone that assists in producing estrogens from peripheral tissues.[23] There was no significant change in E_2 with increasing age in female chimpanzees, although there was a clear trend toward lower E_2 levels after the age of 40 y (Figure 2). Further research is needed to examine changes in dehyrdoepiandrosterone sulfate and other estrogens in female chimpanzees to understand this relationship. In women, perimenopausal changes in hormones are coupled with follicular depletion and oocyte loss.[21] However, little is known about follicular endowment or depletion in chimpanzees. Additional research is needed on follicular endowment and depletion and the potential relationship between estrogen

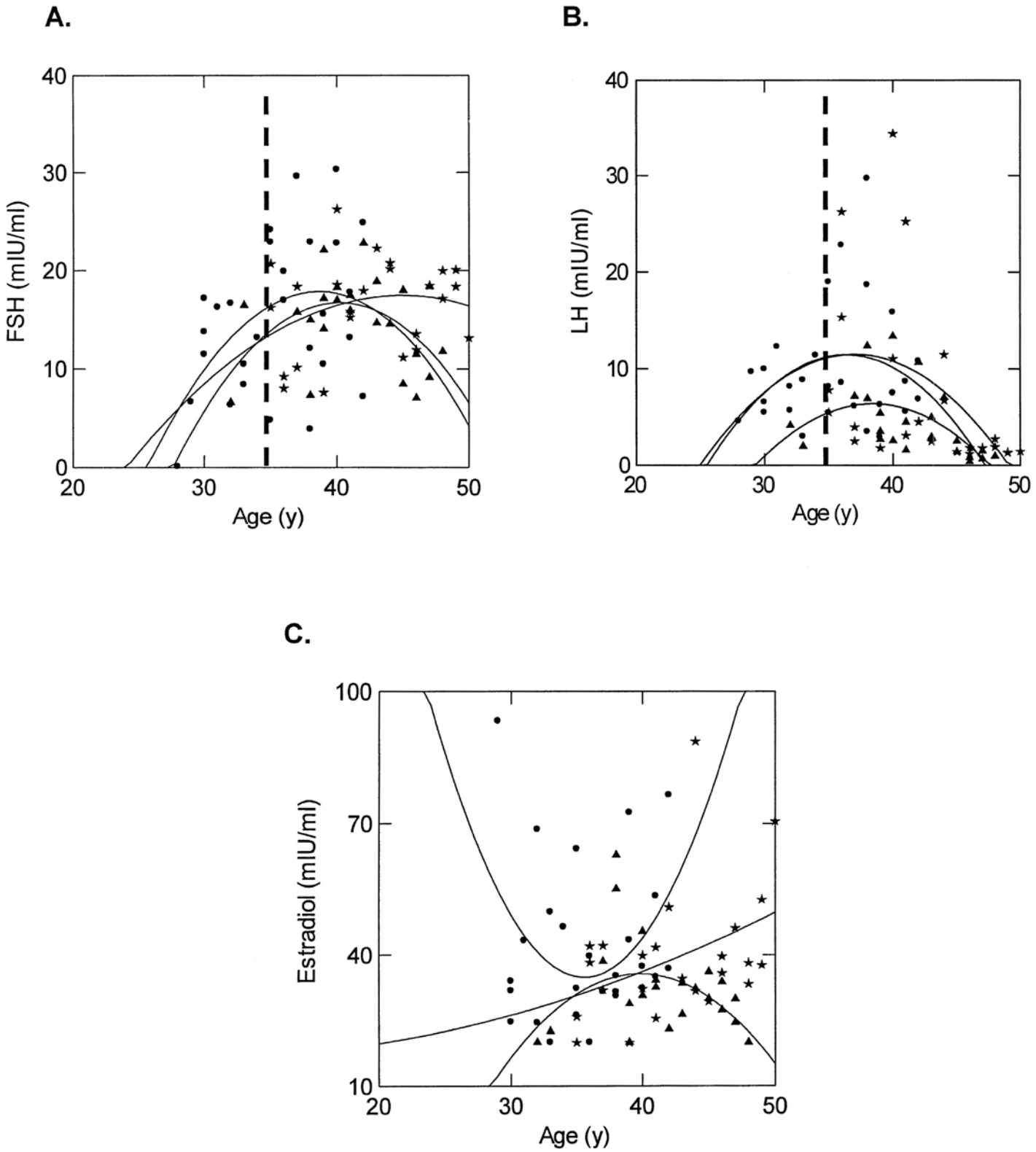

Figure 5. Relationship of (A) total luteinizing hormone (LH, mIU/ml), (B) follicle-stimulating hormone (FSH, mIU/ml), and (C) estradiol (pg/ml) with age (y) in female chimpanzees older than 40 y (n = 3). Individual regression lines are shown for each female. The horizontal line indicates the estimated threshold above which female chimpanzees would be classified as menopausal (see text for details). The vertical dashed line represents hypothesized menopausal age of 35 y.

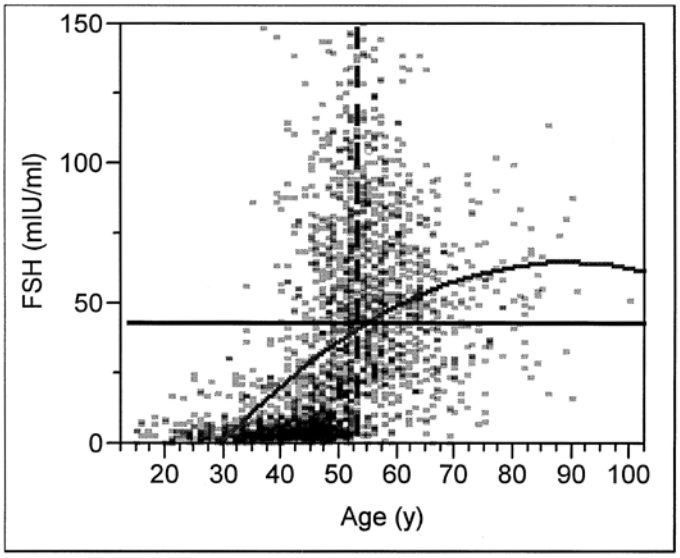

Figure 6. Relationship of follicle-stimulating hormone (FSH, mIU/ml) to age (y) in human females (n = 2030), reproduced with permission.[18] The horizontal line indicates the estimated threshold above which females are classified as menopausal (see text for details). The vertical dashed line represents the average human menopausal age of 50 y.

levels and follicular counts in older chimpanzees.

In humans, menopause has historically been defined as the age of final menstrual period, after which the woman experiences at least 12 consecutive months of amenorrhea.[21] In 2 of the 3 aged (44 to 50 y) female chimpanzees in this study, aged 49 and 50 y, visible signs of anogenital swelling ceased at ages 46 and 48 y. After this neither animal showed signs of estrous cycling, which by the historical human definition classified them as menopausal. Cycle length increased dramatically after age 40 y in all 3 of our aged females, with periods of maximal detumescence 60 to 90 d in length by the early to mid-40s (Figure 4). As we have stated, these long periods of maximal detumescence most likely represented periods of amenorrhea. In women, periods of amenorrhea lasting 60 d or longer are a hallmark of late perimenopause or early menopause.[30] The anogenital swelling data support an onset of menopause around age 45 y in female chimpanzees. However, evidence of anogenital swelling during periods of adolescent sterility and during pregnancies suggest that this marker may not be a reliable indicator of ovulatory function.[1,11,39] Anogenital swelling may serve to assist in group transfer, as changes in social group composition have been shown to influence anogenital swelling patterns.[39] In addition, during periods of anogenital swelling, females receive more social grooming from both male and female group members.[38] Therefore, continuation of anogenital swelling may not be an accurate gauge of reproductive status and may instead serve to maintain affiliative relationships within the social group.

Microscopic examination of the ovarian epithelium in late postmenopausal women typically shows signs of atrophy and fibrosis with scar tissue and follicular cysts common as well.[27] Postmortem examination of the ovarian tissue of animal 1009 showed atrophy and signs of ovarian cysts.[36] The immunohistology of this female chimpanzee suggests she was in a late postmenopausal phase at her death, further supporting that the menopausal transition occurred prior to senescence of anogenital swelling. However, this animal represents only 1 datapoint, and additional research is needed on ovarian and follicular status in older female chimpanzees.

Physiologic definitions of menopause focus on endocrine changes, most notably a prominent rise in FSH levels and a dramatic peak in LH levels.[10,21] Examination of the hormone profiles of our 3 oldest female chimpanzees revealed dramatic peaks in LH, above the adult mean, beginning at 35 y of age. Levels of LH reached 4 times the normal level (approximately 10 mIU/ml) around age 40 y (Figure 5). Similar peaks in FSH levels, above the hypothesized threshold, were observed in these females during the same time period. This evidence supports that menopause occurs around age 35 to 40 y, despite the fact that we have visual indications (that is, anogenital swellings) that appear contradictory. Perhaps most surprising were the steady levels of E_2, which were observed both perimenopausally and postmenopausally in these female chimpanzees (Figure 4). Further research is needed on additional estrogens in aged female chimpanzees to elucidate the function, if any, of the steady levels of E_2 during and after the menopausal transition. It is not entirely clear what regulates tumescence and detumescence in female chimpanzees.[6] Early research proposed that genital swelling was controlled by estrogen, but more recent research suggests it may be controlled by either the ratio of progesterone to estrogen or progesterone alone.[6] Additional information on estrogen and progesterone production in aged female chimpanzees may help in understanding the physiology of persistence of anogenital swelling after hormonal indications of menopause in chimpanzees.

Previous research has led to statements that chimpanzees do not experience menopause and therefore provide a poor model for studying the evolution of menopause in humans.[5] Longitudinal studies on wild chimpanzees[28] have suggested the possibility of a postreproductive period in female chimpanzees, but evidence thus far suggests that anogenital swelling, and thus ovarian function, in female chimpanzees continues until death. The present study has shown evidence that female chimpanzees exhibit estrous cycle and hormonal changes that mirror many of those observed in perimenopausal and menopausal women. In addition, hormone profiles suggest that anogenital swelling is not an accurate indicator of reproductive potential in older females. These data, together with immunohistology results, provide evidence of perimenopause at 30 to 35 y and menopause at 35 to 40 y in the chimpanzee.

This estrous cycle and hormonal evidence of reproductive senescence in captive chimpanzees will affect long-term breeding programs. Both captive and field studies have consistently demonstrated a dramatic decrease in fertility in female chimpanzees beginning around 30 to 35 y of age and continuing until death.[25,28,31] Perimenopause in women is associated with a sharp decline in fertility due to simultaneous endocrine changes.[12,37] The similar patterns of endocrine and estrous cycle changes observed in the female chimpanzees in the present study provide evidence that reproductive function is compromised as early as 30 y of age. Placing perimenopause in female chimpanzees at 30 to 35 y, with menopause occurring prior to 40 y of age, effectively reduces the reproductively viable portion of the chimpanzee population, likely excluding all those over the age of 35 y. Therefore, management and breeding strategies for captive chimpanzees must address the increasing age of the captive population.

Acknowledgments

Thanks to all PFA care and research staff, especially Kelly Carbone and Erika Evans, and to all Kronos Science Laboratories staff. This study was supported in part by the University of Texas, MD Anderson Cancer Research Center (subcontract U42 RR 15090-05) within the National Institutes of Health Biomedical Research Program and in part by Kronos Science Laboratories (Phoenix, Arizona). PFA is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International.

References

1. **Anderson CM, Bielert CF.** 1994. Adolescent exaggeration in female cattarrhine primates. Primates **35:**283–300.
2. **Atsalis S, Margulis SW, Bellem A, Wielebnowski N.** 2004. Sexual behavior and hormonal estrus cycles in captive aged lowland gorillas (*Gorilla gorilla*). Am J Primato **62:**123–132.
3. **Backer LC, Rubin CS, Markus M, Kieszak SM, Schober SE.** 1999. Serum follicle-stimulating hormone and luteinizing hormone levels in women aged 35–60 in the US population: the third national health and nutrition examination survey (NHANES III, 1988–1994). Menopause **6:**29–35.
4. **Baker K.** 2000. Advanced age influences chimpanzee behavior in small social groups. Zoo Biol **19:**111–119.
5. **Bellino FL, Wise PM.** 2003. Nonhuman primate models of menopause workshop. Biol Reprod **68:**10–18.
6. **Bettinger T, Cougar D, Lee DR, Lasley BL, Wallis J.** 1997. Ovarian hormone concentrations and genital swelling patterns in female chimpanzees with Norplant implants. Zoo Biol **16:**209–223.
7. **Bowden D.** 1979. Aging in nonhuman primates. New York: Van Nostrand Reinhold.
8. **Bowden D, Short R, Williams D.** 1990. Constructing an instrument to measure the rate of aging in female pigtailed macaques (*Macaca nemestrina*). J Gerontol **45:**B59–B66.
9. **Bryk AS, Raudenbush SW.** 1992. Hierarchical linear models. Newbury Park (CT): Sage Publishing.
10. **Cooper GS, Baird DD, Darden FR.** 2001. Measures of menopausal status in relation to demographic, reproductive, and behavioral characteristics in a population-based study of women aged 35–49 years. Am J Epidemiol **153:**1159–1165.
11. **Dahl JF.** 1999. Perineal swelling during pregnancy in common chimpanzees and puerperal pathology. J Med Primatol **28:**129–141.
12. **Ebbiary NAA, Lenton EA, Cooke ID.** 1994. Hypothalamic–pituitary aging: progressive increase in FSH and LH concentrations throughout the reproductive life in regularly menstruating women. Clin Endocrinol **41:**199–206.
13. **Ghiglieri M.** 1984. The chimpanzees of the Kibale Forest: a field study of ecology and social structure. New York: Columbia University Press.
14. **Goodall J.** 1986. The chimpanzees of Gombe: patterns of behavior. Cambridge (MA): Belknap Press.
15. **Gould KG, Flint M, Graham CE.** 1981. Chimpanzee reproductive senescence: a possible model for the evolution of the menopause. Maturitas **3:**157–166.
16. **Graham CE.** 1979. Reproductive function in aged female chimpanzees. Am J Phys Anthropol **50:**291–300.
17. **Harr, R.** 1989. The importance of charting estrous cycles in captive chimpanzees. Anim Keeper Forum **16:** 95–99.
18. **Heward, CB.** Unpublished data.
19. **Hiraiwa-Hasegawa M, Hasegawa T, Nishida T.** 1984. Demographic study of a large-sized unit-group of chimpanzees in the Mahale Mountains, Tanzania: a preliminary report. Primates **25:**401–413.
20. **Huffman MA.** 1990. Some socio-behavioral manifestations of old age. In: Nishida T, editor. The chimpanzees of the Mahale Mountains: sexual and life history strategies. Japan: University of Tokyo Press.
21. **Johnson BD, Bairey Merz CN, Braunstein GD, Berga SL, Bittner V, Hodgson TK, Gierach GL, Reis SE, Vido DA, Sharaf BL, Smith KM, Sopko G, Kelsey SF.** 2004. Determination of menopausal status in women: the NHLBI-sponsored women's ischemia syndrome evaluation (WISE) study. J Womens Health **13:**872–887.
22. **Klein NA, Battaglia DE, Miller PB, Branigan EF, Guidice LC, Soules MR.** 1996. Reproductive aging: accelerated ovarian follicular development associated with a monotropic follicle-stimulating hormone rise in normal older women. J Clin Endocrinol Metab **81:**1038–1045.
23. **Labrie F, Luu-The V, Bélanger A, Lin S-X, Simard J, Pelletier G, Labrie C.** 2005. Is dehydroepiandrosterone a hormone? J Endocrinol **187:**169–196.
24. **Lee SJ, Lenton EA, Sexton L, Cooke ID.** 1988. The effect of age on the cyclical patterns of plasma LH, FSH, estradiol, and progesterone in women with regular menstrual cycles. Hum Reprod **3:**851–855.
25. **Littleton J.** 2005. Fifty years of chimpanzee demography at Taronga Park Zoo. Am J Primatol **67:**281–298.
26. **Miro F, Parker SW, Aspinall LJ, Coley J, Perry PW, Ellis JE.** 2004. Relationship between follicle-stimulating hormone levels at the beginning of the human menstrual cycle, length of follicular phase, and excreted estrogens: the FREEDOM study. J Clin Endocrinol Metab **89:**3270–3275.
27. **Motta PM, Heyn R, Makabe S.** 2002. Three-dimensional microanatomical dynamics of the ovary in postreproductive aged women. Fertil Steril **78:**360–370.
28. **Nishida T, Corp N, Hamai M, Hasegawa T, Hiraiwa-Hasegawa M, Hosaka K, Hunt KD, Itoh N, Kawanaka K, Matsumoto-Oda A, Mitani JC, Nakamura M, Norikoshi K, Sakamaki T, Turner L, Uehara S, Zamma K.** 2003. Demography, female life history, and reproductive profiles among the chimpanzees of Mahale. Am J Primatol **59:**99–121.
29. **Overlie I, Moen MH, Morkrid L, Skjæraasen JS, Holte A.** 1999. The endocrine transition around menopause—a five-year prospective study with profiles of gonadotropines, estrogens, androgens, and SHBG among healthy women. Acta Obstet Gynecol Scand **78:**642–647.
30. **Park SJ, Goldsmith LT, Weiss G.** 2002. Age-related changes in the regulation of luteinizing hormone section by estrogen in women. Exp Biol Med **227:**455–464.
31. **Roof KA, Hopkins WD, Izard MK, Hook M, Schapiro SJ.** 2005. Maternal age, parity, and reproductive outcome in captive chimpanzees (*Pan troglodytes*). Am J Primatol **67:**199–208.
32. **Sherman BM, West JA, Korenman SG.** 1976. The menopausal transition: analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women. J Clin Endocrinol Metab **42:**629–636.
33. **Shimizu K, Douke C, Fujita S, Matsuzawa T, Tomonaga M, Tanaka M, Matsubayashi K, Hayashi M.** 2003. Urinary steroid, FSH, and CG measurements for monitoring the ovarian cycle and pregnancy in the chimpanzee. J Med Primatol **32:**15–22.
34. **Steinetz BG, Randolph C, Mahoney CJ.** 1992. Serum concentrations of relaxin, chorionic gonadotropin, estradiol-17β, and progesterone during the reproductive cycle of the chimpanzee (*Pan troglodytes*). Endocrinology **130:**3601–3607.
35. **Thompson ME.** 2005. Reproductive endocrinology of wild female chimpanzees (*Pan troglodytes schweinfurthii*): methodological considerations and the role of hormones in sex and conception. Am J Primatol **67:**137–158.
36. **Varki N, Benirschke K.** 2004. Personal communication.
37. **Velde ERT, Pearson PL.** 2002. The variability of female reproductive ageing. Hum Reprod Update **8:**141–154.
38. **Wallis J.** 1992. Chimpanzee genital swelling and its role in the pattern of sociosexual behavior. Am J Primatol **28:**101–113.
39. **Wallis J, Goodall J.** 1993. Anogenital swelling in pregnant chimpanzees of Gombe National Park. Am J Primatol **31:**89–98.