The Evolution of Menopause by Antagonistic Pleiotropy

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Abstract

Recent endocrinological findings concerning the role of follicular depletion in the regulation of ovarian cycles suggest a new hypothesis for the evolution of the menopause. Follicular depletion, the apoptotic process that ultimately causes menopause, occurs throughout premenopausal life and is integral to the set of hormonal feedback relationships that maintain regular cycles. The characteristics of the follicular-depletion system that determine the age at menopause, including the size of the initial follicle reserve and the rate of atresia, are important for ovarian cycles at younger reproductive ages and appear to be highly conserved between humans and chimpanzees (which do not normally experience menopause in the wild). We suggest that menopause and post-menopausal life do not confer evolutionary benefits in themselves, but rather evolved by antagonistic pleiotropy because of selection operating on the follicular-depletion system to maintain regular ovarian cycles at young adult ages.

From an evolutionary perspective, one of the more puzzling features of the human life course is the cessation of female reproductive function at the menopause, often combined with many years of post-menopausal life even in populations with high mortality rates[1]. It seems obvious that any foregone opportunity for reproduction, such as that following the menopause, must entail a fitness cost to the individual, a cost that must be countered by a larger fitness gain if the missed opportunity is to evolve as a normal feature of a species' life history. With respect to menopause, the problem is usually (but, in our opinion, erroneously) formulated in terms of possible fitness advantages of post-reproductive life itself. For example, the "grandmother hypothesis," currently one of the most popular explanations for the evolution of menopause, suggests that women can gain fitness benefits from prolonged post-reproductive life by helping care for their offspring's children[2,3]. The only attempt thus far to model the grandmother hypothesis indicates that the benefits of grandmaternal investment must be large for menopause to evolve by this mechanism alone[4]. Field studies of traditional societies, however, have yet to provide convincing evidence for any measurable fitness effect of grandmaternal investment[2,5]. In addition, the grandmother hypothesis is inconsistent with current theory about the evolution of aging, which holds that senescent traits evolve precisely because they have only weak effects on fitness[1,6]. We argue that attention to the physiological mechanisms that cause menopause suggests an alternative hypothesis. As we discuss below, menopause is not a discrete event, but is rather the end-point of a decades-long, continuous process known as *follicular depletion*. Follicular depletion, in turn, is essential for the control of female reproductive function at *all* reproductive ages. If follicular depletion is beneficial at earlier, pre-menopausal ages, then it may have been possible for menopause to evolve through antagonistic pleiotropy[6,7]. If this were the case, there would be no need to argue that menopause and post-reproductive life confer benefits in themselves. In this paper, we present new endocrinological data that support this alternative hypothesis.

According to the concept of antagonistic pleiotropy, genes that have deleterious effects at late ages can be actively selected if they also have beneficial effects at early ages. The mathematical foundation for this idea was provided by Hamilton[8], who showed that the effect of a phenotypic trait on an individual's total fitness declines monotonically with the age at which the trait is expressed. Thus, a given trait expressed, say, at age 50 has a smaller fitness consequence than the same trait expressed at 20. By the same logic, a deleterious trait expressed at age 50 may have less effect on fitness than a beneficial trait expressed at 20, even if the absolute magnitude of the deleterious trait's effect on fertility or mortality is much larger than that of the beneficial trait. Now imagine a gene that has pleiotropic effects at different ages – in particular, one with positive fitness effects at early ages but negative effects at late ages (the "antagonistic" part of antagonistic pleiotropy). Building upon Hamilton's models, Charlesworth[9] has shown that, under a wide variety of conditions, a modest benefit early in reproductive or pre-reproductive life can more than off-set a larger disadvantage that does not appear until late in reproductive life. It is now widely accepted that antagonistic pleiotropy is an important

mechanism for the evolution of senescent traits, especially traits that decline in function more rapidly than other parts of the soma, as does female reproductive capacity in mammals[1,6,10].

If menopause were a distinct event that is superimposed on a reproductive system that would otherwise continue to function normally, it would be difficult to imagine how antagonistic pleiotropy might play a part in its evolution. But in fact menopause is caused by an underlying process of follicular depletion that is essential for the regulation of reproduction at all ages. We suggest that it is the follicular-depletion system as a whole that is the evolutionarily-relevant phenotype, not just its terminus at the menopause.

Ovarian follicles are the histological structures that contain and nurture immature oocytes. They are also the primary sites of ovarian steroid production, secreting oestradiol during the follicular (preovulatory) phase of the cycle and, once they have been transformed into corpora lutea, progesterone (and some oestradiol) during the cycle's luteal (postovulatory) phase. At birth, the ovaries contain approximately one million primordial follicles, each housing a single primary oocyte[11]. Since mitosis among the developing germ cells ends late in the second trimester of gestation, a female will never again have more follicles than the number she possesses at birth. Instead, she will undergo a continual process of follicular loss, reducing the initial pool of follicles to near zero at the time of menopause[12,13,14]. Ovulation itself explains very little of the loss: most women will lose fewer than 500 oocytes and follicles by this route. Most follicles are lost *in situ* through a process of apoptosis known as atresia[15,16,17]. As final exhaustion of the pool of follicles is neared, the ability of the ovary to produce oestradiol is increasingly compromised. Entry into the perimenopausal transition, with its irregular cycles and distinct hormonal characteristics, occurs when approximately 1000 follicles are left in each ovary; menopause itself corresponds to the ultimate exhaustion of the follicle reserve[14].

The follicular-depletion system which in humans causes menopause is by no means unique to humans. Indeed, it is universal in mammals – and probably in vertebrates in general, at least in the small fraction of species that have been studied by reproductive biologists[18]. No known female vertebrates produce oocytes from a pool of self-renewing stem cells; in all species, mitosis in the cell lines giving rise to oocytes ends early in pre-reproductive life, and from that point on a large fraction of the oocytes are lost through atresia[18]. Although the details of the system vary from species to species, follicular depletion is clearly primitive to mammals.

Restricting attention to the higher primates, it appears that the common chimpanzee (*Pan troglodytes*) has a follicular-depletion system that is very similar to that of humans in both the rate of atresia and the size of the initial follicle pool[19]. While chimpanzees rarely undergo reproductive cessation in the wild, older females do experience declining fecundity and irregular cycles similar to those that characterize perimenopausal women[20,21]. In captivity, chimpanzees occasionally survive long enough to undergo menopause: not only do their cycles stop, but their ovaries show follicular exhaustion as well as other histological changes observed in post-menopausal women[19]. Captive chimpanzees that experience menopause do so at about age 50 years, similar to the mean age at menopause in women[19]. Based on this limited evidence, it would appear that the follicular-depletion system, including such details as atresia rates, initial follicle pool, and age at follicular exhaustion, is primitive to hominids; the difference between humans and chimps is that women routinely survive long enough to experience the inevitable end-point of the system's operation (a point to which we return below). It appears that there exists additive genetic variation for at least one feature of the follicular-depletion system, since laboratory mice show inter-strain differences in atresia rates, with intermediate rates exhibited by

F_1 hybrids[22]. Thus, there is no obvious genetic reason the system could not have changed over the course of hominid evolution. If indeed the system is highly conserved between chimpanzees and humans, as seems to be the case, it would imply that stabilizing selection has acted on it in both lineages – stabilizing selection that is unlikely to have anything to do with menopause or post-reproductive life since neither is a normal feature of chimpanzee life history in the wild.

To understand the selective importance of follicular depletion, it is necessary to review some basic facts about the biological system that regulates normal reproductive cycles in the adult female primate: the hypothalamic-pituitary-ovarian (HPO) axis (Fig. 1)[23]. Central to this system is the so-called GnRH pulse generator located in the hypothalamus; this neural complex controls pulsatile secretion of gonadotropin-releasing hormone (GnRH) by other neurons in the hypothalamus. GnRH, in turn, is carried to the anterior lobe of the pituitary gland, where it stimulates secretion of the two gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH acts upon the ovary to stimulate the growth and development of the follicles. LH induces ovulation and also directs redifferentiation of the ruptured follicle into the corpus luteum. The oestradiol secreted by the developing preovulatory follicle – as well as the progesterone produced by the corpus luteum – feed back on the hypothalamus and pituitary to modulate pulsatile secretion of GnRH, LH, and FSH. It is this set of feedback relationships that maintains regular reproductive cycles in the adult female.

Menopause represents the breakdown of normal HPO function through loss of feedback regulation by ovarian steroids, a loss caused by exhaustion of the follicle reserve. The hormonal pattern that typifies the menopausal transition is illustrated in Fig. 2, which tracks a 48-year old woman across some two months as she experiences her final menstrual bleed[24]. It is clear from her plasma progesterone levels that the cycle preceding her final menses was anovulatory. Following the last menses is an interval of one or two weeks during which some oestradiol is present, reflecting the activity of her last few follicles, none of which proceeds to ovulation. After this interval, the levels of both oestradiol and progesterone are very low, and they will remain low for the rest of the woman's life since there are no follicles left to secrete these steroids. Coinciding with the decline in ovarian steroids is a marked elevation in LH and FSH, indicating that the hypothalamus and pituitary have been freed from negative feedback by ovarian steroids. From this point on, at least until very late in her life, this woman's gonadotropin levels are likely to be high and variable[25].

HPO function in women starts changing well before follicular depletion has reached its inevitable conclusion. Indeed, menopause is preceded by a period of up to five or six years during which cycles are extremely variable and both steroid and gonadotropin secretion are less predictable than at earlier ages[26,27,28]. HPO function is "disordered" for several years during this perimenopausal transition period, inducing what appear to be unusually long and variable cycles (where cycle length is conventionally defined as the time interval between onsets of distinct episodes of menstrual bleeding) (Fig. 3)[29]. It used to be thought that the long cycles observed during perimenopausal life were caused by unusually long follicular phases[30] and represented some aging phenomenon distinct from the process of follicular depletion[31]. More recent evidence (summarized below) suggests that large parts of those apparent follicular phases are not characterized by follicular development at all, but represent genuine ovarian quiescence. We believe that these variable periods of ovarian quiescence are themselves attributable to follicular depletion – a conclusion that provides insight into the selective forces likely to be operating on the follicular-depletion system at younger ages.

This conclusion is based in part on a recurring hormonal pattern we have observed in perimenopausal women, illustrated for one particular 45-year old woman in Fig. 4. Throughout most of the period of observation, this woman experienced normal ovulatory cycles, as shown by her urinary oestradiol, progesterone, LH, and FSH patterns. (E3G and PdG are the major urinary metabolites of oestradiol and progesterone, respectively.) Beginning at about Day 2 of the third observed cycle, however, she went through a ten-day period during which she showed little if any sign of ovarian steroidogenesis (top panel); at the same time, her gonadotropins quickly became high and (in the case of LH) variable. As a consequence, that particular cycle (considered purely as an interval between menstrual onsets) was inordinately long, as is often the case during the perimenopausal transition. Had we taken a single urine specimen in the middle of the ten-day period of no steroidogenesis, we might well have concluded that this women was post-menopausal (compare Fig. 2). But clearly she was not: indeed, this brief period of "false menopause" was followed immediately by an ovulatory cycle.

We call such transient episodes of ovarian quiescence accompanied by loss of feedback control on LH and FSH "inactive phases" of the cycle. Inactive phases have been reported previously in perimenopausal women[25,27,28] and even in aging macaques[32], but no functional significance has heretofore been attached to them. We suggest that inactive phases directly reflect follicular depletion or, more precisely, stochastic fluctuations in HPO function resulting from a very small pool of remaining follicles. Entry into the follicular phase involves a complicated interaction between gonadotropins and steroids: FSH needs to rise slightly to stimulate further follicular development, but at the same time both LH and FSH must be kept at relatively low levels by oestradiol negative feedback. The oestradiol needed to accomplish this latter task is provided by an entire cohort of follicles that start to grow at about the same time, only one of which will normally progress to ovulation while the rest undergo atresia. When the pool of surviving follicles is large, as at young reproductive ages, there will almost always be a sizable number of follicles initiating development at any one time, even if the per-follicle probability of doing so is very small. At older ages, however, when the follicle reserve is low, there will by chance be periods when no follicles initiate development. We hypothesize that inactive phases, whose most salient feature is an absence of ovarian steroidogenesis, correspond to those random intervals when no follicles are recruited. If this hypothesis is correct, the distribution of inactive phases should, in theory, be predictable from the underlying process of follicular depletion. And the frequency of such phases should increase with age as the follicular reserve approaches exhaustion. If so, this phenomenon would explain much of the observed variability in cycle length and "slippage" of HPO function characteristic of the perimenopausal transition.

To derive the distribution of times t spent in the inactive phase for a woman age a, assume that each woman begins with n_0 follicles at birth. Further assume that her follicles initiate growth at any given time at a constant rate λ per follicle, that all follicles eventually initiate growth, and that all but a negligible subfraction of follicles undergo atresia. Then the number of follicles surviving in a woman at age a is $n_a = n_0 e^{-\lambda a}$. The distribution of times spent in the inactive state for a woman age a is a function of the number of surviving follicles at that age and the probability that at least one follicle becomes active. In other words, after exiting the luteal phase, her probability of remaining in an inactive state is the probability that all n_a follicles remain inactive – a problem akin to the survival of a series system with n_a identical exponentially-distributed components. The probability density function for the length of the

inactive phase is then simply the probability that none of the follicles becomes active by a given time t, which is $P(T > t|\lambda,n_a) = \exp(-t\lambda n_0 e^{-\lambda a})$. The mean time in the inactive state at age a is $E(T|a) = (\lambda n_0 e^{-\lambda a})^{-1}$ and the variance is $V(T|a) = (\lambda n_0 e^{-\lambda a})^{-2}$.

Fig. 5 shows several hypothetical examples of the time spent in the inactive phase. For the parameter values used in these examples, the mean time in the inactive phase is low at younger ages but increases markedly by age 50; variation in the length of the inactive phase also increases sharply at later ages. Although these parameter values are informal estimates, they are based on actual follicle counts from autopsy and oophorectomy materials[12,13]. It is striking, then, that the qualitative patterns in Fig. 5 correspond in a general way to what little we know about the distribution of inactive phases by age[25,27,28], as well as to the better-documented variability in cycle length at later ages[29].

One prediction of the model is that, in a large sample, we ought to observe an occasional, albeit brief, inactive phase in women at young reproductive ages. Fig. 6 shows an example in a 25-year old woman monitored in our laboratory, one of a small number of cases we have observed. This example shows that inactive phases *can* occur at young reproductive ages. The reason that they do not occur more often – and that, when they do occur, they are of short duration – is that the values of λ and n_0 do not permit long and frequent inactive phases at these ages. We believe this is no accident, but rather reflects selection for values of λ and n_0 that will maintain regular, predictable cycles at early adult ages when reproductive function is closely related to fitness. But the values of λ and n_0 also determine the age at menopause. To delay or prevent menopause, we would need to alter either λ or n_0 – in other words, we would need to change a system that appears to be subject to stabilizing selection in chimpanzees and humans, presumably at the cost of disrupting cycles in young adult females. While it might be argued that n_0 could be enlarged (perhaps by one more round of mitosis in the proliferating primitive germ cells) without increasing the frequency of inactive phases in young women, Hamilton's model[8] of the relationship between age and fitness suggests that the benefits of such a change are likely to be small – too small, we suspect, to offset the risks involved in changing an already well-established physiological system. We would argue, then, that any advantage to postponing menopause in the longer-lived human species was too minor – or accrued at too late an age, which is another way of saying the same thing – to warrant modifying the follicular-depletion system.

Thus, the occurrence of menopause in humans is, in itself, unsurprising. But why do women routinely survive to ages well *past* the menopause? We suggest, again, that post-reproductive life in human females is not adaptive in itself but is an "artifact" of processes acting at earlier ages. Survival to, say, age 70 involves survival to every age preceding that point. Any evolutionary or cultural change that favors survival to some earlier age, say 50, will *mutatis mutandis* favor survival to 70. A simple metaphor may be useful here[33]. Imagine that we want to send a space probe to fly past Pluto and take photographs of it. Our engineers will do their best to maximize the probability that the probe will reach Pluto. But a well-designed probe that makes it to Pluto will also have a good chance of surviving well after it has flown past its target. It would take more engineering – and more money – to include a special self-destruction package that would make the probe "die" once it has completed its mission, and there is absolutely nothing to be gained from investing the necessary resources in such a package. Who cares if our probe continues taking photographs of empty space for the next several decades as long as it has already done what it is supposed to do? It has been suggested that survival to advanced ages may

involve a similar "fly-by" phenomenon[34]. With respect to menopause, the "fly-by" in humans is illustrated in Fig. 7, which compares the age-specific survival functions estimated for a wild chimpanzee population and a preindustrial human population[35,36]; also shown is the observed distribution of ages at menopause in US women[37]. It is immediately obvious that most of the difference in survival between the two groups occurs well before menopause, and that post-reproductive survival in the human group is simply a second-order effect of enhanced survival at earlier ages (since the survival curve must eventually drop to zero). We do not profess to understand why humans survive better than chimpanzees at reproductive and pre-reproductive ages, but we believe that *post*-reproductive survival in humans is purely an artifact of enhanced survival at younger ages. And, while the higher survival of humans at earlier ages has the secondary consequence of making phenotypes expressed late in life somewhat more important for fitness than they would otherwise have been, in actual fact the change is small: as we have shown elsewhere[38], the partial derivative of fitness with respect to fertility would be very close to zero by age 55 under the mortality conditions observed in the human population shown in Fig. 7, even in the absence of menopause.

In contrast to what is claimed in the grandmother hypothesis, then, menopause and post-reproductive life are not adaptive in themselves, but are the pleiotropic effects of selection acting at earlier reproductive ages. Menopause is nothing more than the final outcome of a decades-long process of follicular depletion, and follicular depletion is essential for the maintenance of regular ovarian cycles at *younger* reproductive ages. It is the follicular-depletion system that is subject to strong selection, not menopause *per se* – hence, the fact that the system appears to be highly conserved in humans and chimpanzees even though menopause is not part of the normal chimpanzee life history. We hypothesize that the selective advantage of particular combinations of atresia rate and initial follicle stock in maintaining cycles at earlier ages – say, in the twenties and early thirties – more than offsets the selective costs of terminating reproduction by the fifties, when no life history phenomenon is expected to have a strong effect on fitness. Menopause, then, appears to be a straightforward case of antagonistic pleiotropy. Post-reproductive life in humans is simply a secondary consequence of higher survival during reproductive and pre-reproductive life, the reason for which is as yet unclear. While the emergence of menopause and post-reproductive life in hominids may have presented new *opportunities* for females to invest in their grandchildren, the grandmother hypothesis is unnecessary as an explanation for the evolutionary origins of menopause and post-reproductive life.

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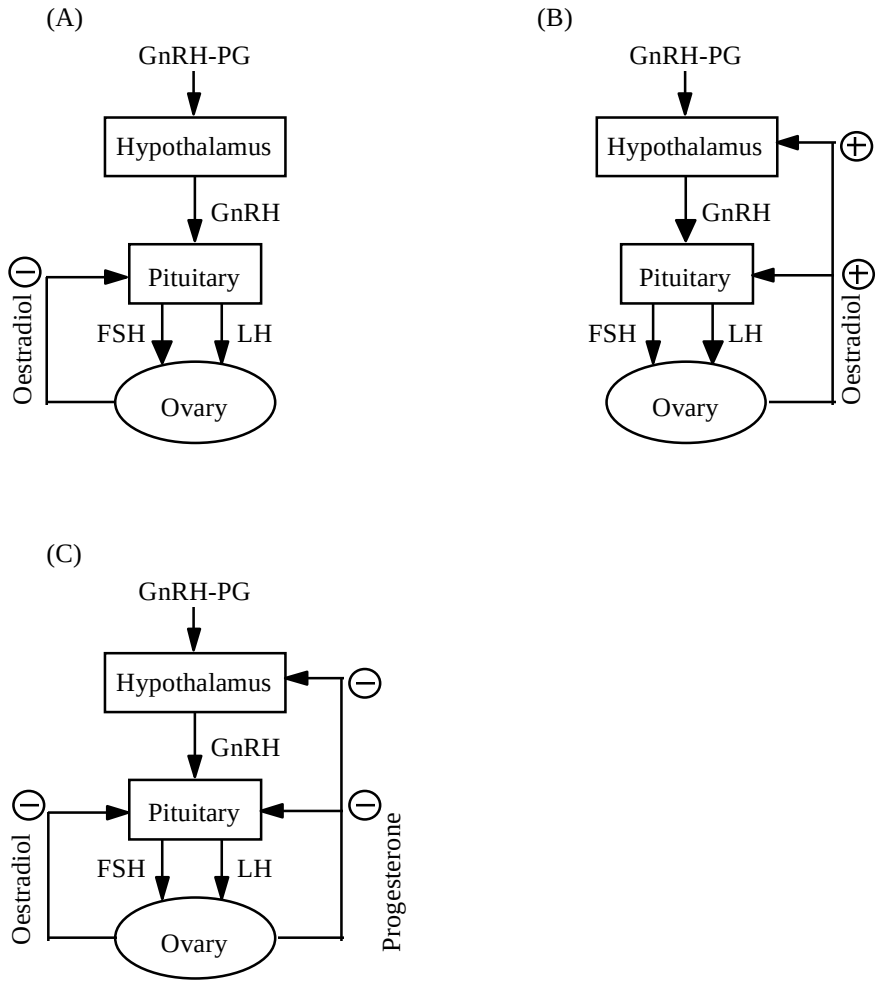

Figure 1. Schematic representation of feedback relationships in the hypothalamic-pituitary-ovarian axis at different stages of the primate ovarian cycle. Pluses and minuses represent the direction of steroid feedback effects. (A) Early follicular (preovulatory) phase. (B) Late follicular phase to about the time of ovulation. Throughout most of the follicular phase, oestradiol feeds back negatively on the pituitary, but just before ovulation the feedback on the pituitary and hypothalamus becomes positive. The resulting surge in FSH and (especially) LH triggers ovulation and luteinization. (C) Luteal (postovulatory) phase. It is the regular oscillation among these sets of feedback relationships that maintains predictable ovarian cycles. *GnRH*, gonadotropin-releasing hormone. *GnRH-PG*, GnRH pulse generator. *LH*, luteinizing hormone. *FSH*, follicle-stimulating hormone. (Adapted from ref. 23.)

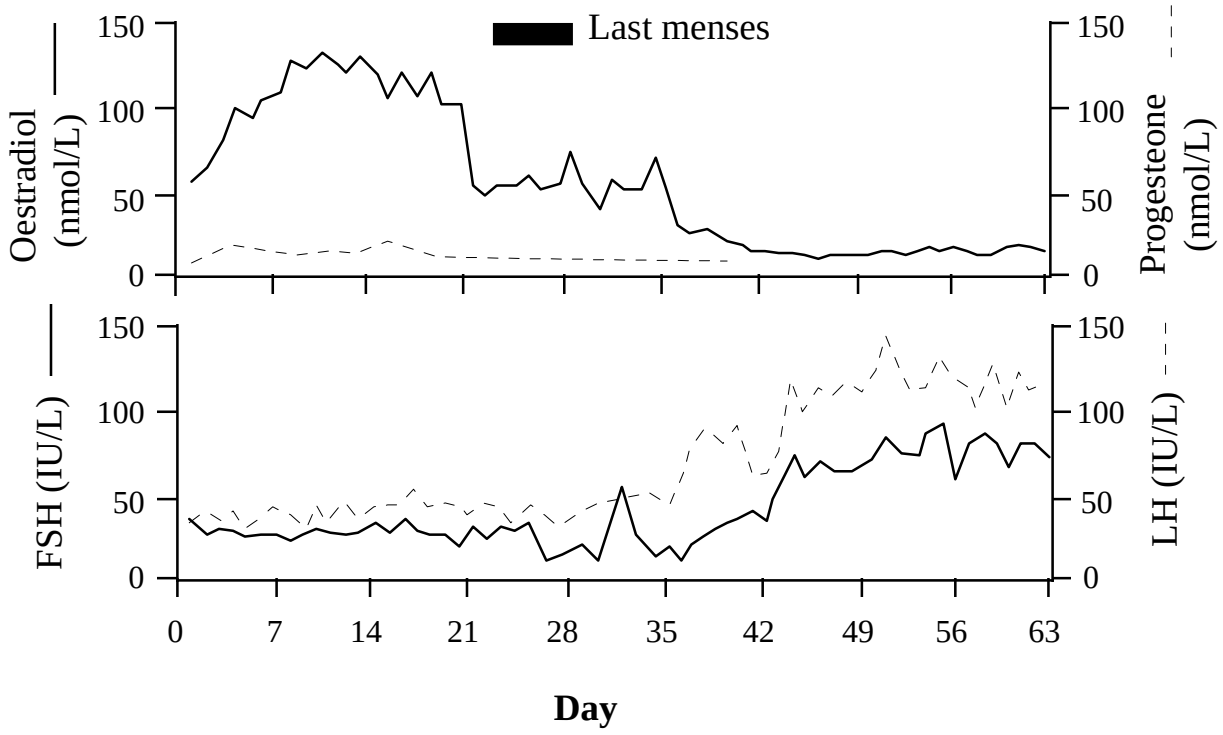

Figure 2. Changes in the plasma concentrations of ovarian steroids (top) and gonadotropins (bottom) during the menopausal transition in a woman age 48 years. Note that the fall in oestradiol concentration results in the last menses and is followed by a marked rise in the concentrations of LH and FSH. (Redrawn from ref. 24.)

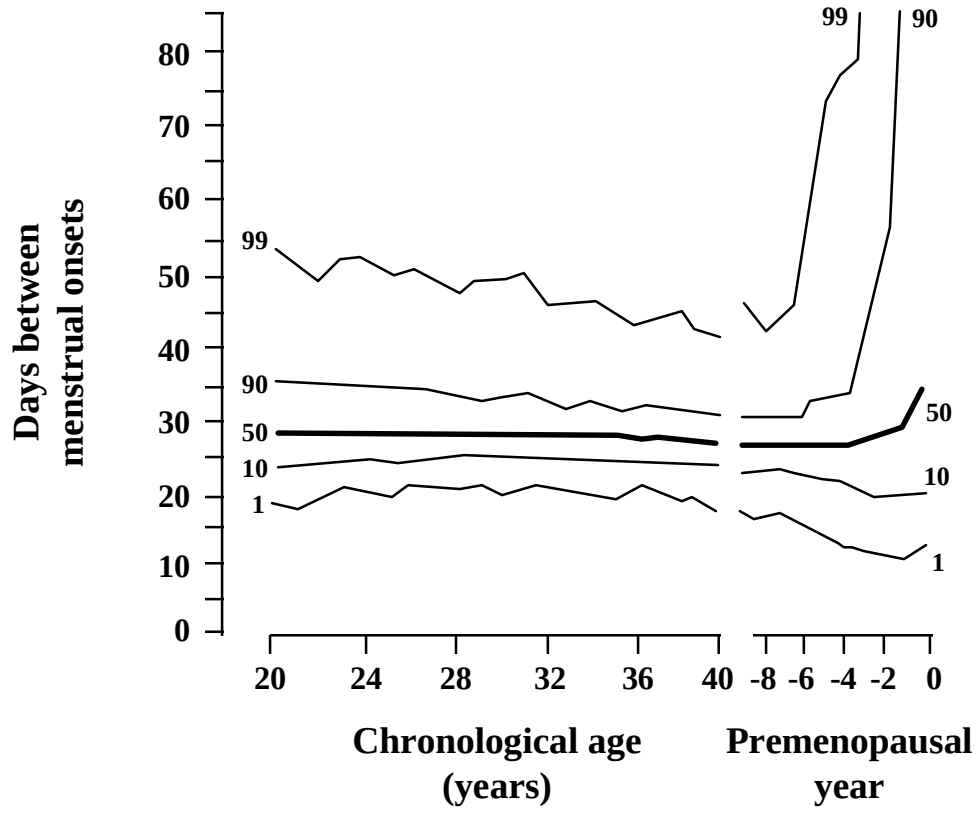

Figure 3. Age-related variation in the length of menstrual cycles as shown by percentiles of the distribution of cycle lengths, based on 25,844 woman-years of menstrual experience in 2,702 US women. (Redrawn from ref. 29.) To separate the effects of chronological and developmental age, the *x*-axis shows chronological age for ages 20-40, and years before menopause for the last nine years of menstrual life.

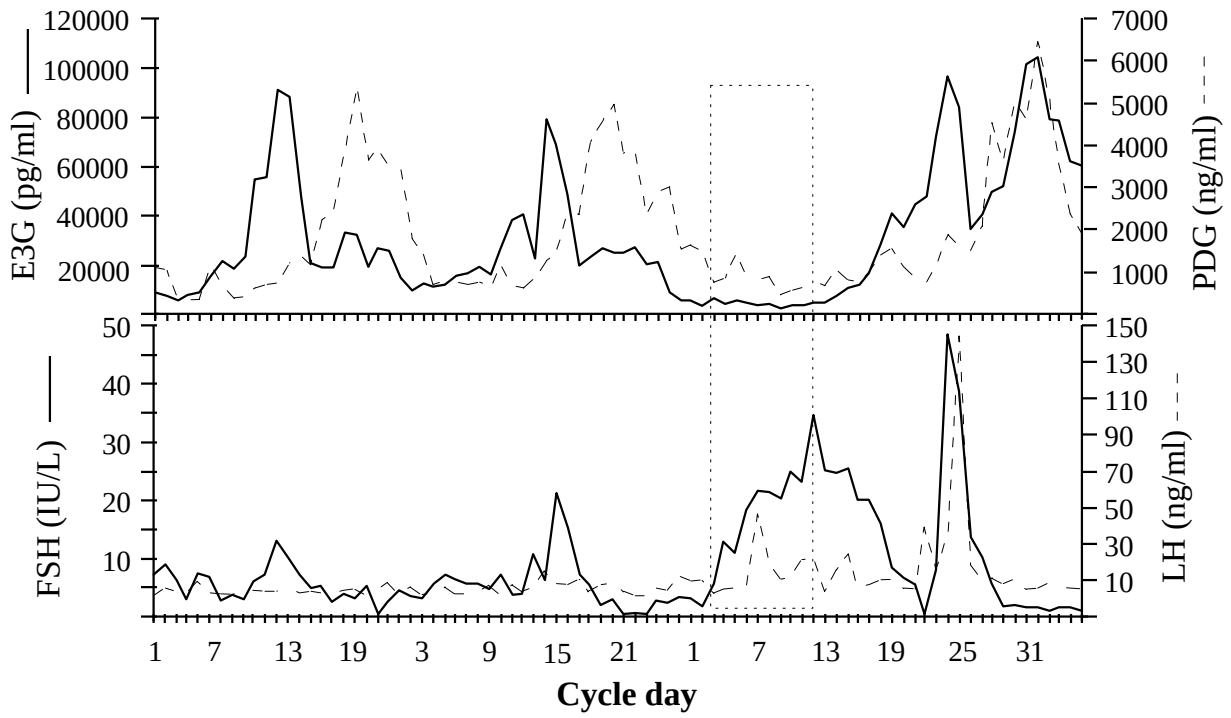

Figure 4. Urinary steroid (top) and gonadotropin (bottom) excretion in a 45-year old US woman during the perimenopausal transition (as indicated by a self-report of irregular cycles). Note the period of ovarian quiescence at Days 2-12 of Cycle 3 (box). *E3G*, oestrone-3α-glucuronide, the major urinary metabolite of oestradiol. *PdG*, pregnanediol-3α-glucuronide, the major urinary metabolite of progesterone. Hormone concentrations are normalized by specific gravity.

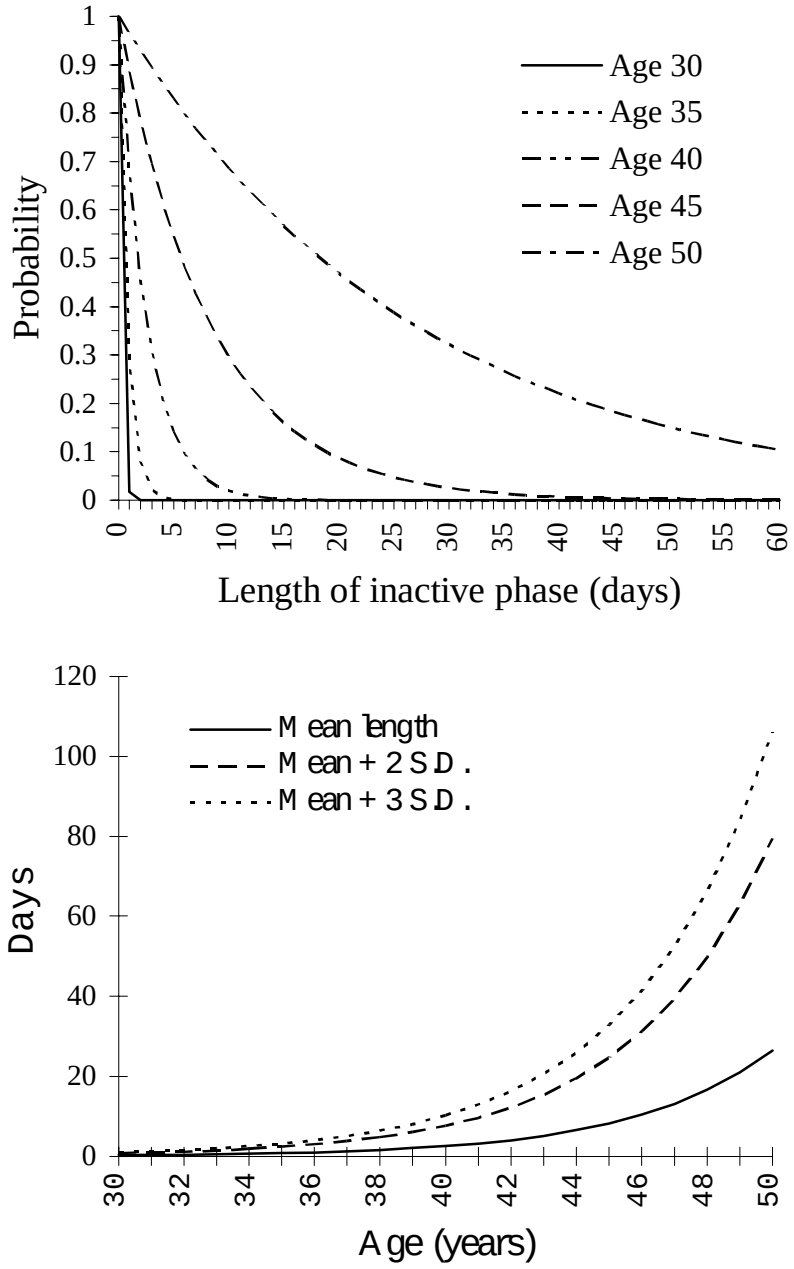

Figure 5. Hypothetical examples of the time spent in the inactive phase by a woman at five different ages, assuming an initial follicle pool (at birth) of one million follicles and a daily rate of a follicle entering the growing state equal to $\lambda = 0.00065$. (Top) The survival function for time spent in the inactive phase; the point at which each curve reaches 0.5 on the *y*-axis corresponds to the median time in that phase. (Bottom) Central tendency and variation in times spent in the inactive phase at different ages in the same woman, shown as the mean phase length plus two or three standard deviations (capping approximately 97.5 and 99.5 percent of all inactive phases, respectively).

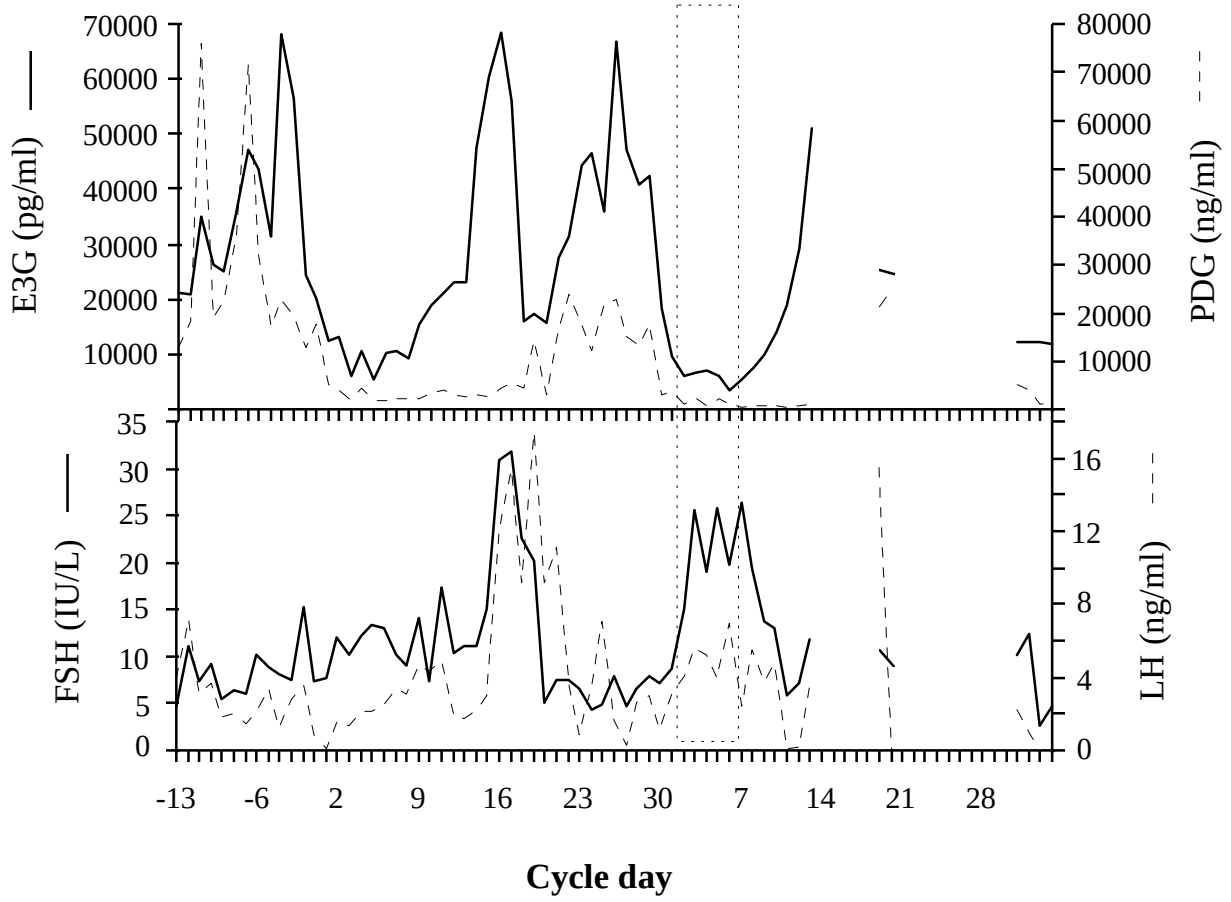

Figure 6. Urinary steroid (top) and gonadotropin (bottom) excretion in a normal 25-year old US woman. Note the period of ovarian quiescence at Days 1-6 of Cycle 2 (box). *E3G*, oestrone-3α-glucuronide. *PdG*, pregnanediol-3α-glucuronide. Hormone concentrations are normalized by specific gravity.

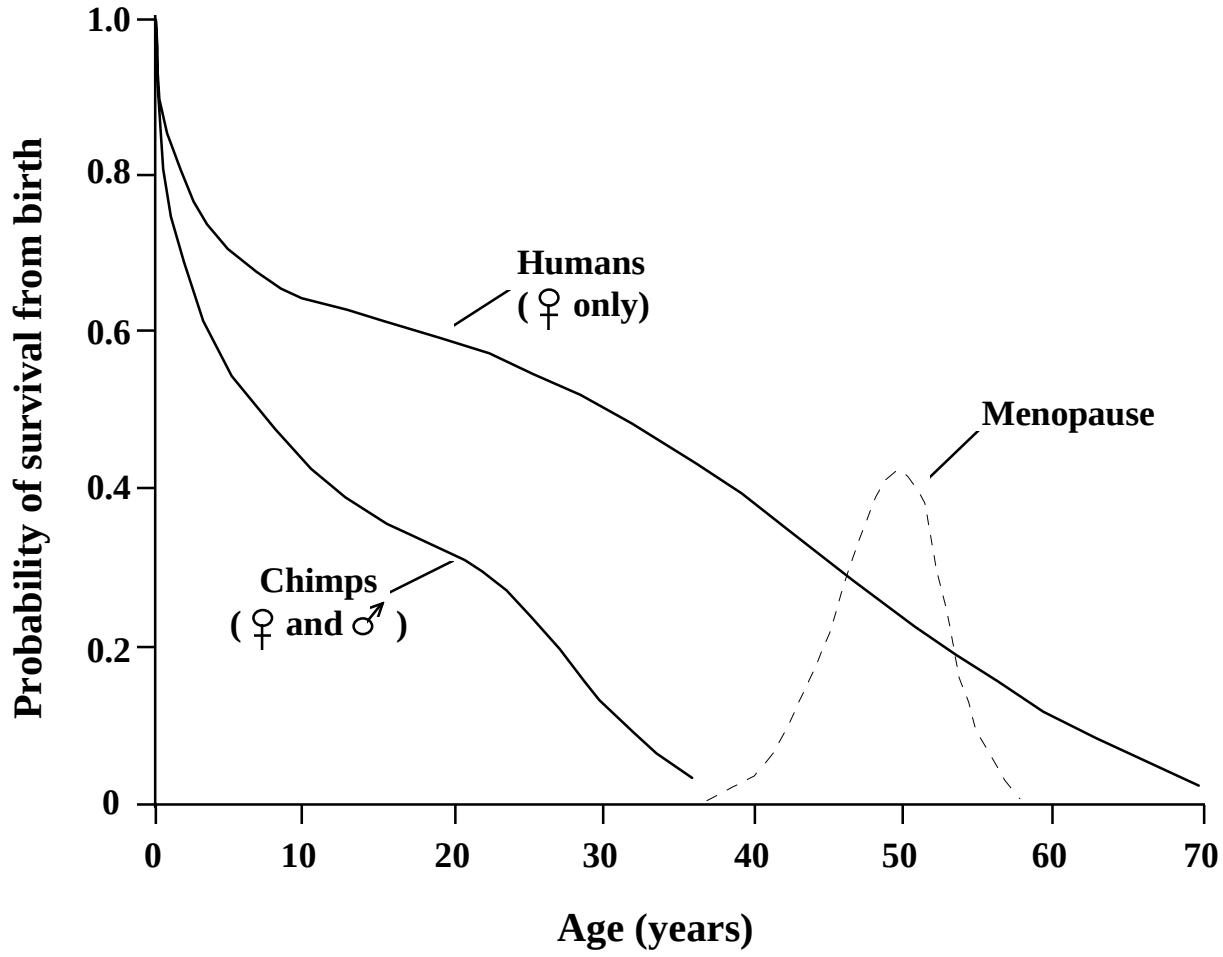

Figure 7. Age-specific survival functions (solid lines) in wild chimpanzees from Gombe Park, Tanzania, and a preindustrial human population, the Gainj of highland Papua New Guinea. The plotted curves are life-table estimates of the probability of surviving from birth to each successive age. The chimpanzee estimates represent 33 observed deaths (both sexes combined) treated as if derived from a stationary population; the Gainj estimates are based on 135 deaths (females only) in 4395 person-years of exposure. The broken curve is the estimated probability density function for age at menopause in 324 US women born in 1910-1925 and monitored prospectively from about age 20. (Data from refs. 35, 36, 37.)