# Center for Studies in Demography and Ecology

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**Abstract**

Menopause, the final cessation of menstrual cycling, occurs when the pool of ovarian follicles is depleted. The one to five years just prior to the menopause are usually marked by increasing variability in menstrual cycle length, frequency of ovulation, and levels of reproductive hormones. Little is known about the mechanisms that account for these characteristics of ovarian cycles as the menopause approaches. Some evidence suggests that the dwindling pool of follicles itself is responsible for cycle characteristics during the perimenopausal transition. Another hypothesis is that the increased variability reflects "slippage" of the hypothalamus, which loses the ability to regulate menstrual cycles at older reproductive ages.

We examine the underlying cause of the increasing variability in menstrual cycle length prior to the menopause. A model of ovarian cycles is developed, based on the process of follicular growth and depletion. Under this model, the follicular phase of each menstrual cycle is preceded by an *inactive phase*, a period of time when no ovarian follicles have left the resting state and begun secreting steroids in response to gonadotropin stimulation. The model makes predictions about the variability in menstrual cycles across the reproductive life span based on the size of the surviving pool of ovarian follicles. We show that the model can explain several characteristics of the perimenopause in humans and macaques.

## Introduction

Across most of the reproductive life span, menstrual cycles exhibit relatively little variability in length around a median of 28 days (Treloar et al., 1967). Beginning from one to five years before menopause (the perimenopause), menstrual cycle length becomes increasingly variable. In particular, this time period is characterized by a higher frequency of long cycles (Figure 1). Additionally, a higher proportion of menstrual cycles are anovulatory (Metcalf, 1983), and hormone levels become increasingly variable. Menopause itself is the complete and irreversible cessation of ovarian cycling.

The mechanism responsible for menopause has long been recognized to be exhaustion or near exhaustion of the pool of ovarian follicles (Richardson et al., 1987; Gougeon et al., 1994, vom Saal et al., 1994). Less is known about the mechanisms responsible for the increasingly variable nature of menstrual cycles across the perimenopausal transition. At least two major ideas have been proposed. One hypothesis is that increasingly variable cycles across the perimenopausal transition result from a breakdown in the signaling between the ovary and the hypothalamus (e.g., Wise et al., 1996; Klein et al., 1996). The pervasive observation of elevated levels of FSH in women at older reproductive ages is cited as support for this hypothesis, although the mechanism(s) contributing to elevated FSH or hypothalamic faltering are unspecified (Santoro et al., 1996; Metcalf et al., 1982; Klein et al., 1996; MacNaughton et al., 1992).

An alternative hypothesis suggests that the increasing variability in menstrual cycle length is almost entirely a result of the diminished number of ovarian follicles remaining in the ovary in the years preceding the menopause (Richardson et al., 1987). In this paper we specify a mechanism for this hypothesis. Specifically, we propose a new model for ovarian cycles that

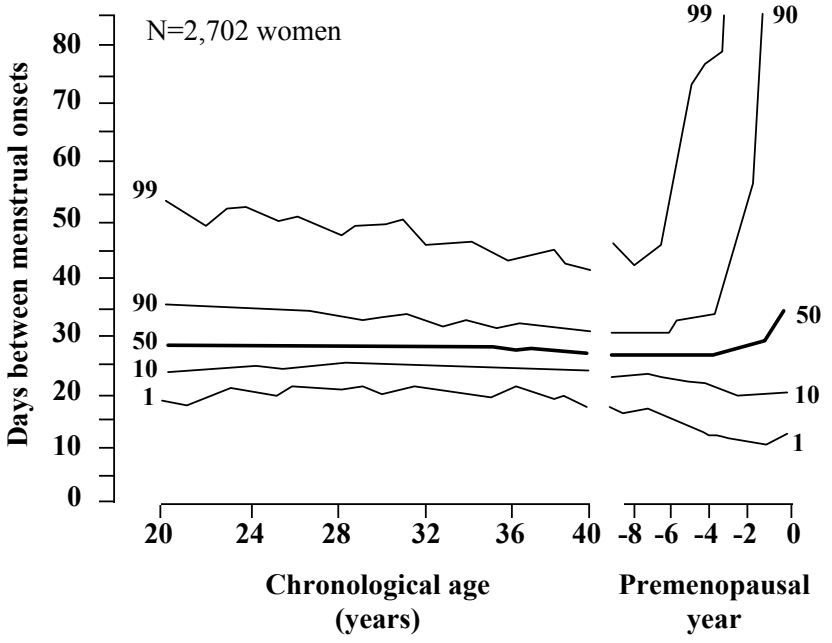


Figure 1. Variation in menstrual cycle length by age and perimenopausal status. Data are from a long term prospective study of American women. Redrawn from Treloar et al. (1967:90).

accounts for many of the observed changes in menstrual cycle variability across the perimenopause, including the observed increase in variability in menstrual cycle length and hormone profiles. Under this model the increased proportion of long menstrual cycles during the perimenopause are a direct result of periods of ovarian inactivity that increase in length as the pool of ovarian follicles diminishes. These so-called 'inactive' phases of the menstrual cycle have a distinct endocrine signature, and we provide evidence of inactive phases from endocrine studies in humans and macaques.

### Follicular development and depletion

The story of menopause begins *in utero*. Early during embryonic development of the female, a lifetime stock of primary oocytes are formed at the gonadal ridge by rounds of mitosis from a pool of oogonia. Each oocyte then undergoes meiosis I through prophase. The final pool of oocytes is formed by the second trimester of pregnancy, and each oocyte is surrounded by a layer of granulosa cells, called a follicle, as the ovaries form (Gougeon, 1996). The follicle is the structure that houses and nourishes the oocyte, and it is the follicle that receives and sends hormonal signals to the other parts of the reproductive axis to maintain regular ovarian cycles.

Since this pool of ovarian follicles and oocytes is non-replenishable, the maximum number of ovarian follicles peaks in utero at about 7 million (Austin and Short, 1982). From this point on, the pool of follicles is depleted through a process called follicular atresia (Figure 2). By the time of birth, the pool of follicles has depleted to roughly one half million per ovary (Block, 1953). By menarche, the pool has been reduced to about 100,000 follicles per ovary. The perimenopausal transition, which may last up to five or six years, begins when approximately 100 to 1,000 follicles are left in each ovary (Richardson et al., 1987; Gougeon 1996). Menopause itself is the ultimate exhaustion of the follicle stock.

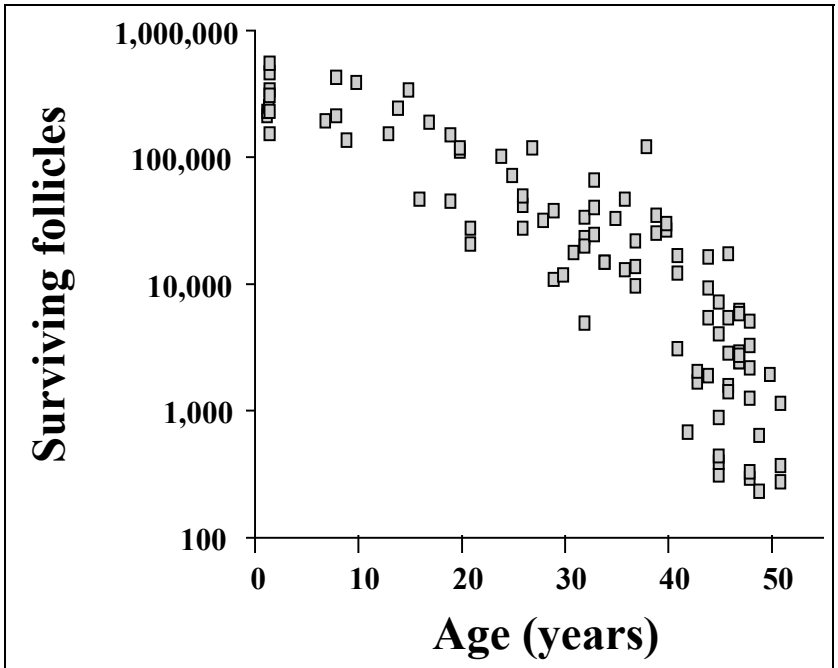


Figure 2. Surviving numbers of follicles in women by age, based on counts of follicles in ovaries removed in autopsies and oophorectomies. Data are from Block (1952, 1953) and Gougeon et al. (1994).

The process by which follicular depletion occurs is not well understood. A resting follicle (one that has not begun to grow) initiates growth by a process that is poorly understood. Definitive endocrine, autocrine or paracrine factors have not been identified (Gougeon 1996), but gonadotrophin hormones are not believed to be necessary to trigger the *initial* growth of the follicle. Each and every follicle appears to have a small and nearly constant probability of entering into this initial growing state at any point in time across the life span.

Mathematically, this can be expressed as an exponential (or log-linear) decline in the numbers of surviving follicles with age (Figure 2). This same pattern of exponential depletion of follicles throughout life is found in other primates and mammals (Austin and Short, 1982; Miller et al., 1999). Data from autopsy and oophorectomy sources are suggestive of an increase in the rate of follicular depletion in the years prior to menopause in women (Faddy and Gosden, 1995) although the mechanism responsible for this acceleration is unclear.

Growing follicles usually survive for only a short time before undergoing atresia. The mechanisms that determine when and why atresia occurs to particular follicles are still unknown. The vast majority of follicles undergo atresia, which is a form of apoptosis (Hsueh et al., 1994; Kaipia and Hsueh, 1997). The few exceptions are those follicles that continue to grow and become the dominant follicle during a menstrual cycle. These follicles are the ones that secrete steroid hormones and participate in ovulation, and luteinization after ovulation.

### The hypothalamic-pituitary-ovarian axis

The ovarian follicles communicate and work closely with the hypothalamus and pituitary to maintain regular ovarian cycles. The GnRH pulse generator, a neural complex located in the hypothalamus, controls pulsatile secretion of gonadotropin-releasing hormone (GnRH) by hypothalamic neurons. GnRH, in turn, is carried to the anterior lobe of the pituitary gland by the portal capillary system, where it stimulates secretion of the protein hormones luteinizing hormone (LH) and follicle stimulating hormone (FSH). These hormones stimulate follicular growth and development, and are necessary for initiating and maintaining follicular production of the ovarian steroids estradiol and progesterone. Feedback relationships between the ovarian steroids on the one hand and the hypothalamic and pituitary gonadotropins on the other maintain the highly regular pattern of ovarian cycles in the adult female.

The four main hormones involved in these feedback relationships, and how they change across the menstrual cycle are shown in Figure 3. These data are from collection and analysis of daily urine samples across three menstrual cycles from a normally cycling woman. The first day of menses is labeled as cycle day one on the *x*-axis. The top panel shows the main urinary metabolites, estrone-3-glucuronide (E3G) and pregnanediol-3α-glucuronide (PDG), of the ovarian steroids estradiol and progesterone. These metabolites parallel serum levels of estradiol and progesterone (Munro et al., 1991). The pituitary hormones LH and FSH are shown in the lower panel of Figure 3.

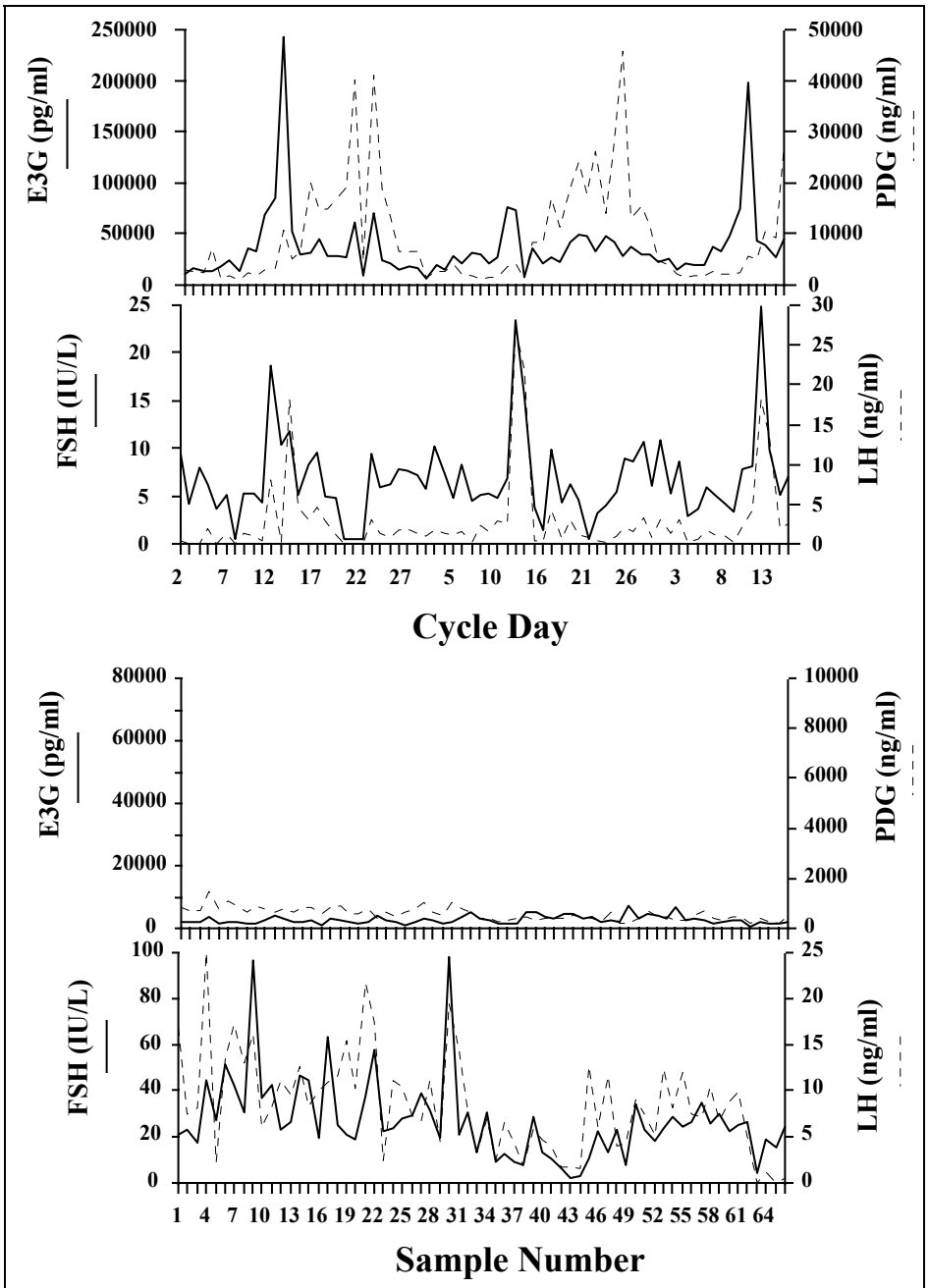


Figure 3. Urinary steroid and gonadotropin profiles for a regularly cycling woman (top panels) and a menopausal woman (bottom panels). Each cycle day one is the first day of menses. Hormone values are corrected by specific gravity. Source: Pennsylvania State University Reproductive Endocrinology Laboratory.

In a typical menstrual cycle, steroid hormones are low at the start of each menstrual cycle (day 1 of menses), reflecting the absence of any follicles large enough to produce measurable levels of estradiol. In the absence of ovarian steroids, the gonadotrophin hormones LH and especially FSH become elevated. The elevated gonadotropins stimulate follicular growth and steroid production in any follicles that have matured to the point of developing receptors for FSH. Follicles responding to FSH will continue to the next stage of growth and begin to secrete

estradiol. This estradiol then acts in a negative feedback loop with the hypothalamus to downregulate gonadotropin secretion. Hence, as estradiol secretion begins, LH and FSH secretion declines. Because growing follicles secrete estadiol in proportion to their size, we see estrogen rising slowly at first and then more rapidly as one or more follicles grow to larger sizes. One follicle will eventually become the dominant follicle through a poorly understood process called follicular selection.

Once the estrogen reaches very high levels (around day 14 or mid-cycle), a surge of LH (and to a lesser extent, FSH) is triggered. This surge causes the dominant follicle to rupture and release the oocyte within it—this is ovulation. The part of the cycle from cycle day one until ovulation is called the follicular phase, because the main activity in this part of the cycle is follicular growth.

After ovulation, the follicle from which the egg erupted differentiates into the corpus luteum, an endocrine gland that secretes mostly progesterone but also some estrogen. This second half of the ovarian cycle is called the luteal phase, after the corpus luteum. The function of progesterone and estrogen in this phase is to finish preparing the uterus for pregnancy. The elevated levels of progesterone and estrogen prevent significant secretion of LH or FSH. In the absence of pregnancy, the corpus luteum regresses until levels of progesterone are too low to maintain the uterine lining. The uterine lining is then shed, resulting in menses and the start of the next menstrual cycle. As the steroid levels decline at the end of an ovarian cycle, LH and FSH slowly elevate as they are released from negative feedback control. The elevated level of FSH then stimulates the next cohort of follicles to develop. This set of feedback relationships of the hypothalamic-pituitary-ovarian (HPO) axis thus serves to maintain regular ovarian cycles throughout the reproductive life span.

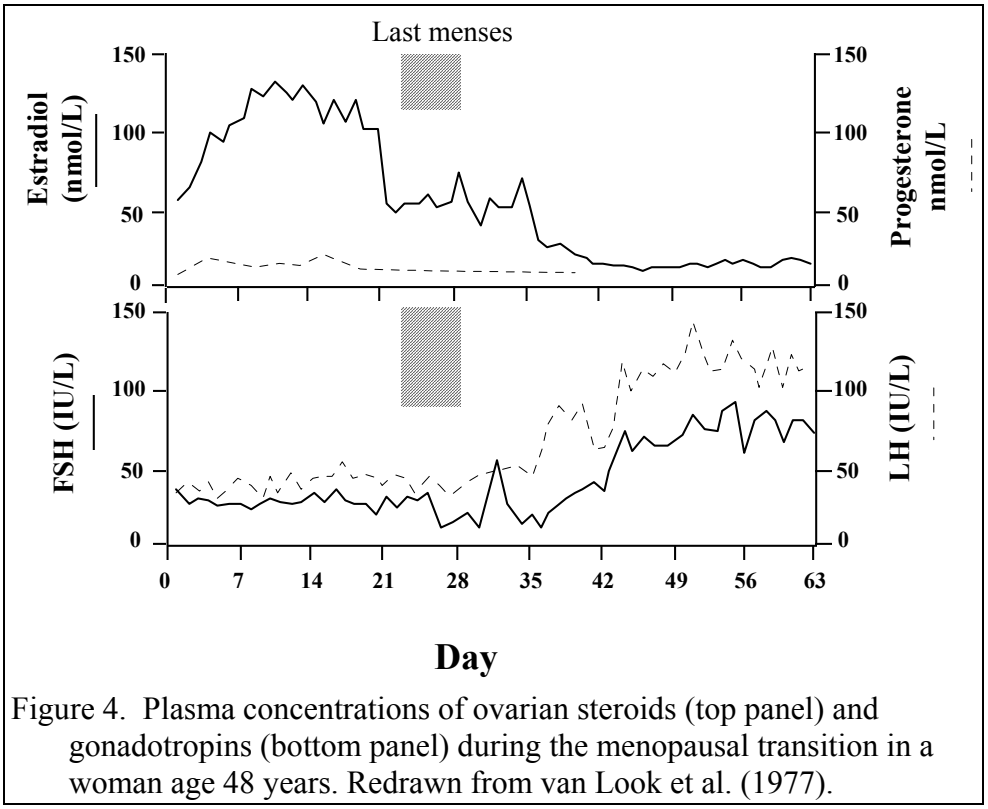


Figure 4. Plasma concentrations of ovarian steroids (top panel) and gonadotropins (bottom panel) during the menopausal transition in a woman age 48 years. Redrawn from van Look et al. (1977).

### Endocrine patterns of the menopause and perimenopause

In menopause, one part of the HPO system breaks down as the ovaries become depleted of follicles. When there are no ovarian follicles, there is no ovarian production of estrogen or progesterone. There is, therefore, a loss of negative feedback at the hypothalamus so that pituitary secretion of LH and FSH increases to high levels. In post-menopausal women, LH and FSH levels are consistently high, reflecting this lack of feedback from ovarian steroids.

This can be clearly seen in the lower panel of Figure 3, which shows daily concentrations of urinary steroids and gonadotropins across three months in a postmenopausal woman. There are negligible levels of ovarian steroids, and in the absence of ovarian steroid feedback, gonadotropin concentrations are about four-fold higher than those found in a cycling woman.

The transition to menopause thus involves a switch from a well-orchestrated system of feedback and control to one of unregulated gonadotropin release in the absence of ovarian production of steroids. The final transition can be seen in Figure 4, which tracks a 48 year old woman across approximately two months as she experiences her last-ever menstrual bleed. 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 about two weeks during which some estradiol is present, presumably reflecting some degree of partial follicular activity. After this interval, the levels of both estradiol and progesterone are very low and unchanging, and will remain so for the rest of the woman's life. Coinciding with the decline in ovarian steroids is a marked elevation in LH and FSH, indicating that the hypothalamic-pituitary axis has been freed from negative feedback by ovarian steroids. Her gonadotropins are likely to be high and variable throughout the rest of her life (Hee et al., 1993).

The period of transition from regular ovarian cycles to an absence of ovarian cycles is characterized by increasingly irregular cycle length, and a rapidly dwindling pool of follicles. We also see increasingly variable hormone profiles during this transitional period. In fact, hormone profiles in the perimenopause often contain elements of both menopausal and cycling hormone profiles.

Figure 5 shows three menstrual cycles for a perimenopausal 45-year old woman. Throughout most of the period of observation, she experiences normal, ovulatory cycles. Beginning, however, at about cycle day 3 of the third cycle (boxed-in area) she goes through about a ten-day period with no sign of ovarian steroidogenesis. At the same time, her LH and FSH rise rapidly, presumably because of an absence of negative feedback from steroids. We believe that this is evidence that there are no follicles at the appropriate developmental state to begin further growth under the influence of FSH. Eventually, however, one or more follicles begins growing, as evidenced by the rising estrogen; LH and FSH levels decline as the steroids down-regulate the hypothalamus, and the cycle continues normally through ovulation and the luteal phase.

This period of time when no follicles are developing looks, hormonally, very much like menopause. If we had analyzed a single urine or blood specimen during this ten-day period, we might have concluded that this woman was menopausal. But clearly she is not; this brief period of “false menopause” is followed by ovulation. One effect of the two-week period of ovarian quiescence is that this particular cycle is inordinately long, as is often the case during the perimenopause.

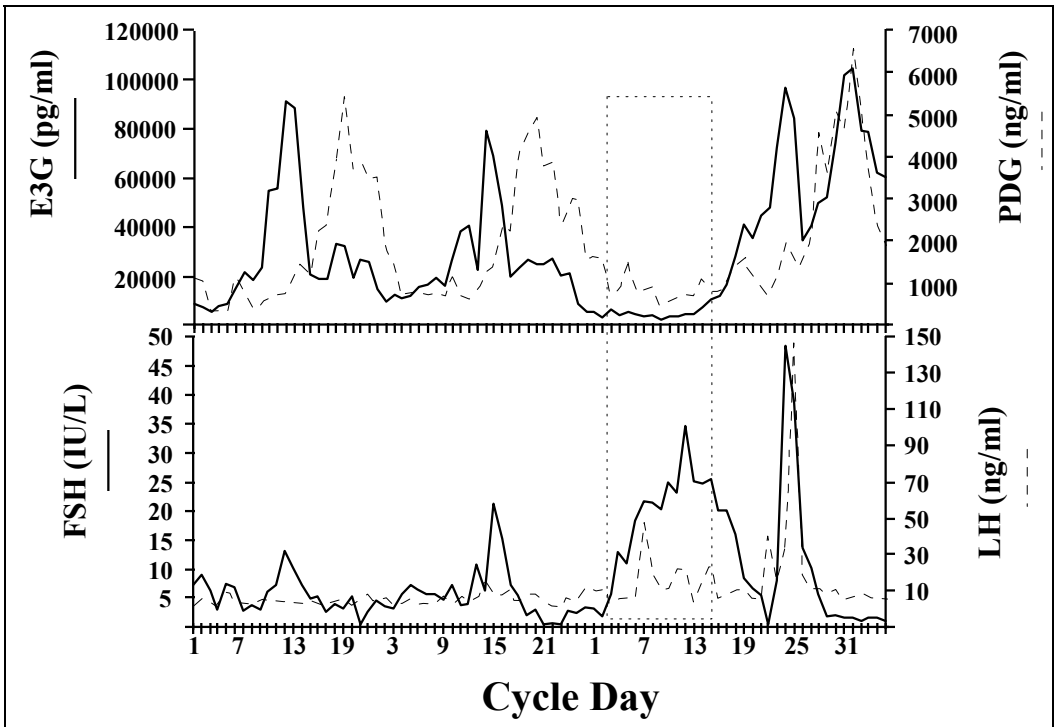


Figure 5. Urinary steroid and gonadotropin excretion in a 45 year-old perimenopausal women (as assessed by self-reports of irregular cycle lengths), showing an inactive phase (boxed-in area) at the beginning of the third menstrual cycle. Each cycle day one is the first day of menses. Hormone values are corrected by specific gravity. Source: Pennsylvania State University Reproductive Endocrinology Laboratory.

### Three phase model of the menstrual cycle

We call these transient episodes of ovarian quiescence "inactive phases" of the menstrual cycle. Our hypothesis is that inactive phases are direct reflections of the very small pool of remaining follicles. Inactive phases are characterized by the absence of steroid production and correspond to those periods of time when no follicles have begun growing. When the stock of follicles is large, as at young reproductive ages, inactive phases will be rare as there will nearly always be a cohort of follicles initiating development at the start of any given menstrual cycle. At older ages, however, when the follicle reserve is low, there will, by chance, be periods of time when no follicles are initiating development. The ovary is, in essence, 'sputtering' when the follicle reserve is very low. Inactive phases are a natural statistical outcome of repeated sampling from a stock containing small absolute numbers of items. Menopause is effectively a permanent inactive phase.

We have observed several examples of inactive phases in our laboratory and the published literature (Sherman et al., 1976; Shideler et al., 1989; Hee et al., 1993; Santoro et al., 1996). The characteristic endocrine pattern is one of low and unchanging levels of reproductive steroids, coupled with elevated concentrations of FSH and to some extent LH. This pattern is seen in Figure 5 from our laboratory, and in Figure 6 from two published studies of the perimenopause (Figure 6 bottom panel; Santoro et al., 1996; top panel from Shideler et al., 1989). Note that in

each example the length of the cycle containing the inactive phase is considerably longer than the cycles preceding or following it.

If our hypothesis that inactive phases are direct reflections of the very small pool of remaining follicles is correct, then the distribution of inactive phases by age should be predictable, given an underlying rate at which follicles initiate growth. The frequency and mean length of inactive phases should increase with age, as the follicular reserve approaches exhaustion.

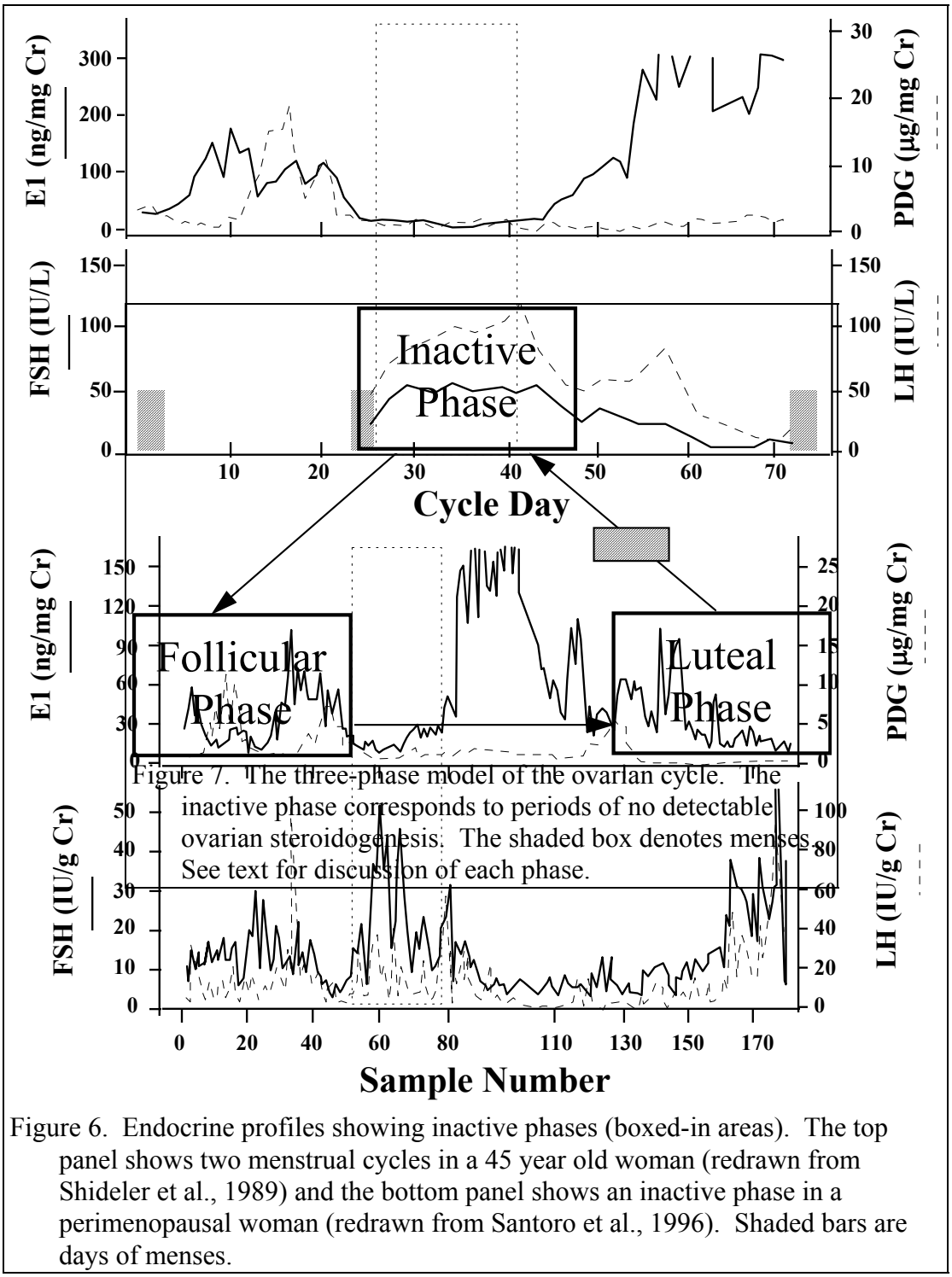


Figure 6. Endocrine profiles showing inactive phases (boxed-in areas). The top panel shows two menstrual cycles in a 45 year old woman (redrawn from Shideler et al., 1989) and the bottom panel shows an inactive phase in a perimenopausal woman (redrawn from Santoro et al., 1996). Shaded bars are days of menses.

We model the distribution of inactive phase lengths by decomposing the ovarian cycle into three distinct phases (Figure 7): the inactive phase, the follicular phase, and the luteal phase (O'Connor et al., 1998). The first phase is the inactive phase—the period of time in which no follicles have initiated growth, or matured to the point of producing estradiol. This phase should usually be vanishingly small in younger women, but may be longer in perimenopausal women. The inactive phase is followed by the follicular phase, which encompasses the period from the

first follicular secretion of estradiol to the time of ovulation. The luteal phase remains as traditionally defined, the time from ovulation to menses. The entire inter-menstrual interval is the sum of these three phases (Figure 7).

In this model, the rate at which follicles initiate growth is assumed to be proportional to the rate of follicular depletion. All follicles are assumed to have the same hazard of initiating growth, and this hazard does not change across the life span. We also assume homogeneity across women in the size of the initial follicle pool, and the rate of atresia. Other versions of the model incorporate unmeasured heterogeneity in the rate of atresia or follicle pool size, or explicitly incorporate covariates (such as cigarette smoking) that might influence the rate of atresia and the timing of menopause. The mathematical details of the model are given in the Appendix.

Figure 8 shows the distribution of inactive phases by age, predicted by the simplest model given in the Appendix. The top panel illustrates the probability of remaining in an inactive phase for a given number of days, at five different ages. Clearly, a 30 year old woman will almost always have extremely short, and largely undetectable, inactive phases. By age 40, the median length is still quite short but there is now some non-negligible probability of an inactive phase being up to 12 days long. By 50 years of age, many cycles are expected to have long inactive phases.

The age-specific mean lengths for inactive phases are shown in the bottom panel of Figure 8. At younger ages, the length of the inactive phase is short enough that the inactive phase almost always adds no measurable time to the overall length of the menstrual cycle, and the variability is low enough that we would rarely expect an inactive phase of any discernible length. As menopause approaches, both the mean and variability in the length of the inactive phase increases greatly, showing a pattern that is strikingly similar to the increased variability in menstrual cycle length during the perimenopause (Figure 1).

One prediction that follows from the model and Figure 8 is that we should very occasionally see inactive phases in young women. Figure 9 shows an example from our laboratory that we believe is a short inactive phase in a healthy, normally cycling 25 year old woman. The boxed-

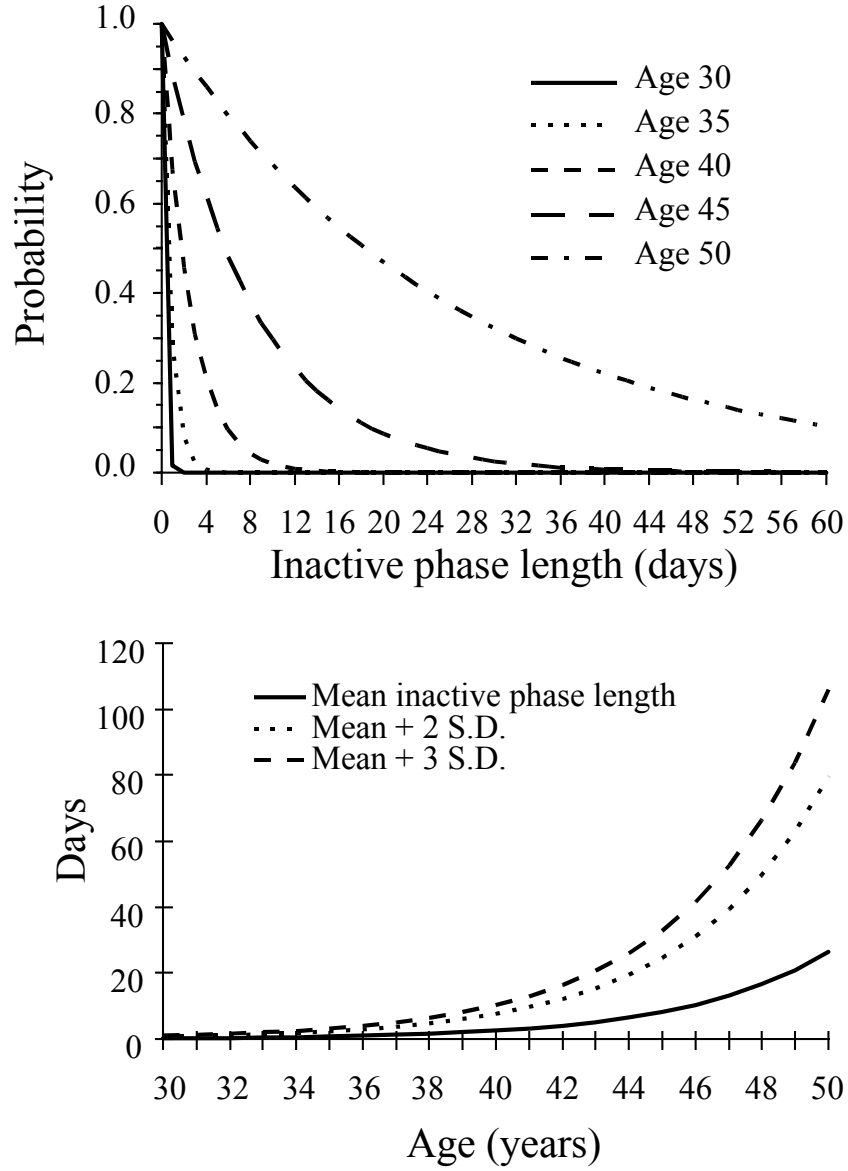


Figure 8. Hypothetical example of times spent in inactive phase, under a simple model that assumes an initial follicle pool (at birth) of one million follicles and a daily hazard of a follicle entering the growing state of $\lambda$=0.00065 (based on data from Block, 1952, 1953, and Gougeon et al., 1994). The top panel shows the probability of no follicles initiating growth, at five different ages. The bottom panel shows the mean and variance in inactive phase length by age of a woman.

in area highlights a brief period where the steroid hormones are quite low and constant, and LH and FSH are elevated due to the absence of negative feedback from reproductive steroids. There

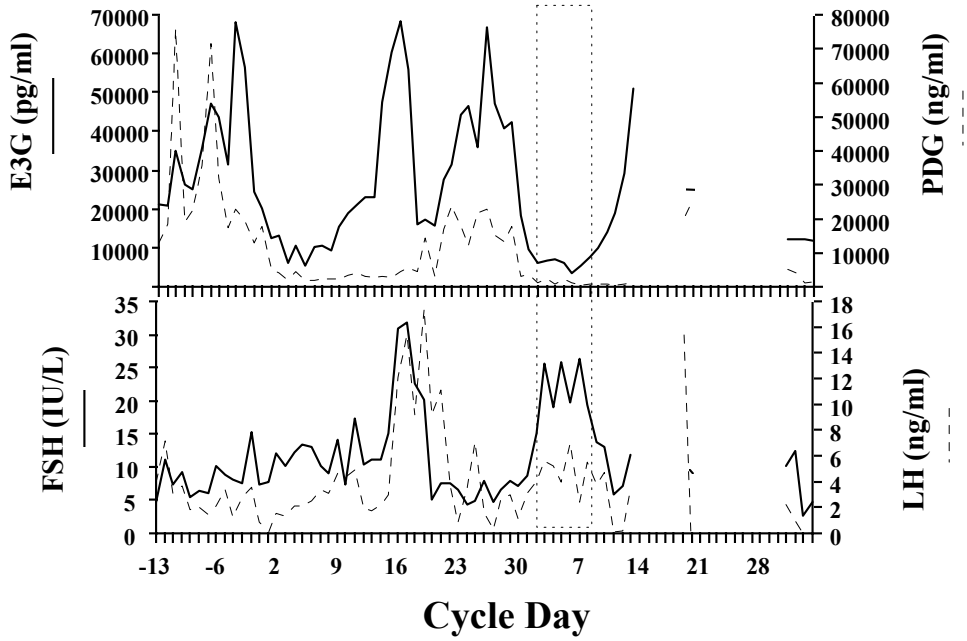


Figure 9. Urinary steroid and gonadotropin excretion in a 25 year-old cycling woman showing a short inactive phase at the beginning of the second menstrual cycle (boxed-in area). Each cycle day one is the first day of menses. Hormone values are corrected by specific gravity. Source: Pennsylvania State University Reproductive Endocrinology Laboratory.

are several missed days of collection following the inactive phase in this study participant, but the rising estrogen and LH peak after the inactive phase indicate that follicular development and ovulation ultimately did occur.

Another prediction following from our model is that we should expect to see inactive phases in other animals with similar reproductive biology and life history traits. If the follicular depletion system is the ultimate cause of the hormonal and ovarian cycle features characteristic of the perimenopause and menopause, then inactive phases should be present in those species possessing follicular depletion. The follicular depletion system is in fact a primitive trait that is highly conserved across most mammals (Austad, 1997) and many vertebrates (Norris, 1997). In most mammalian species, the stock of follicles tends to last longer than the average life span, therefore evidence of inactive phases should be expected only in long-lived species that survive beyond reproductive ages.

Hormonal data for large-bodied or long-lived mammals are rare. One example is from Gilardi and colleagues (1997), who have published daily hormonal data for rhesus macaques from the California Regional Primate Center. The top panel of Figure 10 shows daily urinary estrogen and progesterone metabolites for a 20-25 year old regularly cycling rhesus macaque. Unfortunately, there are no LH or FSH data for these macaques, but we can see clearly here that this animal is experiencing regular cycles, and they are remarkably like those seen in human females. The middle panel shows hormone data for another macaque from the same study, but this animal is 29 years old and amenorrheic. This is the hormone profile of a menopausal macaque. The bottom panel shows a perimenopausal macaque in her mid twenties. The first forty or so days of collection for this animal look menopausal, but then there is a period of sustained estrogen production indicative of follicular development. This is followed by a rise in

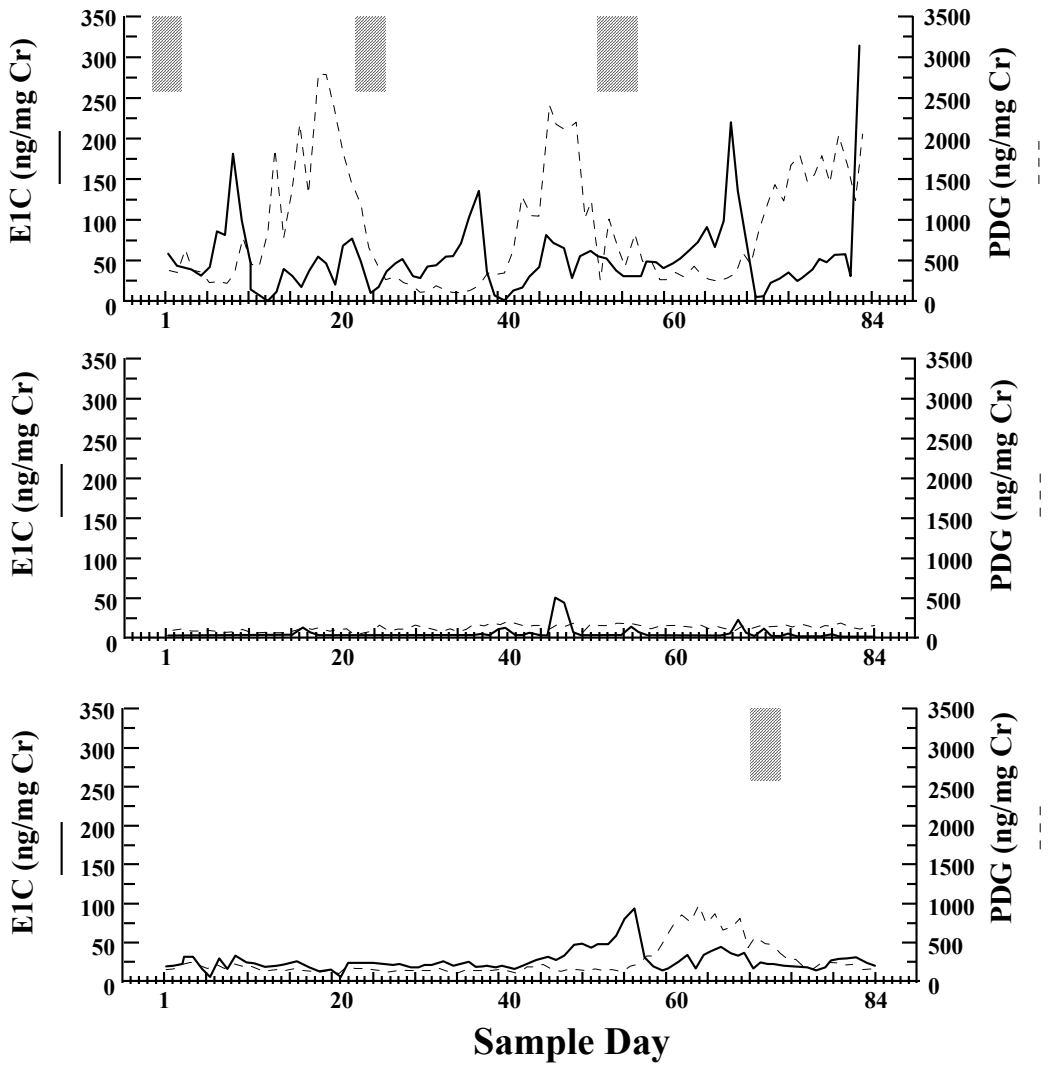


Figure 10. Urinary estrone conjugates (E1C) and progesterone excretion for three rhesus macaques. The top panel is from a normally cycling macaque. The stippled bars show days of menses. The middle panel is from a menopausal macaque. The bottom panel is from a perimenopausal macaque and shows a long inactive phase followed by follicular development, ovulation and menses. Redrawn from Gilardi et al. (1997).

progesterone, suggesting ovulation has occurred, and then a menses. Without LH and FSH it is hard to be absolutely sure that the prolonged period of steroid inactivity here is an inactive phase, but this profile looks exactly as we would predict during the perimenopause.

**Conclusions**

We have proposed that follicular depletion and the inactive phase are the mechanisms underlying the increasing variability in menstrual cycle length and hormone patterns of the perimenopause. The cases of inactive phases that we have found in our laboratory studies and the literature are broadly consistent with our theoretical model.

If the model is correct, then the process of follicular depletion can, by itself, explain most of the age-related menstrual cycle features of the perimenopause and menopause. In particular, the

process of follicular depletion can account for the age-related increase in the frequency of long menstrual cycles, the increasing variability in menstrual cycle length with age, the increase in follicular phase length with age, and the higher LH and especially FSH levels observed in perimenopausal women (Klein et al., 1996, MacNaughton et al., 1992; Metcalf et al., 1982; Santoro et al., 1996). The follicular depletion model is attractive because it is parsimonious: one biological process can explain most of the salient menstrual cycle features of the perimenopause and menopause. In contrast, hypothalamic aging models cannot account for all of these various characteristics of reproductive aging, nor do they specify the mechanism(s) producing, for example, elevated gonadotropin levels.

The current formulation of the model does not, however, offer concise or complete explanations for some other characteristic features of the perimenopause. For example, the model does not account for the slight increase in short menstrual cycles observed in the years well before menopause (Treloar et al., 1967). Additionally, follicular depletion may not be the only mechanism producing the elevated levels of FSH frequently seen at the older reproductive ages; elevated levels of FSH and LH are often observed in older adult women even in the presence of adequate progesterone and/or estrogen.

## Appendix

A probability model of inactive phase lengths is given to illustrate stochastic behavior and implications of the model for menstrual cycle length variability. Assume that women begin with an initial pool of $n_0$ follicles, that follicles initiate growth with a constant hazard $\lambda$ per follicle (roughly corresponding to the constant rate of follicular atresia seen in Figure 2), all follicles eventually initiate growth, and all but a small fraction of follicles undergo atresia. For this version of the model we assume that $\lambda$ does not vary across follicles, and that there is no variation in $n_0$ among women (most of these assumptions are relaxed in more complicated versions). From these assumptions, the number of follicles remaining in the ovaries at age $a$ is $n_a = n_0\exp(-\lambda a)$. This gives rise to the distribution of times for a woman age $a$ to be in the inactive phase as a function of the number of surviving follicles in her ovaries and the probability that no follicles initiate growth. An inactive phase occurs when all $n_a$ surviving follicles have not begun growing at the beginning of a menstrual cycle. From this it follows that the probability of an inactive phase exceeding length $t$ at age $a$ is $\Pr(T > t|\ \lambda, n_0, a) = \exp(-t\lambda n_0 e^{-\lambda a})$. The mean time in the inactive phase at age $a$ is $E(T\,|a) = (\lambda n_0 e^{-\lambda a})^{-1}$ and the variance is $V(T\,|a) = (\lambda n_0 e^{-\lambda a})^{-2}$.

The model can be made somewhat more realistic by two changes. The first change is to explicitly model the requirement that early growing follicles must survive until they begin producing estradiol in the presence of gonadotropins (which typically happens at a size of about 2 mm; Gougeon, 1996) before they can terminate the inactive phase. One simple way to accommodate this extension is to assume a proportional fraction $\eta$ of early growing follicles survive to 2 mm. This revision gives $\Pr(T > t|\ \lambda, n_0, \eta) = \exp(-t\lambda\eta n_0 e^{-\lambda\eta a})$. Essentially, this model is the same as the simplest model, except that $\lambda$ has been rescaled by $\eta$. More complex versions would treat the survival to the 2 mm as a multistate process.

The second useful change is to explicitly model an increase in the rate at which follicles are depleted at later reproductive ages. One possible mechanism for the increase rate of depletion, which has found experimental support in the work of Flaws et al. (1997), is that exposure to high gonadotropin levels may directly damage ovarian follicles. If so, then gonadotropin damage may increase at later reproductive ages when LH and FSH concentrations periodically increase during inactive phases. Thus, there would be two common routes by which follicles are depleted from the ovaries: atresia, which is expected to remain a negative exponential process, and gonadotropin damage, which would be some function of inactive phase length at a given age. Together these two causes of depletion describe a multifactorial process proposed by Leidy et al. (1998).

Under one such multifactorial model, some proportion $\phi$ of surviving follicles would die in proportion to the expected length of the inactive phase at age $a$. A first order approximation of this model (which ignores second order effects when the follicle pool is very small) is $dn_a/da = -[\lambda n_a + \phi n_a(\lambda n_a)^{-1}]$, and simplifies to $dn_a/da = -[\lambda n_a + \phi/\lambda]$. The term $\phi n_a(\lambda n_a)^{-1}$ is the expectation from the exponential atresia process, weighted by the fraction of susceptible follicles ($\phi n_a$) that might be damaged by a long inactive phase. The surviving number of follicles at age $a$, $S(a) = \exp(-\lambda a) + \phi[\exp(-\lambda a) - 1]/(n_0\lambda^2)$, which shows a nearly log-linear decline in follicle numbers with an accelerated depletion at the oldest ages, similar to Figure 2.

## References


Austad SN. 1997. Postreproductive Survival. In: Wachter KW and Finch CE (eds.) Between Zeus and the Salmon: The Biodemography of Longevity. Washington DC: National Academy Press.

Austin and Short. 1982. Germ Cells and Fertilization. Cambridge: Cambridge University Press.

Block E. 1952. Quantitative morphological investigations of the follicular system in women: Variations at different ages. Acta Anat 14 (suppl 16):108-123.

Block E. 1953. A quantitative morphological investigation of the follicular system in newborn female infants. Acta Anat. 17:201-206.

Faddy MJ, Gosden RG. 1995. A mathematical model of follicle dynamics in the human ovary. Hum Reprod 10:770-775.

Flaws JA, Abbud R, Mann RJ, Nilson JH, Hirshfield AN. 1997. Chronically elevated luteinizing hormone depletes primordial follicles in the mouse ovary. Biol Reprod 57:1233-1237.

Gilardi KVK, Shideler SE, Valverde CR, Roberts JA, Lasley BL. 1997. Characterization of the onset of menopause in the rhesus macaque. Biol Reprod 57:335-340.

Gougeon A. 1996. Regulation of ovarian follicular development in primates: Facts and hypotheses. Endocrine Rev 17:121-155

Gougeon A, Ecochard R, Thalabard JC. 1994. Age-related changes of the population of human ovarian follicles: Increase in the disappearance rate of non-growing and early-growing follicles in aging women. Biol Reprod 50:653-663.

Hee J, MacNaughton J, Bangah M, Burger HG. 1993. Perimenopausal patterns of gonadotropins, immuno-reactive inhibin, oestradiol and progesterone. Maturitas 18: 9-20.

Hsueh AJW, Billig H, Tsafriri A. 1994. Ovarian follicle atresia: A hormonally controlled apoptotic process. Endocrine Rev 15:707-724.

Kaipia A, Hsueh AJW. 1997. Regulation of follicle atresia. Ann Rev Physiol 59:349-363.

Klein NA, Battaglia DE, Clifton DK, Bremner WJ, Soules MR. 1996. The gonadotropin secretion pattern in normal women of advanced reproductive age in relation to the monotropic FSH rise. J Soc Gynecol Invest 3:27-32.

Leidy LE, Godfrey LR, Sutherland MR. 1998. Is follicular atresia biphasic? Fertil Steril 70:851-859.

MacNaughton J, Banah M, McCloud P, Hee J, Burger H (1992). Age related changes in follicle stimulating hormone, luteinizing hormone, estradiol and immunoreactive inhibin in women of reproductive age. Clin Endocrinol 36:339-345.

Metcalf MG. 1983. Incidence of ovulation from the menarche to the menopause: observations of 622 New Zealand women. NZ Med J 96(738):645-648.

Metcalf MG, Donald RQ, Livesey JH. 1982. Pituitary-ovarian function before, during and after the menopausal transition: A longitudinal study. Clin Endocrinol 17:484-489.

Miller PB, Charleston JS, Battaglia DE, Klein NA, Soules MR. 1999. Morphometric analysis of primordial follicle number in pigtailed monkey ovaries: symmetry and relationship with age. Biol of Reprod 61:553-556.

Munro CJ, Stabenfeldt GH, Cragun JR, Addiego LA, Overstreet JW, Lasley BL. 1991. Relationship of serum estradiol and progesterone concentrations to the excretion profiles of their major urinary metabolites as measured by enzyme immunoassay and radioimmunoassay. Clin Chem 37:838-844.

Norris DO (1997) Vertebrate Endocrinology. San Diego: Academic Press.

O'Connor KA, Holman DJ, Wood JW. 1998. Declining fecundity and ovarian aging in natural fertility populations. Maturitas 30:127-136.

Richardson SJ, Senikas V, Nelson JF. 1987. Follicular depletion during the menopausal transition: Evidence of accelerated loss and ultimate exhaustion. J Clin Endocrinol Metab 65: 1231-37.

Santoro N, Brown JR, Adel T, Skurnick JH. 1996. Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab 81: 1495-1501.

Sherman BM, West JH, 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.

Shideler SE, DeVane GW, Kalra PS, Benirschke K, Lasley BL. 1989. Ovarian-pituitary hormone interactions during the perimenopause. Maturitas 11: 331-339.

Treloar AE, Boynton RE, Behn BG, Brown BW. 1967. Variation of the human menstrual cycle through reproductive life. Int J Fertil 12:77-126.

van Look PFA, Lothian H, Hunter WM, Michie EA, Baird DT. 1977. Hypothalamic-pituitary-ovarian function in perimenopausal women. Clin Endocrinol 7:13-31.

vom Saal FS, Finch CE, Nelson JF. 1994. Natural history and mechanisms of reproductive aging in humans, laboratory rodents, and other selected vertebrates. In Knobil E, Neill JD, Greenwald GS, Markert CL, Pfaff DW (eds.) The Physiology of Reproduction. Vol. 2 (second edition). New York: Raven Press.

Wise PM, Krajnak KM, Kashon ML. 1996. Menopause: The aging of multiple pacemakers. Science 273:67-70.