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# Reproductive Aging and Risk for Chronic Disease: Insights from Studies of Nonhuman Primates

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## Abstract

Reproductive aging and ovarian senescence have considerable public health relevance because they are associated with increased risk for coronary heart disease (CHD), osteoporosis and other degenerative conditions including cognitive decline and potentially the metabolic syndrome. It has been suggested that the hormonal dysregulation that occurs during the perimenopausal transition may play a role in the initiation of pathobiological changes (e.g., adverse lipid profiles, atherosclerotic plaques) that will increase risk for chronic disease (e.g., CHD) during the postmenopausal years. Moreover, these early changes are suspected to establish a trajectory of disease progression that may be difficult to alter if interventions are not begun until after menopause. Even a slight increase in the rate of disease progression during the pre- or perimenopausal years could have substantial consequences for health and quality of life over the postmenopausal lifespan. Thus, the years leading up to menopause may offer a "critical window" for interventions aimed at reducing the postmenopausal disease burden. The relationship between perimenopausal hormonal dysregulation and the risk for chronic disease is poorly understood due, in large part, to the lack of available nonhuman primates (NHP) undergoing the perimenopausal transition and natural menopause. In this review we assesses studies of NHPs evaluated in various reproductive stages (naturally pre-, peri- and postmenopausal, surgically menopausal) and their contribution to our understanding about risk factors for chronic disease. Finally, because large numbers of naturally perimenopausal and menopausal NHPs are not available for research at present, experimental approaches that have the potential to hasten the onset of the perimenopausal transition will be described.

### Keywords

Reproductive aging; ovarian senescence; nonhuman primates; chronic disease

## Introduction

Nearly 175 million women worldwide are postmenopausal [1] and many of these women are expected to live well beyond (~30 years) menopause [2]. Consequently, the postmenopausal years are of considerable public health relevance because reproductive aging and ovarian

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senescence are associated with increased risk for coronary heart disease (CHD), osteoporosis and other degenerative conditions including cognitive decline and potentially the metabolic syndrome.

It has been hypothesized that the hormonal dysregulation that occurs during the perimenopausal transition may play a role in the initiation of pathobiological changes (e.g., adverse lipid profiles, atherosclerotic plaques) that will increase risk for chronic disease (e.g., CHD) during the postmenopausal years. Moreover, these early changes are suspected to establish a trajectory of disease progression that may be difficult to alter if interventions are not begun until after menopause [3,4]. Even a slight increase in the rate of disease progression during the pre- or perimenopausal years could have substantial consequences for health and quality of life over the postmenopausal lifespan. Thus, the years leading up to menopause may offer a “critical window” for interventions aimed at reducing the postmenopausal disease burden.

The relationship among perimenopausal hormonal dysregulation, ovarian senescence and the development of chronic disease is understood poorly, due in large part to the lack of animal models of the perimenopausal transition and natural menopause. The development of an experimentally induced perimenopausal mouse model [5] represents a significant research advance; however, this model has characteristics that limit its applicability for research on some issues in women’s health. For example, the mouse estrus cycle occurs every 4–5 days and sloughing of uterine epithelial cells does not occur. In contrast, Old World anthropoid primates have a menstrual cycle of approximately 28 days, cyclic sloughing of endometrial cells and nearly identical reproductive hormonal patterns to women. Therefore, nonhuman primates (NHP) are the most suitable model to help clarify the impact of the perimenopausal transition on the trajectory of risk for chronic disease.

In this review we discuss the peri- and postmenopausal NHP model and its contribution to our understanding of risk factors for chronic disease. In addition, in situations where there were limited data available from natural models the contributions from the ovariectomized model are discussed. Finally, because large numbers of naturally perimenopausal and menopausal NHPs are not available for research currently, experimental approaches that have the potential to hasten the onset of the perimenopausal transition will be described.

## Reproductive Senescence in Nonhuman Primates

Reproductive senescence (menopause) has been reported to occur in numerous old world monkeys and great apes. The majority of these studies have been of rhesus monkeys (*Macaca mulatta)* [6–17]; however, numerous other species also experience menopause including cynomolgus macaques (*M. fascicularis*) [18,19], Japanese macaques (*M. fuscata*) [20], langur monkeys (*Presbytis entellus*) [21], baboons (*Papio* spp.) [22], chimpanzees (*Pan troglodytes*) [23–27] and gorillas (*Gorilla gorilla*) [28]. The hormonal profiles of perimenopausal and postmenopausal macaques, baboons, chimpanzees and gorillas have many similarities to those of women including elevated FSH and LH, decreased estradiol, decreased inhibin B and low antimüllerian hormone (AMH) [6,26,29,30]. Furthermore, compared to premenopausal macaques, perimenopausal monkeys have increased variability in menstrual cycle length, decreased estradiol and significant elevations in peak FSH concentrations [7, 31]. Finally, the age-related decline in primordial follicle number in macaques [13] and chimpanzees [24] occurs in a similar pattern to that of aging women [32].

It is noteworthy that there is some controversy about the existence of a postmenopausal phase in NHPs. The majority of studies examining captive populations indicate that menopausal and postmenopausal phases do exist in NHPs, although the postmenopausal phase may be shorter (only a few years) than that of women [29]. In contrast, data from some wild populations (mainly chimpanzees) indicate that the post-reproductive lifespan is nearly non-existent [33].

The potential evolutionary reasons for the relative difference in post-reproductive life span between NHPs (0–25% of lifespan) and women (>30% of lifespan) [2] is the subject of much debate [29,33–36] and is beyond the scope of this review. Relevant to this discussion, however, is a recent review on menopause in NHPs by Walker and Herndon [29] in which the authors point out that, irrespective of age at onset of menopause, there are numerous physiologic similarities between NHPs and women with respect to the gradual decline and eventual cessation of reproductive capacity. Taken together, the hormonal and menstrual cycle changes observed in nonhuman primates as they approach menopause and become postmenopausal, indicates that they are the most appropriate animal model available for investigating the effect of reproductive aging and ovarian senescence on risk for chronic disease.

Macaques (rhesus and cynomolgus) and baboons offer the greatest potential for study with respect to availability and regulatory requirements for interventional studies. However, experiments designed to extend our understanding of the relationship between ovarian senescence and chronic disease risk depends, in part, on the availability of reasonably large numbers of naturally peri- and postmenopausal subjects. These animals are generally not available for several reasons. First, the majority of known-aged female NHPs exist in managed breeding colonies and are culled as soon as declining fecundity is detected (~14 years in baboons [22] and ~10 years in rhesus [8]). Second, culled females are used for various discrete, often terminal, studies because financial mechanisms to support the sequestration and maintenance of these animals in large numbers do not exist currently. Third, as mentioned previously, menopausal females (as defined by cessation of menstrual cycles) are generally at an advanced age (25 years for macaques) relative to their maximal life expectancy, resulting in a short postmenopausal period [29]. The opportunity exists, however, to improve the availability of aging female monkeys for women's health research and this is discussed further in this review in the section on model development.

## Insights from Nonhuman Primates

### Atherosclerosis

Atherosclerosis and its sequelae are the major causes of morbidity and mortality among postmenopausal women in Western societies [37,38]. These demographics underscore the need to improve our understanding of factors associated with the initiation and progression of atherosclerosis in women.

Extensive research on atherosclerosis progression has been done using menopausal (ovariectomized) cynomolgus macaques and several important concepts have emerged as a result of these investigations (for a complete review see [39,40]). First, studies of cynomolgus monkeys provided some of the early evidence implicating estrogen depletion in the pathogenesis of coronary artery disease. For example, ovariectomized monkeys fed a diet containing saturated fats and cholesterol, in amounts similar to that which is consumed by women in industrialized societies, develop significantly more coronary artery atherosclerosis than their reproductively intact counterparts [41]. Estrogen treatment of monkeys immediately following ovariectomy results in beneficial effects on cardiovascular risk factors including decreased total plasma cholesterol (TPC), decreased LDL+VLDLC [40] and modest increases in HDLC [42] compared to placebo. Of significant clinical relevance is the finding that if estrogen treatment is initiated at the time of ovariectomy, atherosclerosis extent is inhibited by nearly 70% [43]. A second major conceptual contribution relates to findings from studies of premenopausal monkeys in which the extent of atherosclerosis present prior to ovariectomy determined the extensiveness of the plaques during the postmenopausal years [44], suggesting that a trajectory for atherosclerosis development may begin well before the onset of menopause. In further support of this hypothesis is a study in which treatment of premenopausal monkeys with estrogen containing oral contraceptives (estrogen + progestin) prior to ovariectomy

reduced the progression of atherosclerosis postmenopausally [45,46]. Similarly, prior oral contraceptive use in women is associated with reduced severity of angiographically determined coronary artery disease and diminished coronary artery calcium, further supporting the suggestion that intervention during pre- or perimenopausal years might be warranted [4]. Finally, when estrogen treatment is delayed in monkeys for the equivalent of 6 woman years after ovariectomy, no beneficial effects on atherosclerosis extent is seen [47]. Taken together, the observations from ovariectomized monkeys have contributed to the development of the "timing hypothesis", which suggests that exogenous estrogens will have beneficial effects if administered when atherosclerosis is in its early stages of development (i.e., during the pre-, peri- and early postmenopausal years) but will have no benefit or adverse effects if given to women who have been estrogen-depleted for several years and have complicated plaques [48–52].

To test the "timing hypothesis" further, perimenopausal monkeys are required. Unfortunately, for the reasons outlined previously, these monkeys are not available in large numbers. In addition, the majority of those that do exist (mainly rhesus), are fed a commercial diet that is low in cholesterol and high in soy isoflavones [53]. Induction of atherosclerosis in NHPs requires a diet containing saturated fats and cholesterol in amounts similar to that consumed by people in Western societies [54,55]. Furthermore, diets containing high concentrations of soy isoflavones are known to decrease atherosclerosis development in macaques [56]. Consequently there are relatively few studies of cardiovascular risk factors in naturally perimenopausal female monkeys and apes. In one such study, perimenopausal baboons (defined by irregular menstrual cycles) fed a diet high in cholesterol and fat had a more adverse lipid profile (greater VLDL+LDL and lower HDL cholesterol) than their premenopausal counterparts [57]. The perimenopausal baboons also had lower activity levels of a liver enzyme (27-hydroxylase) thought to be important in regulating plasma lipid concentrations in responses to diet. This led the authors of that study to suggest that declining 27-hydroxylase activity may be a result of the assumed decline in estrogen ($E_2$) in perimenopausal baboons. In another study, naturally postmenopausal rhesus monkeys (n=5, 25 years and older) treated with $E_2$ for 4 weeks experienced a 50% reduction in plasma LDL concentrations, an increase in LDL size and enhanced resistance to LDL oxidation [58]. Finally, naturally postmenopausal cynomolgus monkeys treated with $E_2$ experience a normalization of FSH and $E_2$ concentrations and subsequent improvements in plasma lipids and lipoproteins (decreased LDL+VLDLC and increased HDLC) and body weight [18]. These data suggest that NHPs are excellent models for cardiovascular disease research and future studies of atherosclerosis progression during the perimenopause will be instrumental in determining the mechanisms involved in the "timing hypothesis".

## Bone loss

Osteoporosis is one of the leading public health problems in the United States, affecting nearly 20 million Americans [59]. Bone loss in aging women is a result of an imbalance between bone formation and bone resorption, with a shift in the bone remodeling process towards increased resorption as women approach menopause. As a result, approximately 50% of women will experience fractures in their lifetime, making fracture a major cause of morbidity and reduced quality of life in older women [59,60]. The bone remodeling processes of both cancellous and cortical bone are very similar among macaques, baboons and women [61,62], making NHPs suitable models in which to study the effects of reproductive aging on bone loss. As is the case for cardiovascular studies, however, investigations of the relationship between reproductive hormones and bone metabolism have mainly used the ovariectomized monkey model [63]. Ovariectomy, and the resultant estrogen depletion, leads to significant bone loss and increases in markers of bone turnover in NHPs [61,64–70], an effect that is reversed with estrogen treatment [71,72]. Consequently this model has been used extensively to test interventions

designed to prevent and reverse bone loss in postmenopausal subjects, but it has not been useful in understanding the effect of perimenopausal hormonal changes on bone loss, nor has it been helpful in determining the contribution of androgen production by the postmenopausal ovary to bone turnover.

There are several studies that have collected bone mineral density (BMD) and bone biomarker data from aging female macaques [31,73–76] and at least one from baboons [77]. Three of the macaque studies were cross-sectional in design and reported age-related declines in forearm (radial) density [31,74,75]. In the first study [74], data were collected from 178 females (10 of which were postmenopausal) ranging in age from ~3–34 years. In that study, a two-piece segmented linear regression ("hockey stick") model was used to examine the relationship between bone loss and age. Interestingly, the slope of the line increased markedly after about 18 years of age, potentially reflecting the effect of changes in estrogen status on bone loss in perimenopausal monkeys. However, hormones were not collected in this study so this is merely speculative. In the second study [75], postmenopausal macaques (n=16) had lower total body, distal radius and spinal bone mass, and increased osteocalcin (a bone formation marker) when compared with premenopausal females (n=19). The most recent of the cross sectional studies [31] found an independent effect of age (8–27 years, n=19) on total body and radial BMD. In support of the cross-sectional data is a longitudinal study of data collected over 4 years from premenopausal females (n=20, age 8–23 years). In that study, age-related bone losses in the middle and distal radius were observed [73]. Conversely, losses in total and lumbar BMD were not observed over 4 years, nor was there an effect of aging on osteolcalcin.

The lack of agreement among the aforementioned studies with respect to the effect of age on total BMD and bone biomarkers may be due to the small numbers of monkeys that were either known to be menopausal or that were old enough to be perimenopausal. In addition, there are other potential confounders that may occur when attempting to determine the relationship between age and bone loss in monkeys. First, the incidence of osteoarthritis (OA) increases significantly in monkeys greater than 19 years of age [78] and as a result, falsely high BMD measurements of the spine may be recorded. A similar problem is encountered in women with lumbar OA [79]. To address this issue, Krueger et al. [78] devised a method of measuring bone density in a central region of interest in the vertebral body, thus avoiding vertebral facets, end plates and disc spaces. Using this analysis, an additional 25% of older animals with decreased bone mass were detected that would otherwise have been classified as having normal bone mass. A second potential problem with studies of bone loss in monkeys published thus far relates to diet. The majority of studies have used monkeys that have been fed a commercial diet (monkey chow) containing concentrations of soy phytoestrogens [53] that are as high as or greater than that consumed by Asian women [80], potentially providing some estrogenic effect on bone. Perhaps even more important, these diets are nutritionally complete with respect to calcium, phosphorous and vitamin D and are fed consistently throughout the life of the monkey. Consequently, the natural variations in nutrient intake that can occur in older women do not occur in aging monkeys and therefore changes in bone metabolism may not be seen in monkeys fed these diets. Notably, serum vitamin D concentrations have been reported to decline with age in females monkeys [73] and variation in the amount of vitamin D added to the diet does affect serum vitamin D levels [75]. Therefore, it is possible that monkeys fed a diet which more closely resembles that of women would allow the detection of bone loss during perimenopausal years.

Together these data suggest that aging female monkeys lose bone in a similar manner to women and changes in hormone status may influence bone loss. However, future NHP studies that include the collection of hormonal data to determine the reproductive status of older monkeys, and use diets free of phytoestrogens and lower concentrations of vitamin D, calcium and phosphorus, could be of great value in disentangling the effect of hormones and age on bone

metabolism. Numerous studies of ovariectomized macaques indicate that the monkey is a suitable model for evaluating the effects of various interventions (pharmacologic or dietary) on fracture risk, as determined by ex-vivo measurements of vertebral, femoral and radial bone strength as well as the microarchitecture of bone [64,81,82]. Given that these studies are not possible in women, the perimenopausal monkey model could provide important data on the association between ovarian senescence and bone quality in addition to the evaluation of novel interventions.

## Cognition

Many women complain of difficulties with concentration and memory during the menopausal transition and early postmenopause [2]. However, there are considerable uncertainties about the relationship between the perimenopausal transition and cognitive decline. These gaps in knowledge are due to the challenges inherent in clinical studies of cognition in women (i.e., the requirement for large numbers of subjects and the need for repeated cognitive testing which is carefully timed in relation to stage of the menopausal transition). Further, investigators are challenged by the "practice effect" which is often associated with repeated testing. Even a large prospective study of perimenopausal women such as the Study of Women Across the Nation (SWAN), is limited in its ability to determine whether endogenous hormones are related to cognition during the menopausal transition [83].

To our knowledge, nearly all NHP studies examining the relationship between reproductive hormones and cognitive function have used the ovariectomized model. Data from these studies are conflicting with respect to the effects of endogenous and exogenous estrogen on learning and memory [84–86]. We could find only one study in which naturally menopausal rhesus monkeys were used to investigate the relationship between endocrine decline and cognitive aging [87]. In that study peri/postmenopausal status was assigned to monkeys that had irregular or absent menstrual cycles over a 12-month period and urinary estrone concentrations that were lower than their age-matched (20–27 years) premenopausal counterparts. A delayed response (DR) task was used to test a monkey's ability to remember the location of a food reward hidden in one of two locations prior to a delay. Learning was significantly impaired in peri/postmenopausal monkeys compared to age-matched premenopausal monkeys. Furthermore, mean estrone concentrations were positively associated with average DR accuracy ($r=0.59$, $p<0.05$). This study indicates that changes in cognitive function similar to that reported in aging women [88] occur in macaques.

Additional studies of aged (23–29 years) rhesus monkeys, not characterized as pre- or postmenopausal and often male, have contributed to our understanding of age-related gross and histopathologic changes in the brain. Older females and males experience an increase in cholinergic cell size [89,90] without a change in hippocampal volume [91]. In addition, a significant decline of gray matter volume occurs with age in macaques [92,93], as it does in humans [94]. Interestingly, aged rhesus monkeys (males and females) fed a calorie restricted diet (CR, 30% restriction from baseline *ad libitum* intake) experience a preservation of gray matter volume in key regions associated with motor and executive function [92]. Although the CR study did not look at males and females separately, it is important to note that CR has not been shown to affect menstrual cyclicity or reproductive hormone profiles in rhesus monkeys [31]. Finally, both male and female vervet monkeys (*Chlorocebus aethiops*) have been reported to have age-related deposition of amyloid β protein (Aβ) [95] and the presence of an apolipoprotein allele (E4) [96] shown to be associated with Alzheimer's Disease (AD). These data, along with the observation that Aβ vaccination of vervets reduced cerebral amyloid β protein [95] suggest that the vervet may provide a useful model to study AD.

### Metabolic Syndrome/Type 2 Diabetes

The metabolic syndrome is a combination of risk factors for cardiovascular disease (CVD) and type II diabetes mellitus (T2DM) that frequently co-occur and are evident in 20% to 30% of middle aged women [97–99]. The risk factors include elevated blood pressure, dyslipidemia (high triglycerides and lowered HDLC), elevated fasting glucose, and increased central adiposity. The occurrence of three or more of these risk factors defines the presence of metabolic syndrome [100]. Studies of women attempting to link menopausal status with components of the metabolic syndrome have been inconsistent. Recently, Janssen and colleagues [101] used data from the SWAN to determine whether the incidence of the metabolic syndrome increases across the menopausal transition, independent of age and other standard CVD risk factors. The authors reported that the odds of developing the metabolic syndrome (after adjustment for ethnicity, site, baseline BMI, change in BMI, education, marital status, smoking, age at final menstrual period and age) were greater during perimenopause (OR=1.45, 95% confidence interval, 1.35–1.56) than after menopause (OR=1.24, 95% confidence interval, 1.18–1.30).

NHPs are similar to women with respect to the development of risk factors for metabolic syndrome and T2DM and both of these conditions have been reported in cynomolgus, rhesus and bonnet macaques [102–106], baboons [107,108] and vervets [109]. In addition, chronic hyperglycemia has been reported to increase CVD risk in macaques [110,111] and insulin resistance is associated with dyslipidemia, obesity and atherosclerosis in baboons [107]. Although we could find no studies directly investigating the effect of hormonal dysregulation (characteristic of perimenopausal monkeys) on risk markers for the metabolic syndrome, there is evidence from NHPs implicating a relationship between ovarian hormones and glucoregulation. First, female macaques spanning a wide age range (4 to >30 years) have higher glucose disappearance rates and better insulin responses to glucose challenge tests than age-matched males [112,113]. Second, a decline in insulin sensitivity has been observed during the luteal phase of the menstrual cycle in both macaques [114] and women [115]. Third, exogenous treatment with a progestogen results in deleterious effects on glucoregulation in macaques [116]. Finally, naturally menopausal rhesus monkeys (27–38 years) tended to have a decreased insulin response compared to midlife females (13–17 years), even after adjustment for age [113]. The similarities among NHPs and humans in the aforementioned risk factors for metabolic syndrome and T2DM support using NHPs for research in this area. The availability of perimenopausal monkeys would allow for further assessment of relationships between reproductive hormones and risk and allow the testing of interventions prior to menopause.

## Approaches to the development of a NHP model of reproductive aging and ovarian senescence

The menopausal transition is difficult to model because of the complex physiological changes that occur during the years leading up to the final menstrual period. These changes include decreased numbers of primordial follicles resulting in decreased production of inhibin B and AMH, a compensatory increase in production of FSH by the pituitary, and an inability to sustain normal estradiol production. These changes all take place gradually over a period of 4–10 years. The situation is further complicated by the fact that the stroma of the naturally menopausal, follicle-depleted ovary continues to produce androgens [117], which directly affects target tissues, and can be aromatized to estradiol. In the absence of monkeys that adequately model the menopausal transition and postmenopausal characteristics of women, researchers have been limited to using ovariectomized animals for interventional studies. Although the ovariectomized model has been valuable in determining the effects of estrogen depletion on health (e.g., pathobiology of atherosclerosis and osteoporosis), the surgical manipulation induces an immediate decline in ovarian hormones to trace amounts, producing a hormonal

condition that does not resemble the perimenopausal transition and does not allow the biological role of the postmenopausal ovary to be determined. As a result, any effects associated with the production of menopausal estrogens and androgens which are thought to influence the pathogenesis of atherosclerosis, bone loss, and cognition are not modeled by studies conducted on ovariectomized individuals.

Our research is focused on overcoming the difficulties of acquiring sufficient numbers of perimenopausal monkeys for study. Recent advances in our laboratory underlie our belief that the development of a monkey model of the perimenopausal transition and menopause is possible. First, we found that AMH is a reliable predictor of primordial follicle numbers in cynomolgus monkeys [118] and therefore it can be used to identify monkeys with reduced ovarian reserve (ROR, low follicle numbers) that may be nearing the perimenopausal transition. Second, significant numbers (~20/100) of midlife cynomolgus monkeys with naturally occurring ROR (low follicle counts and low AMH) exist in a managed monkey colony in Indonesia (Pusat Studi Satwa Primata, PSSP at the Institut Pertanian Bogor, Indonesia) and midlife and aged rhesus monkeys (~10/156) with low ovarian reserve (low AMH) exist in domestic colonies in the Unites States. Third, we found that after 3 years of consuming a diet comprised of animal protein and fats, in ratios and content similar to that typically consumed by many women in industrialized societies, female cynomolgus monkeys had significantly less primordial follicles than those fed a soy-based diet [119]. Taken together, these findings suggest that it should be possible to identify monkeys with naturally occurring low ovarian reserve and feed them a diet that will hasten their transition into perimenopause; thus providing a population of monkeys in which to study the effects of reproductive aging on risk for chronic disease.

A second approach taken by our laboratory is the creation of an experimental monkey model of ovarian senescence (beginning with reduced ovarian reserve and progressing to perimenopause and finally postmenopause). To mimic the experience of women, the experimental monkey model of reproductive aging should be characterized by ovaries that are nearly depleted of primordial follicles but retain a pool of larger, developing follicles and an intact, androgen-producing stroma. The use of the chemical, 4-vinylcyclohexene diepoxide (VCD), has been shown to selectively destroy primordial and primary follicles in rodents while leaving the stroma intact [5]. Consequently, our research has been focused on translating the rodent model to NHPs (macaques) [120,121]. Preliminary data from our laboratory indicate that treatment of monkey ovaries with VCD markedly reduces primordial follicles while preserving larger estradiol- and testosterone-producing follicles and ovarian stroma, a condition that mimics the early stages of reproductive aging in women (unpublished data – submitted for publication February 2010). The advantage of the experimental perimenopausal monkey model is that it can be applied to monkeys of all ages, removing age as a confounding variable and allowing the disentanglement of hormonal and age related effects on risk for chronic disease.

## Conclusion

Postmenopausal women are at increased risk for chronic disease (e.g. coronary heart disease, cognitive decline, bone loss and metabolic syndrome). It has been hypothesized that the hormonal dysregulation that occurs in the years leading up to menopause (perimenopause) may play a role in the initiation of risk factors for the aforementioned diseases and that interventions (pharmacologic, lifestyle, etc.) initiated during the perimenopause could markedly decrease postmenopausal disease burden. To further understand the relationships among reproductive aging, ovarian senescence and chronic disease risk, an appropriate animal model is needed. Studies of naturally peri- and postmenopausal NHPs indicate that they have a nearly identical pattern of hormone dysregulation to women. Consequently, peri- and postmenopausal NHPs

are the most suitable animal model to help clarify the impact of the perimenopausal transition on the trajectory of risk for chronic disease. Although large numbers of naturally perimenopausal and menopausal nonhuman primates are not available for research at present, alternative experimental approaches that have the potential to hasten the onset of the perimenopausal transition hold promise for the future availability of such models.

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