We are IntechOpen,
the world's leading publisher of Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Menopause in Nonhuman Primates: A Comparative Study with Humans

María de Jesús Rovirosa-Hernández,
Marisela Hernández González,
Miguel Ángel Guevara-Pérez,
Francisco García-Orduña,
Abril de los Ángeles Aguilar-Tirado,
Abraham Puga-Olguín and
Brisa Patricia Vásquez-Domínguez

Additional information is available at the end of the chapter

Abstract

Although menopause is a phenomenon predominantly studied in humans or laboratory animals, this chapter discussed the case of nonhuman primates (NHPs), not only with the objective of employing them as study models but also to better understand phylogenetic divergence among species. Those taxonomic differences are reflected in reproductive processes that may be similar to those of human beings, with the presence of a defined cycle or periods of estrus, but perhaps at different ages as well, where menopause plays a crucial role. First, it is important to delimit the concept of menopause by considering its anatomical, physiological, and biochemical parameters, including the cessation of menstrual bleeding or perineal swelling—when present—or follicular depletion and hormonal changes. Thus, the aim of this chapter is to discuss some of the similarities between NHPs and human females, during the menopause period. Studying these phenomena should help us achieve a better understanding of the social, physiological, and environmental factors without adopting any particular cultural view of menopause.

Keywords: nonhuman primate, ovarian cycle, reproductive cessation, new world monkeys, old world monkeys

1. Introduction

Menopause is a process of the reproductive aging [1] manifested in the depletion of ovarian follicles, the reduction of ovarian hormones to castration levels, and the increase in the concentration of serum gonadotropins [2]. In human beings, this process occurs in midlife, heralded by the gradual disappearance of menstrual cycles accompanied by the end of reproductive capacity, which correlates with functional and structural changes in the hypothalamic-pituitary-ovarian axis [3].

This process is not exclusive to humans, for it also occurs in all iteroparous organisms that exhibit declining fertility as a function of general senescence [4]. However, in contrast to human beings, nonhuman primates (NHPs) and even longer lived species like tortoises, elephants, and whales retain their capacity to reproduce until relatively advanced age [5]. Studies in NHPs, such as monkeys and apes, both in the wild and in conditions of captivity, have reported menopause as a physiological phenomena [6–8], but they clearly show that the reproductive changes observed in NHPs differ from those of human menopause, at least from a perspective of comparative life history [6]. This is because most of the oldest individuals in all wild species studied showed no signs of ovarian failure, while studies of captive primate species have observed that 67% of old females continued reproducing throughout their lives [7].

It has been suggested that the differences between the human fertility pattern and those of other NHPs are evident in the maximum age of reproduction and mean life expectancy at maturity of both. This refers to the fact that human beings have an early fertility peak that begins to decrease when they are in their mid-1920s, followed by a general decline and then a steep drop that normally begins around age 35; being this age the specific moment fertility functions of NHPs as macaques remain relatively constant over a long period, terminating abruptly only a few years before age death [9].

NHPs are used in medical and scientific research due to their similarities in physiology, neuroanatomy, reproduction, development, cognition, and social complexity to humans, which reflect their close phylogenetic relationship between NHPs and human beings. Primates are divided phylogenetically into strepsirrhines (galagos, lorises, and Malagasy lemurs) and haplorhines (tarsiers and anthropoids). There are three major branches of extant anthropoids or higher primates: the Platyrrhini or New World monkeys (South and Central America) and two groups of Catarrhini (the Cercopithecoids or Old World monkeys (Africa, Europe, and Asia) and Hominoids (Apes and human beings)) (**Figure 1**) [10].

The aim of the present chapter is to discuss and analyze some similarities between female NHPs and human females during natural or surgically induced menopause, since expanding our knowledge of this phenomenon in mammals with such a close phylogenetic relationship so to human beings should lead to a more comprehensive understanding of this biological process.
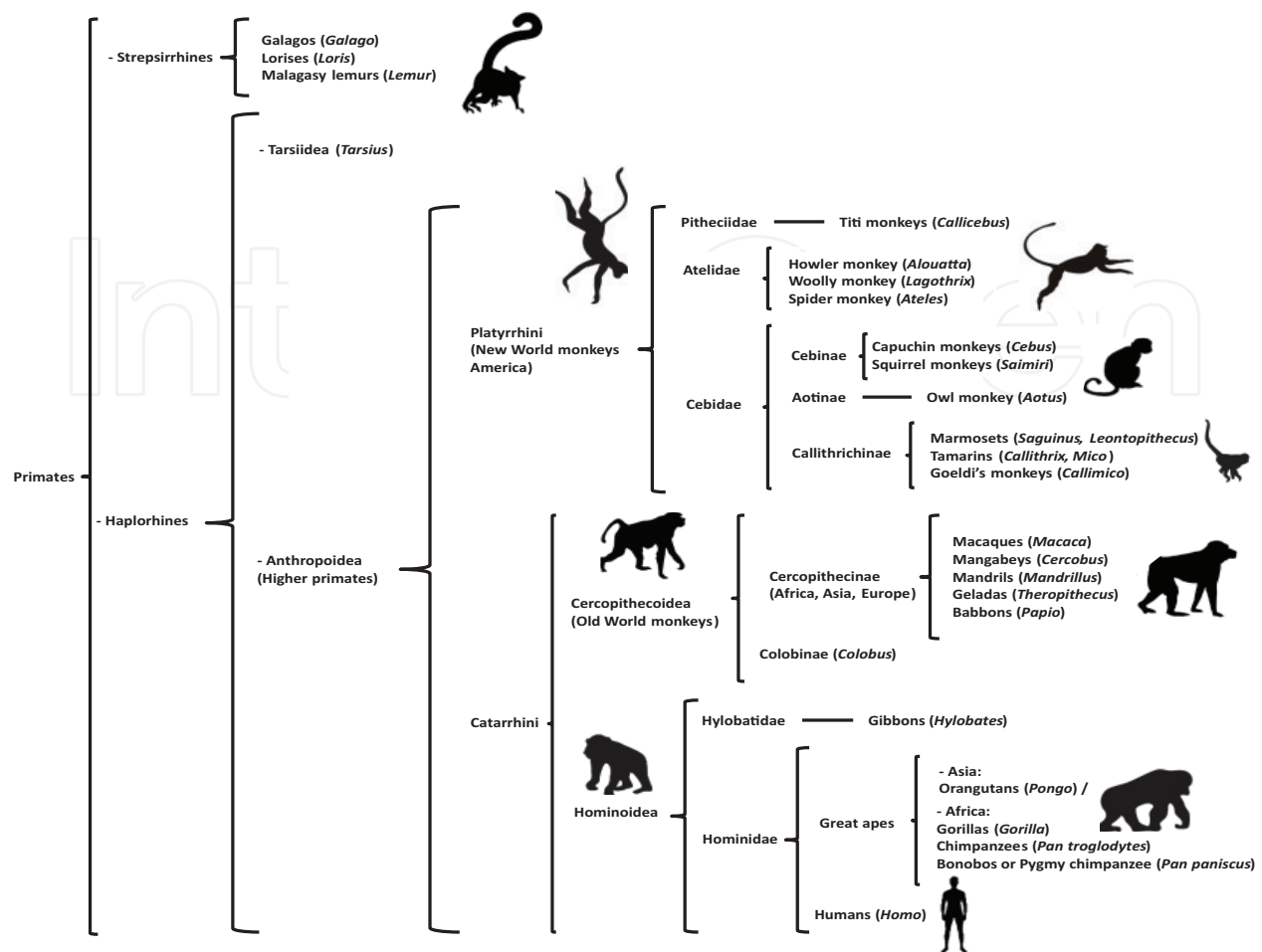
Figure 1. Taxonomic classification of extant primates with branch lengths in millions of years. Representative genus is shown in brackets (modified from Ref. [10]).

2. Reproductive cycles in nonhuman primate females and their relation with cycles in human beings

For many mammals, estrus is not only confined to a brief portion of the reproductive cycle that is characterized by an increase in attractivity and in the proceptive and receptive behaviors of females but is also strictly seasonal. In NHPs the reproductive cycles occur for only a few weeks of the year, as occurs among Madagascar prosimians, such as the sifakas. In some New World primates, such as squirrel monkeys, sexual cycles occur only during 3 months of the year [11], but many catarrhine primates do not follow this strict pattern circumscribed by the estrous period [12]. The literature mentioned that apes, human beings, and many monkeys have reproductive cycles that differ in two ways: first, the cycles include menstruation, a cyclical sloughing of the uterine lining. Second, there is greater flexibility in the time of proceptive and receptive behaviors with a longer duration of estrus [13]. Apes and Old World

monkeys, meanwhile, exhibit menstrual cycles that range from 25 to 35 days similar to those human females. Also in NHPs, mating activity is not restricted to the periovulatory period as occurs in other mammals since female receptivity is not under strict control of ovarian hormones, but is more closely related to the social context, also as in human beings [14]. Finally, circulating steroid hormones reflect the process of ovulation and ovarian cycling [15].

2.1. Ovarian cycle in nonhuman primates

Ovarian cycles in primates begin with a follicular phase during which the follicle matures, follicular secretion of estrogen increases, and the circulating concentration of progesterone (P_4) decreases [16]. In most primates, only one follicle ovulates in each cycle. It emerges during the mid-follicular phase and inhibits maturation of other follicles by secreting large amounts of estrogen that, in turn, reduce concentrations of the follicle-stimulating hormone (FSH) below the threshold level required for maturation of early antral follicle [17]. Second, ovulation occurs immediately after the follicular phase, and this maintains high circulating concentrations of estrogens from the mature follicle while exerting positive feedback on the hypothalamus and pituitary that triggers secretion of the gonadotropin-releasing hormone (GnRH), as well as FSH and luteinizing hormone (LH). The increased LH reaches the ovaries where it causes the follicle to rupture [18]. Third, during the luteal phase, the concentration of P_4 rises, but that of estrogens declines. Fertilization can take place during the early luteal phase of the cycle only during the first 24 h after ovulation. This is because the oocyte has a short life span. If the ovum is fertilized, then the corpus luteum does not degrade and continues to secrete P_4 until the placenta develops [19].

Some of these processes are similar to the ovarian cycles in the human beings [20]; however, studies have found that in all primate species studied, follicular development, ovulation, and corpus luteum formation occur spontaneously and independent of mating-induced stimuli [21]. Also, NHPs have been shown to have extended ovarian cycles, especially prolonged luteal phases, compared to those of other mammals [22]. Also, the duration of the follicular and luteal phases differs among NHPs. Cycle lengths vary among different primate groups: in prosimians, from 30 to 50 day; in New World monkeys, from 16 to 30 days; in Old World monkeys, from 24 to 35 days; in lesser apes, from 20 to 30 days; and in great apes—including humans—from 25 to 50 days [14, 15, 21, 23]. In contrast, squirrel monkeys have a mean cycle length of just 7–12 days, with a follicular phase of about 5 days [24].

Menstruation appears to be absent in all prosimians and possibly in tarsiers, presumably associated with the noninvasive form of placentation characteristic of these primates [21]. However, menstruation does occur in most Old World monkeys and apes, as well as in several New World monkeys [25], and prosimians may be considered to have an estrous cycle, because they exhibit distinct cyclical changes in relation to sexual receptivity, with a peak during the periovulatory period. Finally, many New World monkeys do not exhibit either menstruation or strict estrous cyclicity [20].

2.2. Ovarian cycle in humans

In human beings menstrual bleeding is the visible sign of cyclicity; it has a length of 3–6 days and occurs at the end of the luteal phase and the beginning of the follicular. While fertile phase

has a length of 5 days and is associated with the end of follicular phase and an increase of estradiol (E_2) before ovulation, during this period conception can occur. Recent studies have found that human females possess dual sexuality, which consists of a fertile phase where they are more sexually attractive to men and a phase extended (non-fertile), which presents a motivation or interest in sex with the aim of obtaining some benefits, without conception occurring [26].

2.3. Reproductive aging

Female reproductive output differs markedly in relation to species and time. As females of many species age, a period of reproductive instability with perimenopausal-like hormonal changes has been observed. Like many other mammals, NHP females show fertility parameters that are related to age [7]. Anovulation, insufficient luteolysis, and impairment of gestation and lactation processes all become more common toward the end of reproductive life [27]. Female reproductive senescence differs among mammalian taxonomic groups. For example, in NHPs, the end of reproductive life is characterized by the loss of the follicular pool, whereas in rodents, variations are seen in the size of the follicular pool that remains at the end of reproductive life. In humans, experiencing follicular depletion early in the maximum life span is not usual; rather, it is the result of an extended period of altered hormonal environments. These alterations may be caused by reduced circulating estrogens, P_4, and inhibin, resulting in elevated gonadotropin concentrations (GTHs) for a time, followed by their decline [28]. Monkeys and apes also experience follicular depletion and associated hormonal alterations [8, 29], but the stage of life at which these occur is generally later than in humans. Some reports on lemurs and callitrichids indicate an age-related decline in reproduction in many species that is reflected in diminished reproductive success [30]. Older female sifakas (*Propithecus edwardsi*), a Madagascar lemur, show decreased rates of infant survival, and studies have affirmed that this effect can be attributed to the females' deteriorating dentition resulting in inability to support lactation [31]. This indicates that reduced fertility in old age does not, in and of itself, reflect impaired neuroendocrine or gonadal function [20].

Considering the taxonomic scale of primates, we can observe the variability in physiological characteristics, like it is reflected in aging process. As much NHPs get closer to human beings, more similarities are found, going through estrous cycles for strepsirrhines (galagos, lorises, and lemurs), to ovarian cycles, and hormonal profiles similar to human being females, in great apes (orangutans, gorillas, and chimpanzees), and Old World monkeys (macacos and baboons). Also in both cases, at the end of their reproductive life, different physiological and hormonal changes occur, which are associated with the loss of ovarian function that are characteristic of aging, where this gives us the opportunity to study in a comparative way different alterations that could be related to the absence of ovarian hormones.

3. Menopause in *Homo sapiens* females and nonhuman primates

Menopause has been defined as a series of changes in the termination of reproductive viability, of which the discontinuation of menstruation is but one component. Menstrual bleeding is a marker of the ovarian and neuroendocrine phenomena of reproductive viability in

humans [32], but not all NHPs exhibit this [24]. Consequently, menopause must encompass hormonal, physiological, and biochemical changes that play essential roles in the cessation of ovarian cyclicity, regardless of whether menstrual bleeding is present. However, Walker and Herndon [1] have defined menopause in NHPs as the permanent, non-pathological, age-associated cessation of ovulation, so to infer this event would require considering such biological parameters as menstrual bleeding, perineal swelling, follicular depletion, and hormonal changes.

Some species of NHPs seem to present processes that are quite similar to what human females experience during menopause, but differences also exist, such as the shorter postmenopausal life span and differences in the timing of hormonal changes during the menopausal transition [33]. It is important to consider the time of menopause relative to the average and maximum life span of individuals. For example, humans may be unique among primates in that they have a long post-reproductive survival potential [34]. In human females, the reproductive function does not begin with puberty nor does it end with menopause at a certain chronological age. Instead, both of these are dynamic periods for the reproductive axis, during which development or senescence occurs relatively rapidly. In fact, the reproductive axis ages to a nonfunctional state (menopause) much earlier than other organs, while the reproductive system reaches the point of failure at a relatively young average age of 51 + 8 years [35]; considering that the maximum span for humans is around 80 years, they spend nearly 35% of her life in a post-reproductive state and in very special cases to 60% (122 years). Also, there are significant differences between species of NHPs and humans in terms of life span. For example, the life span of animals after menopause is short compared to humans, as they usually die not long after menopause [1].

Human females are born with a finite number of oocytes; thus, reproductive aging entails the steady loss of these oocytes through atresia and ovulation, processes that do not necessarily occur at constant rates [36]. Peak fertility in humans occurs in the mid-20s, after which it declines steadily until a steep decrease begins after age 35 [37]. This decline in fertility occurs despite normal hormone secretion by the ovaries of "older" reproductive-age humans, which continues until 3–4 years prior to menopause [38].

In spite of the wide age range at which ovarian dysfunction and reproductive failure occur in these species, the sequence of terminal events is fairly predictable. At the beginning of the process, the menstrual cycle length is shortened due to early follicular development and ovulation [39], which reduces fertility (premenopause). This is followed by disruption of regular menstrual cyclicity (perimenopause) and, finally, complete ovarian failure (menopause). Studies have observed that perimenopause is an indication that the number of remaining ungrown ovarian follicles has dropped below a critical threshold [40]. The period of transition from the reproductive phase to the nonreproductive state is called climacteric. Finally, postmenopause is the period following climacteric and occurs when the hormonal instability that characterizes perimenopause is replaced by the relative stability of the post-reproductive life stage when the reproductive function has ceased [41].

Declining fertility with age is manifested more commonly in monkeys and apes, to the point that some females cease to reproduce altogether before they die. Some reports on Old World

monkeys in the wild mention that old toque macaque (*Macaca sinica*) and gray-cheeked mangabey (*Lophocebus albigena*) females no longer breed, perhaps due to increasingly long birth intervals that terminate with death or the cessation of ovulation [42]. In contrast, NHP females living in captivity may show life cycles marked by irregular and lengthened menstrual cycles, reduced estrogen levels, very long birth spacing and, in a few cases—such as chimpanzees—total cessation of ovulation [8, 43]. In captive rhesus monkeys (*Macaca mulatta*), menstruation ends at approximately 25 years of age [44], and their maximum life span is around 30 years [45]; thus, this species may have a maximum post-reproductive life span of approximately 20%, similar to what happens in chimpanzees (*Pan troglodytes*). There are also differences in life span among species of NHPs and humans. For example, the life span of other animals after menopause is short compared to humans, since they usually die after only a short time, while humans have an extended postmenopausal life expectancy [1].

The perimenopause period is also highly variable in human beings, as age at the onset of this period ranges from the mid-1930s to the early 1950s [46]. This wide range impedes gaining a better understanding of the mechanisms that control the onset of menopause in humans. In NHPs, this is even more difficult, since reproductive cessation occurs so late in their life span that relatively few individuals actually live to those ages. However, there are data that support the existence of a perimenopausal in NHPs [33, 47–49], a condition that indicates a transitional stage between fertility and age-associated infertility. Also, it has been reported that patterns of vaginal bleeding and serum hormone profiles of macaques in the third decade of life are similar to those described for peri- and postmenopausal human [29].

Although originally the term menopause was coined in human being context, there are some approaches toward NHPs, which let us build it, considering not only the cessation of menstrual bleeding but also other changes, such as the cessation of perineal swelling, follicular depletion, and hormonal-associated changes. So this term has been adapted focusing in the physiological characteristics of each species. By other hand the life span between species should be considered, because unlike human beings, some species usually transit immediately from the reproductive end to death. Therefore, it is of great importance to know what are the differences between species that could help us identify the age of onset of menopause according to the species of the study, and, since this information, it will depend on whether or not our data can be extrapolated to the human.

4. Menopause in nonhuman primates in wild versus captive conditions

Specific studies over physiological mechanisms that govern the timing of menopause in wild NHPs are scarce [42, 50], because many factors could mask the accuracy of these results, including the ages of subjects—which often must be estimated [51]—predation pressures [52], limited survivability [23], infant mortality [53], food availability and nutrition [54], and social dynamics [55]. Therefore, this information is taken as complementary to data derived from captive animals [1].

4.1. Macaques (*Macaca* spp.)

Hodgen et al. [29] reported that female rhesus monkeys (*Macaca mulatta*), in captivity and at least 22 years of age, showed true menopause, confirmed by circulating levels of pituitary and ovarian hormones and the pattern of vaginal bleeding. Female rhesus monkeys older than 22 years are considered aged, as the maximum average life span for this species is estimated at 30 years [44, 45]. Hence, these females are close to the end of their life span, compared to humans, who are considered as "aged" at around 75 years.

Graham et al. [8] examined the reproductive history and histology of pigtail macaques (*Macaca nemestrina*) by observing females divided into three age classes (4, 10, and 20 years). They reported that one female over 20 years of age showed functional, hormonal, and morphological characteristics of human menopause (i.e., complete follicular depletion, absence of luteal tissue, amenorrhea, increased LH levels, atrophic uterus, and vagina). Miller et al. [56], meanwhile, reported an age-associated decline in fertility in pigtail macaques, similar to the findings for *Macaca sylvanus* reported by Paul et al. [57].

Walker's study [47], of 15 female *Macaca mulatta* aged 8–34 years, was designed to characterize the endocrine and menstrual changes associated with menopause in this species. Findings indicate that females aged 24–26 years were in transition to menopause, evidenced by elevated LH concentrations consistent with a low E_2 concentration and no indication of bleeding menstrual. Also, the histological analysis of their ovaries showed little or no evidence of follicular activity. Finally, the females aged 27–34 years clearly showed a postmenopausal process, marked by high LH concentrations and uniformly low E_2 concentrations. This finding was corroborated by Gilardi et al. [48], who suggest that in female rhesus monkeys menopause does not occur until the second half of the third decade of life. Recent studies have also reported that postmenopausal females show low E_2 and P_4 levels, high indexes of FSH and LH, and a significant decline in the anti-Mullerian hormone and inhibin B. All these findings indicate that these endocrine parameters may be associated with menopause [49]. On the other hand, Johnson and Kapsalis [58] reported a median age >27 years for menopause in free-ranging rhesus monkeys.

Recent studies have concluded that reproductive senescence correlates with overall health [23]. Gore et al. [59], for example, reported that neuroendocrine changes in senescent rhesus monkeys are consistent with those reported in humans [60] and that ovarian changes are related to menopause [61], thus suggesting that these NHPs undergo ovarian changes as a function of aging, similar to humans [40] and chimpanzee [62]. A study of Japanese macaques (*Macaca fuscata*) reported that in free-ranging individuals, fertility rates diminish at around 25 years of age [63], but those normal menstrual cycles continue when they are in captivity, despite a loss of fertility [64]. Finally, recent studies of cynomolgus monkeys (*Macaca fascicularis*) have shown an endocrine pattern similar to that of humans during the postmenopause period [65].

4.2. Great apes

The menstrual cycles, pregnancy, and genital pathology of common chimpanzees (*Pan troglodytes*) were analyzed to determine the extent of perimenopausal changes in females

with aged approximately 35–48 years. However, those analyses showed no clear evidence of menopause, because several females continued cycling until death [8]. But the authors did observe a reduced likelihood of conception in those female chimpanzees, even though they did not "run out" of oocytes before the end of the maximum life span. They concluded that female chimpanzees aged 35 years of age or more show increased reproductive senescence that is quite comparable to what is seen during human climacteric.

Other studies of common chimpanzees aged approximately 48–50 years and of bonobos— pygmy chimpanzees (*Pan paniscus*)—aged approximately 40 years reported that even though the former were extremely aged, they continued to have menstrual cycles and perineal swelling but with increased cycle length. Also, these aged females continue to secrete GnRH in a pulsatile fashion, although the levels of this hormone are higher than younger females [43]. Recent studies by Lacreuse et al. [66] found that many aged chimpanzees continued to menstruate at age 50 or more, but the length of their cycles increased after age 20. Similar results were reported by Videan et al. [67], who concluded that menopause in *Pan troglodytes* occurs at approximately 35–40 years of age. These data concur with the report on wild chimpanzee by Nishida et al. [50]. These authors reported that the females ceased cycling after 30 years of age. On the other hand, Thompson et al. [68] observed that healthy free-ranging chimpanzees remained reproductively viable well past 40 years. They suggested that in *Pan troglodytes*, menopause occurs as a by-product of ill health, interpreting that the onset of menopause may be delayed in relatively healthy, long-lived animals. Studies of female chimpanzees have shown that reproductive aging is similar to that seen in human females, including higher fetal loss as a function of advancing age [69] and the age-related depletion of ovarian follicles [62]. Thus, these studies showed that *Pan troglodyte* females continued cycling into extreme old age, which distinguishes them from human females in terms of menopause.

Other studies in *Pan paniscus* females, aged at least 40 years, showed no external evidence of menstrual cycling preceding death, and hormone levels consistent with clinically observed amenorrhea, but an exaggerated response to the exogenous GnRH challenge. Histological examination of ovaries showed similar characteristics to those described for senile ovarian tissue in humans [43].

Studies of captive orangutan (*Pongo* ssp.) females have reported the endocrine characteristics of their menstrual cycle and similarities to the human cycle [70]. These reports considered births and inter-birth intervals across the life span and demonstrated an age-specific decline in the fertility of captive female orangutans (*Pongo pygmaeus*; [7]). Other studies with wild female Sumatran orangutans (*Pongo abelii*) failed to document menopause, inferred from increased inter-birth intervals in females of estimated age [51]. Interpreting data from wild animals is difficult because of such countervailing factors as female rank, uncertain age, infant mortality, and food availability [1].

An earlier study that described the reproductive physiology of female gorillas (*Gorilla gorilla*) mentioned a correlation of perineal tumescence with circulating hormones and reported a pattern of cyclic hormone secretion similar to that of humans [71]. Recently, fecal hormone determination in two captive female gorillas aged approximately 40 years showed evidence of the protracted luteal phases that are typical of aging human females [72].

Information related to the occurrence of menopause in baboons (*Papio* ssp.) was based on menstrual cycle length, total cessation of cycling that occurs at 26 years of age in captivity [73]. Similar results were reported by Lapin et al. [74], and other studies of wild baboons have reported increased cyclic variability with age and a complete loss of fertility by the age of 25 years. This suggests that baboons undergo age-linked alterations in reproductive function similar to those of humans.

The living conditions of primates have an impact over the animal life span, so the observations in captivity are not always the same as in wild conditions. Although there are some reports about NHP aging process and menopause, they are scarce. Most of the studies report animal physiology and behavior in captivity, because to follow animals in wild by a long period is a very difficult process due to the NHP living conditions.

5. Nonhuman primates as a model to study human being menopause

Due to the biological similarities between human beings and NHPs, the latter have been studied in the search for an adequate model of menopause. However, it is necessary to clearly delimit the similarities and differences among reproductive characteristics, perimenopausal and menopausal changes, and the average life span of different species [1]. Establishing similarities with humans during this search requires considering the characteristics of menopausal processes when animals are in captivity versus those who are free-ranging, in order to avoid the confusions that have led to the assertion that menopause is a uniquely human event [1]. Walker and Herndon [1] suggested that a comparative analysis of female reproductive senescence should focus on the anatomical, physiological, and biochemical changes that are essential to the cessation of ovarian cyclicity, regardless of the presence of menstrual bleeding. There are few reports on menopause in New World primates compared to Old World monkeys, but studies of the latter have observed declines in sexual activity and decreased birth rates. Also, reports on captive apes suggest a long post-reproductive life span, though this has not been confirmed in the wild [30].

Among the different primate taxa, menopause is manifested along an evolutionary continuum: in some species—such as cercopithecines and apes—it is followed by an extended post-reproductive life span, while in others it may presage death. In terms of NHPs as models for menopause, the species that have most often been employed are baboons and chimpanzees. Studies of these primates have attempted to simulate all the consequences that characterize menopause, namely, hormonal and cognitive changes, cardiovascular alterations, and osteoporosis.

Until recently, the occurrence of reproductive termination in NHPs was widely questioned. However, numerous studies have reported that this does indeed occur in several species of Old World monkeys and great apes. Most of this research has been conducted with *Macaca mulatta* [29, 33, 47–49, 59, 61], but other species also experience menopause, including *Pan troglodytes* [43, 62, 67] and *Gorilla gorilla* [27]. For example, the hormonal profiles of peri- and postmenopausal macaques, chimpanzees, and gorillas [1, 61, 67], as well as the age-related decline in the number of primordial follicle in macaques [61] and chimpanzees [62], share many similarities

and occur in a pattern like to that of aging women [40]. On the basis of data from various studies, Fedigan et al. [75] affirmed that "from an endocrinological perspective, reproductive decline may well follow a similar pattern in all primates, and we could use cases of individual post-reproductive monkeys and apes as clinical models of the physiological basis for menopause in human being. However, from an evolutionary perspective, these studies fail to demonstrate similarity between reproductive senescence in NHPs and menopause in the human female. Instead, they highlight the critical differences: female macaques and chimpanzees that cease to cycle very close to age at death, whereas human females cease to cycle in middle age; female macaques and chimpanzees cease to cycle on an idiosyncratic basis, whereas human females universally cease to cycle at the average age of approximately 50 years."

In light of these data, it is clear that regardless of the age at the onset of menopause, there are numerous physiological similarities between the females of NHPs and human females with respect to the gradual decline and eventual cessation of reproductive capacity. For this reason, several authors of excellent reviews [1, 29, 30] have proposed that NHPs provide the most appropriate animal models available for analyzing menopause in human females and the processes associated with it.

Although NHPs present a rich opportunity to study the process of reproductive senescence or menopause (i.e., the permanent, non-pathological, age-associated cessation of ovulation, [1]) and play a unique role in translational science by bridging the gap between basic and clinical research [76], their use as experimental subjects is limited by the lack of available NHPs that are undergoing the perimenopausal transition and natural menopause, their short menopausal compared to that of human being, high costs, and the strict ethical guidelines that researchers must follow when studying them (see Ref. [33, 76]).

Despite these difficulties, the use of NHPs as study models has several advantages. Macaques (*Macaca* spp.), including *Macaca mulatta* and *Macaca fascicularis* monkeys, for example, have been particularly useful due to their availability, moderate size, and ability to adapt to laboratory conditions. Also, approximately 95% of the overall genetic coding sequence of macaques is identical to that of humans [77], and many of their physiological systems are comparable. Finally, because they are relatively long lived, they are effective models for studying a number of diseases and conditions that increase in frequency with aging. These factors explain why female macaques have been the preferred model for examining critical health concerns of human beings, including luteal phase deficiencies and hypothalamic amenorrhea [78], obesity and diabetes [79], cardiovascular diseases [80], osteopenia, osteoporosis [81], osteoarthritis [82], cognitive deficits associated with age [76], and—at least potentially—decreased interest in mating [83].

If a single conclusion can be gleaned from this brief summary, it is that a large number of physiological conditions and pathologies that human beings experience during their lifetime appear to be broadly manifested in primate taxa, though information is lacking in other regards, such as the interaction between deficits in cognitive processes and their effect on the modulation of social and sexual interaction.

Primates are mammals distinguished by their large brains, advanced cognitive abilities, flexible behavior, and sophisticated social systems [84]. For example, chimpanzees have the ability

to recognize themselves in a mirror [85] and perform tasks involving concept formation [86]. Moreover, the structure and function of human and NHP brains are very similar. In this regard, we can mention nuclear organization, projection pathways, and innervation patterns [87], as well as similar cortical development and organization [88], including visual cortical functional divisions and prefrontal cortex subdivisions [89] that are critical for cognitive processes [90].

In human beings and NHPs, cognitive and reproductive functions decline gradually with advancing age and more precipitously with the loss of circulating estrogen that occurs during menopause. Cognitive deficits in NHPs can be quantified over their life span using a battery of cognitive tests that are similar to, if not the same as, those used with humans [91]. These include the monkey version of the Wisconsin Card Sorting Test (WCST) [92], which is the gold standard for assessing cognitive flexibility in humans. Using a version of WCST (without the numerosity category), executive function deficits have been reported in both middle-aged and older rhesus monkeys [93], as well as in middle-aged menopausal rhesus monkeys [91]. However, the limited availability of animals of adequate age [33] means that studies with monkeys typically involve only a few animals and use premenopausal ovariectomized subjects rather than naturally menopausal females.

Given the dramatic effects of sex steroids on neuronal morphology and brain activity in regions involved in cognition, one might expect that age-related changes in the endocrine milieu will have important consequences for cognitive functions. In effect, data on aged, naturally or surgically menopausal monkeys indicate that estrogen does indeed modulate a broad range of cognitive domains, such as learning and memory. These effects observed appear to be task specific and sensitive to the time that passed without estrogen prior to estrogen replacement. For example, on the delayed response (DR) task—a test of prefrontal functioning—it was noted that performance was impaired in postmenopausal individuals compared to age-matched premenopausal rhesus monkeys [94]. This result suggests that the absence of estrogen, associated with menopause, could be detrimental to prefrontal functioning.

Although the effects of the menstrual cycle, estrogen withdrawal, and estrogen replacement in young monkeys appear limited to non-mnemonic functions, such as attention or aspects of face processing [95], a broad range of cognitive functions, including memory, are sensitive to estrogen deprivation and replacement in older monkeys [92]. Neurobiological data are consistent with such cognitive findings and demonstrate an array of morphological and physiological changes following ovariectomy and/or estrogen replacement in brain areas that are important for cognition.

Although the specific mechanisms through which estrogens may affect cognition remain to be elucidated, it is clear that these hormones have broad effects on areas of the brain that play key roles in cognitive functions [96]. Estrogen receptors are found in the cerebral cortex, hippocampus, and amygdala in both monkeys [97] and human beings [98]. Estrogens alter the neuronal morphology and physiology of some of these areas [99].

NHPs provide valuable animal models that have significantly advanced our understanding of numerous behavioral and biological phenomena in humans and other primates. Their value

as models for studying menopause in humans derives from their common ancestry, as well as a series of hormonal, cognitive, and social influences that are similar to those experienced by human beings. The aging process or menopause has been also explored focusing through the neural basis of cognitive functioning, revealing not only alterations over specific neural systems but also differences in the affectation level among brain regions and neurobiological parameters. Therefore, further research into the interactions among hormones and various neurotransmitter systems could potentially produce improved knowledge of the neural and hormonal bases that comprehend the gamma of alterations that human beings suffer before, during, and after menopause.

5.1. Anxiety and depression during natural or surgical menopause of nonhuman primates

The decrease in ovarian hormones during natural and surgical menopause is associated with a higher incidence of psychiatric disorders, such as anxiety and depression in vulnerable women, where the decrease of hormones—principally E_2 and P_4—can induce neural changes that exert affects on both the emotional and affective levels [100]. In this regard, ovariectomies in NHPs have been used as a model of surgical menopause at the experimental level, given that the absence of certain hormones induced by ovariectomy can reproduce the physiological, emotional, and affective change characteristic of menopause.

At the behavioral level, ovariectomized primates may exhibit anxiety and depression-related behaviors. For example, long-term ovariectomy may increase anxiety in Japanese macaques (*Macaca fuscata*), associated with decreases in such behaviors as positive social contact, dominance, and the time spent receiving grooming. Similarly, temperament tests performed on these individuals show an increase in anxiogenic behavior [101]. Furthermore, ovariectomized pigtail macaques (*Macaca nemestrina*) present higher scratching rates [102], a well-established indicator of anxiety in NHPs, while in Japanese macaques, a reduction in locomotion has been observed after ovariectomy [101], in association with depressive behavior. Therefore, these behavioral alterations are probably due to the absence of ovarian hormones, given that after ovariectomy in rhesus (*Macaca mulatta*) and pigtail macaques a reduction in E_2 and P_4 concentrations is detected, in relation to increased anxiety [102].

The absence of ovarian hormones in NHPs may also generate neural changes in the brain (**Table 1**). Studies of ovariectomized Japanese monkeys have detected downregulation of estrogen receptor beta (ER-β) in the subiculum of hippocampal formation, while postmenopausal monkeys of the same species have shown upregulation of ER-β [103]. On the other hand, in ovariectomized African green monkeys (*Cercopithecus aethiops sabaeus*), a reduction of synaptic plasticity of the hippocampus was detected [104]. Given that the reduced density of dendritic spines and ER-β in the hippocampus is related to an increase in indicators of anxiety and depression in ovariectomized rodents [105], this is probably occurring as well in nonhuman primates that experience surgical menopause. In addition, the long-term absence of ovarian hormones may impact serotonergic activity. For example, it has been demonstrated that ovariectomy in rhesus macaques reduces expression of the mRNA of the tryptophan

Species	Natural menopause/ ovariectomy	Neural changes	Related behavior	References
African green monkeys (*Cercopithecus aethiops sabaeus*)	Ovariectomy	Reduced density of dendritic spines in the CA1 layer of the hippocampus	Not reported	[104]
Pigtail macaques (*Macaca nemestrina*)	Ovariectomy	Not reported	Anxiety	[102]
Rhesus macaques (*Macaca mulatta*)	Ovariectomy	Increased expression of MAO-A protein and decreased expression of TPH and SERT proteins in the dorsal raphe nucleus	Not reported	[107]
Rhesus macaques (*Macaca mulatta*)	Ovariectomy	Decreased expression of TPH2 mRNA in the dorsal raphe nucleus	Not reported	[108]
Rhesus macaques (*Macaca mulatta*)	Ovariectomy	Increased DNA fragmentation of serotonin neurons in the dorsal raphe nucleus	Not reported	[106]
Japanese macaques (*Macaca fuscata*)	Ovariectomy	Not reported	Anxiety and depression	[101]
Japanese macaques (*Macaca fuscata*)	Ovariectomy	Reduced Fev, TPH-2, SERT, and $5HT_{1A}$ gene expression in the dorsal raphe nucleus	Not reported	[109]
Japanese macaques (*Macaca fuscata*)	Natural menopause	Upregulation in the ER-β immunoreactivity in the subiculum of the hippocampal formation	Not reported	[103]
Japanese macaques (*Macaca fuscata*)	Ovariectomy	Downregulation in the ER-β immunoreactivity in the subiculum of the hippocampal formation	Not reported	[103]

Table 1. Neural changes related to anxiety and depressive-like behaviors in nonhuman primates with natural or surgical menopause.

hydroxylase-2 (TPH-2) enzyme, increases the expression of MAO-A, and increases DNA fragmentation of serotonin neurons in the dorsal raphe nucleus [106]. These events could lead, on the one hand, to greater serotonin degradation and, on the other, neuronal death and, finally, a malfunction of the serotonergic system.

Furthermore, long-term ovariectomy in Japanese macaques reduces the expression of serotonergic neurons and gene expression of TPH-2, the serotonin reuptake transporter (SERT), and $5HT_{1A}$ autoreceptors in the dorsal raphe nucleus [109]. This agrees with data showing that in depressed female of *Macaca fascicularis* the binding potential of $5HT_{1A}$ receptors is reduced in the hippocampus, amygdala, and cingulate cortex [110], three of the structures involved in the pathophysiology of anxiety and depression. In contrast, stress-sensitive female monkeys of the same species decrease levels of Fev (transcription factor that determines whether a neuron is serotonergic),

TPH-2, SERT, and $5HT_{1A}$ mRNAs in the dorsal raphe nucleus [111]. Thus, in the long term, the reduction of TPH-2, which is important for serotonin synthesis, together with determinant markers for serotonergic function, could generate a higher incidence of anxious and depressive behaviors in NHPs with menopause, as occurred in human beings.

On the other hand, exogenous administration of E_2 or P_4 in ovariectomized primates has the capacity to restore serotonergic neurotransmission [106]. Further, serotonin neurons can express the ER-β protein and ER-β mRNA [112]. And, therefore, estrogens could increase the availability of serotonin in the brain by interacting with its receptor. Thus, the absence of ovarian hormones, such as E_2 and P_4, has the ability to induce changes at the level of the the central nervous system in primates [103]. This evidence suggests that neural changes could be related to anxiety and depression behaviors, which could indicate some vulnerability in NHPs that experience natural or surgical menopause or suffer changes in different neurotransmission systems in which ovarian hormones participate, all of which could affect the emotional and affective state of these individuals.

6. Conclusion

Menopause is a natural process that entails the permanent cessation of ovulation. It is associated with physiological and structural changes in aging females. Although it has long been assumed that menopause occurs only in human beings, the search for medical/clinical models to aid in research on this process has revealed that some species of NHPs also exhibit menopause. However, certain differences between human females and NHPs are clear: shorter postmenopausal life spans and variations in the timing of hormonal changes during the menopausal transition. But NHP models allow us to better understand not only several of the processes that occur during human aging—such as cognitive changes, cardiovascular alterations, and osteoporosis—but also similarities among species along the taxonomic scale.

On the other hand, increases in anxiety and depression behaviors may be observed in NHPs that undergo natural or surgical menopause. In a comparative perspective, these findings could improve our understanding of the neurobiological mechanisms that underlie emotional and affective disorders associated with the absence of ovarian hormones, given that experiments have demonstrated that long-term hormonal absence has the ability to affect numerous neurotransmission systems involved in mood disorders. In addition to reproducing various neural changes that can be correlated with depressive and anxious behaviors in NHPs, this might help understand the neurobiological substrate of emotional and affective disorders that can appear in women who experience natural or surgical menopause.

Acknowledgements

Author details

María de Jesús Rovirosa-Hernández[1]*, Marisela Hernández González[2], Miguel Ángel Guevara-Pérez[2], Francisco García-Orduña[1], Abril de los Ángeles Aguilar-Tirado[1], Abraham Puga-Olguín[3] and Brisa Patricia Vásquez-Domínguez[4]

*Address all correspondence to: jrovirosa@uv.mx

1 Instituto de Neuroetología, Universidad Veracruzana, Xalapa, Veracruz, México

2 Instituto de Neurociencias, Universidad de Guadalajara, Jalisco, México

3 Posgrado en Neuroetología, Universidad Veracruzana, Xalapa, Veracruz, México

4 Facultad de Medicina, Universidad Veracruzana, Zona-Xalapa, Veracruz, México

References

[1] Walker ML, Herndon JG. Menopause in nonhuman primates?. Biology of Reproduction. 2008;**79**:398-406. DOI: 10.1095/biolreprod.108.068536

[2] Rance N. Menopause and the human hypothalamus: Evidence for the role of kissepeptin/neurokinin B neurons in the regulation of estrogen. Peptides. 2009;**30**:111-122. DOI: 10.1016/j.peptides.2008.05.016

[3] Hall J. Neuroendocrine changes with reproductive aging in women. Seminars in Reproductive Medicine. 2007;**25**:344-351. DOI: 10.1055/s-2007-984740

[4] Wilson EO. The Relevant Principles of Population Biology: Sociobiology. Cambridge: The Belknap Press; 1975. pp. 32-47

[5] Hill K, Hurtado A. Ache life history: The ecology and demography of a foraging people. American Ethonologist. 1996;**26**:531-532. DOI: 10.1525/ae.1999.26.2.531

[6] Pavelka M, Fedigan L. Reproductive termination in female Japanese monkeys: A comparative life history perspective. American Journal of Physical Anthropology. 1999;**109**: 455-464

[7] Caro TM, Sellen DW, Parish A, Frank R, Brown DM, Voland E, Borgerhoff Mulder M. Termination of reproduction in nonhuman and human primate females. International Journal of Primatology. 1995;**16**:205-220. DOI: 10.1007/BF02735478

[8] Graham CE, Kling OR, Steiner RA. Reproductive senescence in female nonhuman primates. In: Bowden DM, editor. Aging in Nonhuman Primates. New York: Van Nostrand Reinhold; 1979. 183-202

[9] Scott P. Menopause: Adaptation or epiphenomenon?. Evolutionary Anthropology. 2001; **10**:43-57. DOI: 10.1002/evan.1013

[10] Fleagle J. Apes and humans. In: Fleagle J, editor. Primate Adaptation and Evolution. 3rd ed. New York, Elsevier; 2013. Pp. 151-168. DOI: 10.1016/B978-0-12-378632-6.0007-0

[11] DuMond FV. The Squirrel Monkey in a Seminatural Environment. New York: Academic Press; 1968

[12] Keverne E. Do Old World primates have oestrus. Malaysian Applied Biology. 1981;**10**: 119-126

[13] Hrdy SB, Whitten P. Patterning of sexual activity. In: Smuts BB, Cheney DL, Seyfarth RM, Wrangham RW, Struhsaker TT, editors. Primates Societies. Chicago and London, University of Chicago Press; 1986; **30**:359-370

[14] Dixson AF. Primate Sexuality: Comparative Studies of the Prosimians, Monkeys, Apes, and Human Beings. Trends in Ecology and Evolution. Inglaterra: Oxford University Press; 1998

[15] Ziegler T, Strier K, Van S. The reproductive ecology of South American primates: Ecological adaptations in ovulation and conception. In: Garber PA, Estrada A, Bicca-Marques JC, Heymann EW, Strier KB, editors. South American Primates: Comparative Perspectives in the Study of Behavior, Ecology, and Conservation. New York: Springer; 2009. pp. 191-210 . DOI: 10.1007/978-0-387-78705-3_8

[16] Yen SC, Jaffe RB. Reproductive Endocrinology: Physiology, Pathophysiology and Clinical Management. Philadelphia: Saunders Company; 1986

[17] Zeleznik AJ, Pohl CR. Control of Follicular development, Corpus Luteum function, the maternal recognition of pregnancy, and the Neuroendocrine regulation of the menstrual cycle in higher primates. Academic Press. 2006; **45**:2449-2510. DOI: 10.1016/b978-012515400-0/50050-6

[18] Bonello N, Jasper MJ, Norman RJ. Periovulatory expression of intercellular adhesion molecule-1 in the rat ovary. Biology Reproduction. 2004;**71**:1384-1390. DOI: 10.1095/biolreprod.104.030650

[19] Hodgen GD, Itskovitz J. Recognition and maintenance of pregnancy. In: Knobil E, Neill J, editors. The Physiology of Reproduction. New York: Raven Press; 1988

[20] Saltzman W, Tardif S, Rutherford J. Hormones and reproductive cycles in primates. In: Hormones and Reproduction of Vertebrates. United States of America, Elsevier Inc. 2011;**5**:291-327. DOI: 10.1016/B978-0-12-374928-4.10013-6

[21] Martin RD. The evolution of human reproduction: A primatological perspective. American Journal of Physical Anthropology. 2007;**50**:59-84. DOI: 10.1002/ajpa.20734

[22] Johnson MH. Everitt B. Essential Reproduction. Oxford, OXF, Inglaterra: Blackwell Science; 2000

[23] Thompson ME. The endocrinology of intersexual relationships in the apes. In Thorpe P, Grey P, editors. The Endocrinology of Social Relationships. Cambridge: Harvard University Press; 2009. pp. 196-222

[24] Dukelow W. Reproductive cyclicity and breeding in the squirrel monkey. In: Rosenblum LA, Coe CL, editors. Handbook of Squirrel Monkey Research. NY: Plenum Press; 1985. pp. 169-190 . DOI: 10.1007/978-1-4757-0812-7_7

[25] Strassmann BI The evolution of endometrial cycles and menstruation. The Quarterly Reviex of Biology. 1996;**71**:181-220. DOI: 10.1086/419369

[26] Gangestad SW, Thornhill R. Human oestrus. Proceeding of the Royal Society B. 2008;**275**:991-1000. DOI: 10.1098/rspb.2007.1425

[27] Atsalis S, Margulis SW. Perimenopause and menopause: Documenting life changes in aging female gorillas. In: Atsalis S, Margulis SW, Hof PR, editors. Primate Reproductive Aging. Switzerland: Kargel AC; 2008. pp. 119-146 . DOI: 10.1159/000137704

[28] Wise PM. Aging of the female reproductive system. In: Masoro EJ, Austad SN, editors. Handbook of the Biology of Aging. London: Elsevier; 2006. pp. 570-590 . DOI: 10.1016/B978-012088387-5/50024-8

[29] Hodgen G, Goodman A, O'Connor A, Johnson D. Menopause in rhesus monkeys: Model for study of disorders in the human climacteric. American Journal of Obstetrics Gynecology. 1977;**127**:581-584. DOI: 10.1016/0002-9378(77)90352-0

[30] Atsalis S, Margulis SW. Primate reproductive aging: From lemurs to humans. In: Atsalis S, Marguli S, Hof P, editors. Primate Reproductive Aging. Switzerland: Kargel AC. 2008. pp. 186-194 . DOI: 10.1159/000137710

[31] Wright P, King S, Baden A, Jernvall J. Aging in wild female lemurs: Sustained fertility with increased infant mortality. In: Primate Reproductive Aging. Vol. **36**. Chicago, New York, Karger Publishers; 2008. pp. 17-28 . DOI: 10.1159/000137677

[32] Vom Saal FS, Finch CE. Reproductive senescence: Phenomena and mechanisms in mammals and selected vertebrates. In: Knobil E, Neill J, editors. The Physiology of Reproduction. New York: Raven Press; 1988. pp. 2351-2413

[33] Bellino FL, Wise PM. Nonhuman primate models of menopause workshop. Biology of Reproduction. 2003;**68**:10-18. DOI: 10.1095/biolreprod.102.005215

[34] Hawkes K, O'Connell JF, Blurton Jones NG, Alvarez H, Charnov EL. Grandmothering, menopause, and the evolution of human life histories. Proceedings of the National Academy of Sciences. 1998:**95**:1336-1339

[35] Hansen K, Knowlton N, Thyer A, Charleston J, Soules M, Klein N. A new model of reproductive aging: The decline in ovarian non-growing follicle number from birth to menopause. Human Reproduction. 2008;**23**:599-708. DOI: 10.1093/humrep/dem408

[36] Soules M, Sherman S, Parrot E, Rebar R, Santoro N, Utian W, Woods N. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Climacteric. 2001;**4**:267-272. DOI: 10.1080/cmt.4.4.267.272

[37] Van Noord-Zaadstra B, Looman C, Alsbach H, Habbema J, te Velde E, Karbaat J. Delayed childbearing: Effect of age on fecundity and outcome of pregnancy. British Medical Journal. 1991;**302**:1361-1365

[38] Hansen K, Thyer A, Sluss P, Bremner W, Soules M, Klein N. Reproductive ageing and ovarian function: Is the early follicular phase FSH rise necessary to maintain adequate secretory function in older ovulatory women? Human Reproduction. 2005;**20**:89-95. DOI: 10.1093/humrep/deh54

[39] Klein NA, Harper AJ, Houmard BS, Sluss P, Soules M. Is the short follicular phase in older women secondary to advanced or accelerated dominant follicle development? The Journal of Clinical Endocrinology and Metabolism. 2002;**87**:5746-5750. DOI: 10.1210/jc.2002-020622

[40] Richardson SJ, Senikas V, Nelson JF. Follicular depletion during the menopausal transition: Evidence for accelerated loss and ultimate exhaustion. The Journal of Clinical Endocrinology & Metabolism. 1987;**65**:1231-1237. DOI: 10.1210/jcem-65-6-1231

[41] Gosden RG. Biology of Menopause: The Cause and Consequence of Ovarian Ageing. London: Academic Press; 1985

[42] Waser P. Postreproductive survival and behavior in a free-ranging female mangabey. Folia Primatologica. 1978;**29**:142-160. DOI: 10.1159/000155836

[43] Gould K, Flint M, Graham C. Chimpanzee reproductive senescence: A possible model for evolution of the menopause. Maturitas. 1981;**3**:157-166. DOI: 10.1016/0378-5122(81)90007-4

[44] Van Wagenen G. Menopause in subhuman primate. The Anatomical Record. 1970;**166**:392.

[45] Tigges J, Gordon TP, McClure HM, Hall EC, Peters A. Survival rate and life span of rhesus monkeys at the Yerkes Regional Primate Center. American Journal Primatology. 1988;**15**:263-273 DOI: 10.1002/ajp.1350150308

[46] Zapantis G, Santoro N. The menopausal transition: Characteristics and management. Best Practice and Research: Clinical Endocrinology and Metabolism. 2003;17:33-52 DOI: 10.1016/S1521-690X(02)00081-7

[47] Walker ML. Menopause in female rhesus monkeys. American Journal of Primatology. 1995;**35**:59-71. DOI: 10.1002/ajp.1350350106

[48] Gilardi KVK, Shideler SE, Valverde CR, Roberts JA, Lasley BL. Characterization of the onset of menopause in the rhesus macaque. Biology of Reproduction. 1997;**57**:335-340. DOI: 10.1095/biolreprod57.2.335

[49] Downs JL, Urbanski HF. Neuroendocrine changes in the aging reproductive axis of female rhesus macaques (*Macaca mulatta*). Biology of Reproduction. 2006:**75**:539-546. DOI: 10.1095/biolreprod.106.051839

[50] Nishida T, Corp N, Hamai M, Hasegawa Y, Hiraiwa-Hasegawa M, Hosaka K, et al. Demography, female life history, and reproductive profiles among the chimpanzees of Mahale. American Journal Primatology. 2003;**59**:99-121. DOI: 10.1002/ajp.10068

[51] Wich SA, Utami-Atmoko SS, Setia TM, Rijksen HD, Schürmann C, van Hooff JA, et al. Life history of wild Sumatran orangutans (*Pongo abelii*). Journal Human Evolution. 2004;**47**:385-398. DOI: 10.1016/j.jhevol.2004.08.006

[52] Hamilton WD III, Busse C, Smith KS. Adoption of infant orphan chacma baboons. Animal Behavior. 1982;**30**:29-34. DOI: 10.1016/S0003-3472(82)80233-9

[53] Teleki G, Hunt EE, Pfifferling JH. Demographic observations (1963-1973) on the chimpanzees of Gombe National Park, Tanzania. Journal of Human Evolution. 1976;**5**:559-598. DOI: 10.1016/0047-2484(76)90004-X

[54] Van Noordwijk MA, Van Schaik CP. Development of ecological competence in *Sumatran orangutans*. American Journal Physical Anthropology. 2005;**127**:79-94. DOI: 10.1002/ajpa.10426

[55] Machatschke IH, Wallner B, Dittami J. Impact of social environment on female chimpanzee reproductive cycles. Hormones and Behavior. 2006;**50**:126-131. DOI: 10.1016/j.yhbeh.2006.02.003

[56] Miller PB, Charleston JS, Battaglia DE, Klein NA, Soules MR. Morphometric analysis of primordial follicle number in pigtailed monkey ovaries: Symmetry and relationship with age. Biology of Reproduction. 1999;**61**:553-556

[57] Paul A, Kuester J, Podzuweit D. Reproductive senescence and terminal investment in female Barbary macaques (*Macaca sylvanus*) at Salem. International Journal of Primatology. 1993;**14**:105-124. DOI: 10.1007/BF02196506

[58] Johnson R, Kapsalis E. Menopause in free-ranging rhesus macaques: Estimated incidence, relation to body condition and adaptive significance. International Journal of Primatology. 1998;**19**:751-765. DOI: 10.1023/A:1020333110918.

[59] Gore AC, Windsor-Engnell BM, Terasawa E. Menopausal increases in pulsatile gonadotropin-releasing hormone release in a nonhuman primate (*Macaca mulatta*). Endocrinology. 2004;**145**:4653-4659. DOI: 10.1210/en.2004-0379

[60] Gill S, Sharpless JL, Rado K, Hall JE. Evidence that GnRH decreases with gonadal steroid feedback but increases with age in postmenopausal women. Journal of Clinical Endocrinology and Metabolins. 2002;**87**:2290-2296. DOI: 10.1210/jcem.87.5.8508

[61] Nichols SM, Bavister BD, Brenner CA, Didier, PJ, Harrison R, Kubisch, HM. Ovarian senescence in the rhesus monkey (*Macaca mulatta*). Human Reproduction. 2005;**20**:79-83. DOI: 10.1093/humrep/deh576

[62] Jones KP, Walker LC, Anderson D, Lacreuse A, Robson SL, Hawkes K. Depletion of ovarian follicles with age in chimpanzees: Similarities to humans. Biology of Reproduction. 2007;**77**:247-251. DOI: 10.1095/biolreprod.106.059634

[63] Itogawa N, Tanaka T, Ukai N, Fujii H, Kurokawa T, Ando A, Watanabe Y, Imakawa S. Demography and reproductive parameters of a free-ranging group of Japanese macaques (*Macaca fuscata*) at Katsuyama. Primates. 1992;**33**:49-68. DOI: 10.1007/BF02382762

[64] Nozaki M, Mitsunaga F, Shimizu K. Reproductive senescence in female Japanese monkeys (*Macaca fuscata*): Age- and season-related changes in hypothalamic-pituitary-ovarian functions and fecundity rates. Biology of Reproduction. 1995;**52**:1250-1257

[65] Kavanagh K, Koudy Williams J, Wagner JD. Naturally occurring menopause in cynomolgus monkeys: Changes in hormone, lipid, and carbohydrate measures with hormonal status. Journal of Medical Primatology. 2005;**34**:171-177. DOI: 10.1111/j.1600-0684.2005.00114.x

[66] Lacreuse A, Chennareddi L, Johnson J, Gould KG, Hawkes K, Wijayawardana S, et al. Menstrual cycles continue into advanced old age in the common chimpanzee (*Pan troglodytes*). Biology of Reproduction. 2008;**79**:407-412. DOI: 10.1095/biolreprod.108.068494.

[67] Videan E, Fritz J, Heward C, Murphy J. The effects of aging on hormone and reproductive cycles in female chimpanzees (*Pan troglodytes*). Comparative Medicine. 2006;**56**:291-299.

[68] Thompson ME, Jones JH, Pusey AE, Brewer-Marsden S, Goodall J, Marsden D, et al. Aging and fertility patterns in wild chimpanzees provide insights into the evolution of menopause. Current Biology. 2007;**17**(24):2150-2156. DOI: 10.1016/j.cub.2007.11.033

[69] Holman DJ, Wood JW. Pregnancy loss and fecundity in women. In: Ellison PT, editor. Reproduction, Ecology, and Human Evolution. New York: Aldine de Gruyter; 2001. pp. 15-38

[70] Collins DC, Graham CE, Preedy JR. Identification and measurement of urinary estrone, estradiol-17-beta, estriol, pregnanediol and androsterone during the menstrual cycle of the orangutan. Endocrinology. 1975;**96**:93-101. DOI: 10.1210/endo-96-1-93

[71] Nadler RD. Reproductive physiology and behavior of gorillas. Journal of Reproduction and Fertility. 1980;(Suppl 28):79-89

[72] Margulis SW, Atsalis S, Bellem A, Wielebnowski N. Assessment of reproductive behavior and hormonal cycles in geriatric western Lowland gorillas. Zoo Biology. 2007;**26**:117-139. DOI: 10.1002/zoo.20124

[73] Martin LJ, Carey KD, Comuzzie AG. Variations in menstrual cycle length and cessation of menstruation in captive raised baboons. Mechanisms of Ageing and Development. 2003;**124**:865-871. DOI: 10.1016/S0047-6374(03)00134-9

[74] Lapin BA, Krilova RI, Cherkovich GM, Asanov NS. Observations from Sukhumi. In: Bowden DB, editor, Aging in Nonhuman Primates. New York: Van Nostrand Reinhold; 1979. pp. 14-37

[75] Fedigan LM, Pavelka MSM Campbell C, Fuentes A, MacKinnon KC, Panger M, et al. Reproductive cessation in female primates comparisons of Japanese macaques and humans. In: Campbell C, Fuentes A, MacKinnon K, Panger M, Bearder S, editors. Primates in Perspective. United Kingdom, Oxford University Press; 2006. pp. 437-447

[76] Shively CA, Clarkson TB. The unique value of primate models in translational research. American Journal of Primatology. 2009;**71**:715-721. DOI: 10.1002/ajp.20720

[77] Magness CL, Fellin PC, Thomas M, Korth M, Agy M, Proll, S, et al. Analysis of the *Macaca mulatta* transcriptome and the sequence divergence between *Macaca* and human. Genome Biology. 2005;**6**:60. DOI: 10.1186/gb-2005-6-7-r60

[78] Kaplan JR, Manuck SB. Ovarian dysfunction, stress, and disease: A primate continuum. ILAR Journal. 2004; **45**:89-115. DOI: 10.1093/ilar.45.2.89

[79] Wagner JD, Kavanagh K, Ward GM, Auerbach BJ, Harwood H, Kaplan JR. Old world nonhuman primate models of type 2 diabetes mellitus. ILAR Journal. 2006;**47**:259-271. DOI: 10.1093/ilar.47.3.259

[80] Shively CA, Kaplan JR, Clarkson T. Carotid artery atherosclerosis in cholesterol-fed cynomolgus monkeys: The effects of oral contraceptive treatments, social factors and regional adiposity. Arteriosclerosis Thrombosis and Vascular Biology. 1990;**10**:358-366. DOI: 10.1161/01.ATV.10.3.358

[81] Jerome CP, Peterson PE. Nonhuman primate models in skeletal research. Bone. 2001;**29**:1-6. DOI: 10.1016/S8756-3282(01)00477-X

[82] Carlson CS, Loeser RF, Purser CB, Gardin JF, Jerome CP. Osteoarthritis in cynomolgus macaques. III: Effects of age, gender, and subchondral bone thickness on the severity of disease. Journal of Bone and Mineral Research. 1996;**11**:1209-1217. DOI: 10.1002/jbmr.5650110904

[83] Wallen K. Sex and context: Hormones and primate sexual motivation. Hormones and Behavior. 2001;**40**:339-357. DOI: 10.1006/hbeh.2001.1696

[84] Hartwig W. Primate evolution and Taxonomy. In: Campbell C, Fuentes A, MacKinnon, K, Bearder S Stumpf R, editors. Primates in Perspective. 2nd ed. New York: Oxford University Press. 2007. pp. 11-22

[85] Povinelli DJ, Rulf AB, Landau KR, Bierschwale DT. Self-recognition in chimpanzees (*Pan troglodytes*): Distribution, ontogeny, and patterns of emergence. Journal of Comparative Psychology. 1993;**107**(4):347

[86] Thompson R, Oden DL. Categorical perception and conceptual judgements by nonhuman primates: The paleological monkey and the analogical ape. Cognitive Science. 2000;**24**:363-396. DOI: 10.1016/S0364-0213(00)00029-X

[87] Amaral D, Lavenex P. Hippocampal neuroanatomy. In: Anderson P, Morris R, Amaral D, Bliss T, O'Keefe J, editors. The Hippocampus Book. New York: Oxford University Press; 2009. DOI: 10.1093/acprof:oso/9780195100273.003.0003.

[88] Hutchison RM, Everling S. Monkey in the middle: Why non-human primates are needed to bridge the gap in resting-state investigations. Frontiers in Neuroanatomy. 2012;**6**:1-19. DOI: 10.3389/fnana.2012.00029

[89] Uylings HBM, Groenewegen HJ, Kolb B. Do rats have a prefrontal cortex?. Behavioural Brain Research. 2003;**146**:3-17. DOI: 10.1016/j.bbr.2003.09.028

[90] Phillips K, Bales K, Capitanio J, Conley A, Czoty P, t Hart B, et al. Why primate models matter. American Journal of Primatology. 2014;**76**:801-827. DOI: 10.1002/ajp.22281

[91] Voytko M, Tinkler G. Cognitive function and its neural mechanisms in nonhuman primate models of aging, Alzheimer disease, and menopause. Frontiers in Bioscience. 2004;**9**:1899-1914. DOI: 10.2741/1370

[92] Lacreuse A, Chhabra R, Hall M, Herndon J. Executive function is less sensitive to estradiol than spatial memory: Performance on an analog of the card sorting test in ovariectomized aged rhesus monkeys. Behavioural Processes. 2004;**67**:313-319. DOI: 10.1016/j.beproc.2004.05.004

[93] Moore TL, Killiany RJ, Herndon JG, Rosene DL. Moss M. Executive system dysfunction occurs as early as middle-age in the rhesus monkey. Neurobiology of Aging. 2006;**27**:1484-1493. DOI: 10.1016/j.neurobiolaging.2006.08.004

[94] Roberts JA, Gilardi K, Lasley B, Rapp PR. Reproductive senescence predicts cognitive decline in aged female monkeys. Neuroreport. 1997;**8**:2047-2051

[95] Landauer N, Kohama SG, Voytko ML, Neuringer M. Effects of menstrual cycle status on visuospatial attention in aged rhesus monkeys. Society for Neuroscience Abstract. 2004;**34**:779-782

[96] McEwen BS, Alves SE. Estrogen actions in the central nervous system 1. Endocrine Reviews. 1999;**20**:279-307. DOI: 10.1210/edrv.20.3.0365

[97] Gundlah C, Kohama SG, Mirkes SJ, Garyfallou VT, Urbanski HF, Bethea C. Distribution of estrogen receptor beta (ERbeta) mRNA in hypothalamus, midbrain and temporal lobe of spayed macaque: Continued expression with hormone replacement. Molecular Brain Research. 2000;**76**:191-204. DOI: 10.1016/S0006-8993(99)02475-0

[98] Osterlund M, Gustafsson JA, Keller E, Hurd YL. Estrogen receptor beta (ERbeta) messenger ribonucleic acid (mRNA) expression within the human forebrain: Distinct distribution pattern to ERalpha mRNA. The Journal of Clinical Endocrinology & Metabolism. 2000;**85**:3840-3846. DOI: 10.1210/jcem.85.10.6913

[99] Tang Y, Janssen WGM, Hao J, Roberts JA, McKay H, Lasley B, et al. Estrogen replacement increases spinophilin-immunoreactive spine number in the prefrontal cortex of female rhesus monkeys. Cerebral Cortex. 2004;**14**:215-223. DOI: 10.1093/cercor/bhg121

[100] Rodríguez-Landa JF, Puga-Olguín A, Germán-Ponciano LJ, García-Ríos RI, Soria-Fregozo C. Anxiety in natural and surgical menopause—Physiologic and therapeutic bases. In: Durbano F, editor. A Fresh Look at Anxiety Disorders. Rijeka: InTech; 2015. pp. 173-198 . DOI: 10.5772/60621

[101] Coleman K, Robertson ND, Bethea CL. Long-term ovariectomy alters social and anxious behaviors in semi-free ranging Japanese Macaques. Behavioural Brain Research. 2011;**225**:317-327. DOI: 10.1016/j.bbr.2011.07.046

[102] Pazol K, Wilson ME, Wallen K. Medroxyprogesterone acetate antagonizes the effects of estrogen treatment on social and sexual behavior in female macaques. Journal of Clinical Endocrinology & Metabolism. 2004;**89**:2998-3006. DOI: 10.1210/jc.2003-032086

[103] Higaki S, Takumi K, Itoh M, Watanabe G, Taya K, Shimizu K, Hayashi M, Oishi T. Response of ERβ and aromatase expression in the monkey hippocampal formation to ovariectomy and menopause. Neuroscience Research. 2012;**72**:148-154. DOI: 10.1016/j.neures.2011.10.007

[104] Leranth C, Shanabrough M, Redmond D. Gonadal hormones are responsible for maintaining the integrity of spine synapses in the CA1 hippocampal subfield of female non-human primates. Journal of Comparative Neurology. 2002;**447**:34-42. DOI: 10.1002/cne.10230

[105] Velázquez-Zamora DA, González-Tapia D, González-Ramírez MM, Flores-Soto ME, Vázquez-Valls E, Cervantes M, González-Burgos I. Plastic changes in dendritic spines of hippocampal CA1 pyramidal neurons from ovariectomized rats after estradiol treatment. Brain Research. 2012;**1470**:1-10. DOI: 10.1016/j.brainres.2012.06.012

[106] Lima FB, Bethea CL. Ovarian steroids decrease DNA fragmentation in the serotonin neurons of non-injured rhesus macaques. Molecular Psychiatry. 2010;**15**:657-668. DOI: 10.1038/mp.2009.97

[107] Smith LJ, Henderson JA, Abell CW, Bethea CL. Effects of ovarian steroids and raloxifene on proteins that synthesize, transport, and degrade serotonin in the raphe region of Macaques. Neuropsychopharmacology. 2004;**29**:2035-2045. DOI: 10.1038/sj.npp.1300510

[108] Sanchez RL, Reddy AP, Centeno ML, Henderson JA, Bethea CL. A second tryptophan hydroxylase isoform, TPH-2 mRNA, is increased by ovarian steroids in the raphe region of macaques. Molecular Brain Research. 2005;**135**:194-203. DOI: 10.1016/j.molbrainres.2004.12.011

[109] Bethea CL, Smith AW, Centeno ML, Reddy AP. Long-term ovariectomy decreases serotonin neuron number and gene expression in free ranging macaques. Neuroscience. 2011;**192**:675-688. DOI: 10.1016/j.neuroscience.2011.06.003

[110] Shively CA, Friedman DP, Gage HD, Bounds MC, Brown-Proctor C, Blair JB, Henderson JA, Smith MA, Buchheimer N. Behavioral depression and positron emission tomography-determined serotonin 1A receptor binding potential in cynomolgus monkeys. Archives of General Psychiatry. 2006;**63**:396-403. DOI: 10.1001/archpsyc.63.4.396

[111] Lima FB, Centeno ML, Costa ME, Reddy AP, Cameron JL, Bethea CL. Stress sensitive female macaques have decreased fifth Ewing variant (Fev) and serotonin-related gene expression that is not reversed by citalopram. Neuroscience. 2009;**164**:676-691. DOI: 10.1016/j.neuroscience.2009.08.010

[112] Gundlah C, Lu NZ, Mirkes SJ, Bethea CL. Estrogen receptor beta (ERβ) mRNA and protein in serotonin neurons of macaques. Molecular Brain Research. 2001;**91**:14-22. DOI: 10.1016/s0169-328x(01)00108-5