

Depletion of Ovarian Follicles with Age in Chimpanzees: Similarities to Humans¹

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ABSTRACT

We retrieved ovarian sections taken from necropsies of 19 captive chimpanzees (*Pan troglodytes*) aged 0–47 yr, counted the number of primordial follicles in each, and compared the rate of decline in numbers to declines previously documented in humans. The follicular depletion rate in this sample was indistinguishable from that shown across the same ages in classic human data sets. This result supports earlier suggestions that ovarian senescence occurs at the same ages in chimpanzees and humans, implying that the influence of declining ovarian function on other physiologic systems may be distinctively buffered in humans.

aging, chimpanzee, follicle, ovary

INTRODUCTION

Mammalian females develop a large pool of oocytes near the time of birth that is subsequently depleted—mostly by atresia—throughout juvenile and adult life [1]. Both the size of the initial pool and the rate of loss vary widely across species [2]. The standard view that oogenesis ceases when the initial store is established has been challenged by evidence from both rodents [3, 4] and primates, including humans [5]. But whether or not stem cells continue to produce some new oocytes, the size of the pool is progressively reduced with age [6].

Details of ovarian ontogeny and aging are far better described for humans than for any other species in the primate order. In humans the store of oocytes is at its maximum during the fifth month of fetal life [7], and is organized into primordial follicles before birth [8]. Most of these follicles are lost to atresia well before maturity, and only about 0.01% of the initial number actually ovulate. The size of the follicle pool at a given age varies widely among individuals, but the rate of decline is steep from before birth to about 40 yr, with subsequent acceleration in the rate of loss [9–16]. As age advances, the declining size of the remaining follicular reserve reaches thresholds associated with reduced fecundability, then sterility, and finally menopause [12, 15, 17, 18]. In historic European populations not practicing family limitation, the average age at last birth is close to 40 yr [19]. Age at menopause is more difficult to assess cross-

culturally than age at last birth, but where it has been well measured, mean age at menopause is about 50 years, and it ranges from ages earlier than 40 yr to 60 yr [20, 21]. Marked individual differences in follicle numbers among women in their forties are more strongly associated with differences in regular, perimenopausal, and menopausal status than with age [12].

Age-related declines in follicle reserves have also been measured in other primate species: *Macaca nemestrina* [22], *Macaca mulatta* [23, 24], and *Macaca fuscata* [25]. Macaque reproductive physiology is very similar to that of humans [26], making these monkeys candidate models of human ovarian senescence, with the advantage for researchers that they reach menopause in their twenties [27–30]. By contrast, the great apes, who are more closely related to humans than monkeys, continue to be fertile through much older ages [31–35]. Similarity in the timing of ovarian senescence in humans and in chimpanzees, our closest living relatives [36], has been recognized for more than 25 yr [37–39], although that view has been contested [40, 41]. Here we report the first counts of primordial follicles in ovaries from chimpanzees and compare them to previously reported human data. This direct assessment of ovarian senescence confirms the close similarity between humans and chimpanzees in the rate of follicular loss with age from near birth to the mid-forties.

MATERIALS AND METHODS

Subjects

Ovarian tissue samples were collected in routine necropsies at the Yerkes National Primate Research Center, where the Animal Care Program is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International and provides state-of-the-art clinical care for the nonhuman primate colony. Ovarian tissue from 19 common chimpanzees (*Pan troglodytes*) ranging in age from 3 mo to 47 yr accumulated over a period of 33 yr. In 16 of these 19 cases, 1–3 microscope slides had been archived. In three more recent cases, the ovaries were systematically processed, and we had 8, 10, or 16 slides to analyze.

Histology

Ovaries obtained at necropsy were fixed in 10% formalin, embedded in paraffin wax, and sectioned at 5- μ m thickness. Sections were mounted onto microscope slides and stained using hematoxylin and eosin to expose the tissue's cellular structure.

A single investigator (K.P.J.) systematically examined one or more archived slides from each of the 19 cases. To count the numerous follicles in the tiny infant sections, 50–170 photomicrographs were taken across a section and marked to avoid double counting. Since the purpose of this study was to assess age-related depletion of the follicle store, we focused on primordial follicles [22], which are defined as oocytes surrounded by one layer of flattened granulosa cells [42].

Analysis and Comparison of Counts

The single section averages of the chimpanzee counts were log-transformed and then regressed on subject age. Human data for comparison came from the

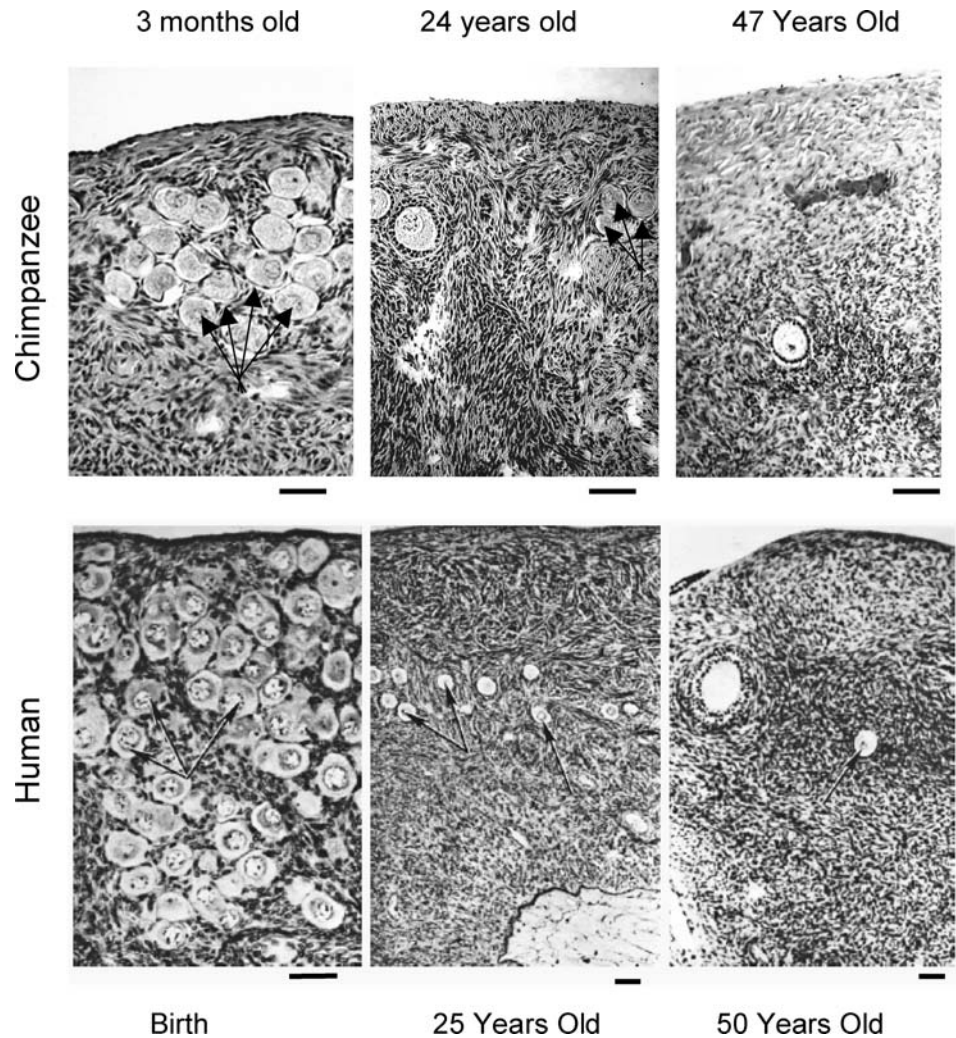
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FIG. 1. Photomicrographs showing the change in follicle density from birth to older ages. Top panels are from three of the chimpanzees included in this analysis. Bottom panels are from humans (from Erickson GF. An analysis of follicle development and ovum maturation. *Seminars in Reproductive Endocrinology* 1986; 4:235. Reprinted by permission) [43]. Arrows indicate primordial follicles. Note that the images in the bottom center and bottom right panels were taken at a lower magnification than those in the top row and bottom left. Bars = 30 μ m.



published studies of normal healthy ovaries previously used by others [13, 15, 16] to characterize changes in follicular reserve with age, except that we only included cases across the age range from 0 to 47 yr to match the chimpanzee sample. The human cases are: 1) Block's primordial follicle counts from 43 subjects aged 6–44 yr [9] and 10 neonates [10] who had died suddenly with postmortem delays ranging from 2 to 4 days, 2) 9 cases aged 45–47 yr for which Richardson et al. [12] reported primordial counts in ovaries fixed for analysis immediately following surgical removal, and 3) 37 cases aged 19–47 yr that were also fixed for analysis immediately after surgical removal, on which Gougeon et al. [14] reported nongrowing follicle counts.

The human counts from both whole ovaries in Block [9, 10] and Gougeon et al. [14], and double the single ovary count reported by Richardson et al. [12] were log-transformed, then regressed on subject age. We then compared the exponential decline with age in the chimpanzee single-section average with the human whole ovary counts.

RESULTS

Figure 1 compares photomicrographs of sections from three chimpanzees to a widely reprinted set of micrographs from human ovaries of similar ages [43]. The left panels show the numerous primordial follicles in the human newborn and a 3-mo-old chimpanzee. Follicular numbers are much reduced in females in their mid-twenties (middle panels), with few if any primordial follicles remaining in the ovaries of much older females, as shown in the panels on the right.

Table 1 lists the ages and the average primordial counts for the ovarian sections from each of the 19 chimpanzees. The exponential decline in numbers of primordial follicles by age in

the chimpanzee ovarian sections and the corresponding published human whole ovary counts are displayed in Figure 2. The slope (-0.05108 ; SEM = 0.007) of the best-fit linear regression for the log-transformed chimpanzee decline (df = 18; Beta = -0.870 ; $P < 0.000$) was not significantly different from the slope (-0.05596 ; SEM = 0.004) of the log-transformed human data (df = 98; Beta = -0.806 ; $P = 0.000$).

DISCUSSION

Whole chimpanzee ovaries have not been regularly archived at Primate Research Centers, but one to three sections with varying orientations and planes across the ovary have sometimes been taken for pathologic examination at necropsy. Single sections are sufficient to show the age pattern of follicular decline in human ovaries [44], and the limited numbers of archived chimpanzee sections were sufficient to show it as well. They displayed a rate and timing of primordial follicular depletion very similar to that of humans over the same range of ages.

Our comparison extends across ages for which human follicular depletion has previously been modeled as biphasic. Faddy and colleagues [13] used the same human data sources but included counts therein from ovaries of women older than 47 yr. Instead of a single exponential rate, they fitted a "broken stick" model to the log-transformed decline in follicle numbers with age. In their biphasic model, one exponential rate of

TABLE 1. Primordial follicle counts on chimpanzee ovarian sections.

Yerkes subject no.	Age (years)	No. of sections inspected	Mean (\pm SD) primordial follicles
95-4	0.3	1	1555.0
95-400	0.3	1	2659.0
92-43	1.1	1	1326.0
03-318	14	2	187.0 (\pm 1.4)
03-22	19	1	163.0
03-270	21	2	99.0 (\pm 59.4)
79-141	22	2	298.0 (\pm 128.7)
80-193	22	1	175.0
01-347	22	1	122.0
03-190	24	2	173.5 (\pm 9.2)
73-144	25	1	27.0
94-186	26	1	37.0
00-461	35	2	17.0 (\pm 12.7)
95-60	38	1	6.0
99-326	38	3	104.7 (\pm 50.1)
01-03	38	1	22.0
05-400	41	16	3.9 (\pm 2.8)
06-108	44	8	20.5 (\pm 8.6)
00-170	45	1	58.0
06-13	47	10	0.2 (\pm 0.4)

decline applied from birth to about 38 yr, and another thereafter. Although the broken stick model, with 37–38 yr as the transition age, is still regularly cited [8, 45], Faddy and Gosden [15] subsequently proposed a more biologically realistic model in which the proportionate rate of loss accelerates continuously as the number of follicles remaining declines (Fig. 3), and they showed that this model predicts a distribution of menopausal ages close to those observed in women [15, 46].

Leidy et al. [16] criticized the broken stick model. Using the same empirical sources, they found that “the data emphatically do not support an abrupt change in the exponential rate of decay at age 37.5. Indeed, the biphasic model that best fits the data places the critical age of change in the exponential rate of decay 10 years later, i.e., closer to the mean age of menopause ... [But] defending a biphasic model with a critical age of 48 seems equally absurd” [16, p. 857]. They concluded that the bend in the point scatter is a necessary artifact of the logarithmic transformation of data values [16, 47–49]. Our chimpanzee cases extend only to ages at which the simple log-linear model is a fair fit in women. Whether such a model continues to fit chimpanzees when older ages are included remains to be seen. If ovarian tissue can be routinely preserved at necropsy, samples necessary to answer that question should soon be available.

The similarity between chimpanzees and humans in the rate of primordial follicle depletion with age into the mid-forties does not support a recent suggestion by Videan and colleagues [41]. They proposed that contrary to earlier accounts [37–39], chimpanzees reach menopause between the ages of 35 and 40 yr, about 10 yr earlier than most women do. Based on analysis of their records of changing ovarian hormone levels and cycling patterns with age for 14 captive chimpanzees, Videan et al. [41] argued that FSH levels may be a better marker of menopause than cessation of cycling in chimpanzees, because estrous swellings may not be closely tied to menstrual cycling in this species. Their study highlighted the important fact that relationships among fecundability, hormonal changes, cycling patterns, and follicular depletion have yet to be determined in chimpanzees. However, FSH levels alone do not distinguish menopausal status in either humans [50, 51] or rhesus macaques (*M. mulatta*) [52]. Other reasons for skepticism

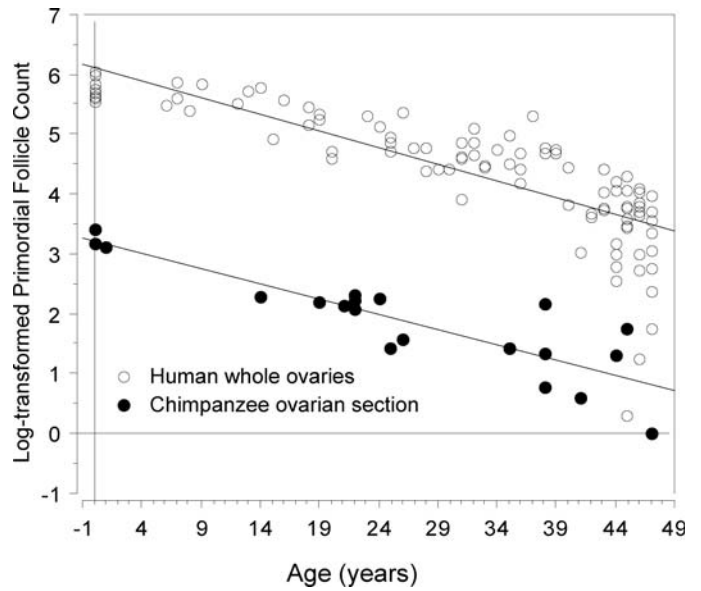


FIG. 2. Log-transformed primordial follicle counts by age in ovarian sections, either single slides or averages of more than one (Table 1), from 16 necropsied chimpanzees ranging in age from 0 to 47 yr compared to primordial follicle counts for whole ovaries from human subjects in the same range of ages. Human data are from Block [9, 10], Richardson et al. [12], and Gougeon et al. [14]. The slope of the best-fit regression for this chimpanzee sample (-0.05108 ; SEM = .007; $n = 19$) is not significantly different from the human slope (-0.05596 ; SEM = .004; $n = 98$).

about their estimates of menopausal ages include fertility rates well above zero around the age of 40 yr in chimpanzees [31, 33] (J.H. Jones, A. Pusey, M.L. Wilson, unpublished Gombe data), just as in women. Those age-specific fertilities, the cycling data provided by Videan et al. themselves [41], and follicle counts indicating essentially the same proportion of

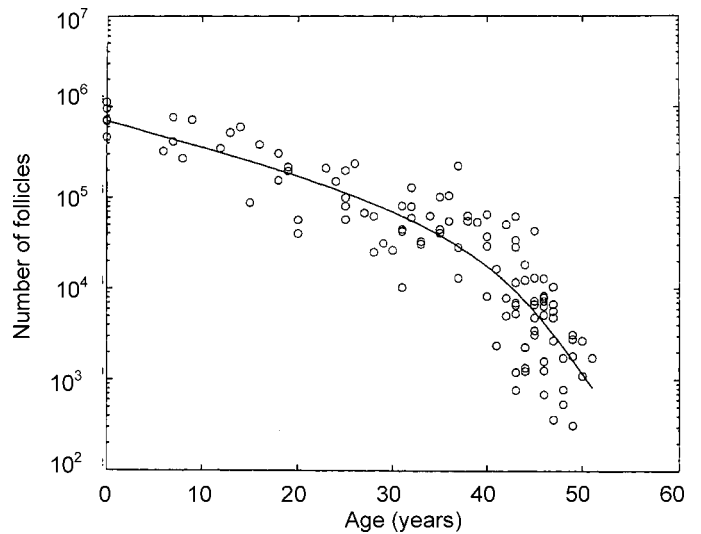


FIG. 3. Observed follicle numbers in women [13; data from 9, 10, 12, 14], with the line indicating the decline predicted by the model of continuously accelerating rate of follicle loss with declining numbers in Faddy and Gosden [15]. Reproduced with permission from Reproduction, Fertility and Development 10(1) (R.G. Gosden and M.J. Faddy). Copyright CSIRO 1998. Published with permission by CSIRO PUBLISHING, Melbourne, Australia. <http://www.publish.csiro.au/journals/rfd> [46]. The decline is well approximated by a simple model of exponential loss into the fifth decade.

primordial stocks remaining in chimpanzees and women through their mid-forties, are more consistent with closer similarity in the timing of ovarian senescence between chimpanzees and humans.

Chimpanzees have a special comparative significance for understanding physiologic associations with ovarian aging in women. In the great apes, last births occur at ages close to those observed in humans [31–35, 53] (J.H. Jones, A. Pusey, M.L. Wilson, unpublished Gombe chimpanzee data). Similarities between chimpanzees and humans in the timing of terminal female fertility were recognized decades ago [37–39]. Initially of interest for the role chimpanzees might play as an animal model of menopause, these similarities are of additional importance because the rates of senescence in other physiologic systems differ between humans and chimpanzees. Chimpanzees begin to show geriatric impairments while they are still fertile [54–56]. In the wild, only a few live into their forties [57]. Humans, in contrast, are the longest-lived terrestrial mammals [58]. While the mean age of human mothers at their last birth is close to 40 yr in historical European populations practicing natural fertility [19], with more than 90% of women past their last birth by the age of 45 yr, girls in these populations who survived to adulthood usually lived well beyond their childbearing years [59, 60].

The fact that human life expectancies have only recently exceeded 50 yr is frequently misinterpreted to mean that living beyond menopause is a 20th century novelty, so that women now face a period of life that has no precedent in our evolutionary history. To the contrary, survival past the childbearing years is common not only in historical populations but among hunter-gatherers, who provide a window into the deeper history of human vital rates because they face the most ancient mortality threats without reliance on farming or herding, institutions of public health, or scientific medicine. High infant and juvenile death rates make life expectancies at birth less than 40 yr among many hunter-gatherers [61–63], yet more than a quarter of the adults are past the age of 45 yr [61–65], and women remain strong and economically productive long past menopause [66–68]. The similarity between chimpanzees and humans in ages of fertility decline, combined with differences in adult mortality rates, suggests that humans may be distinctively buffered from the influence that ovarian senescence has on the function of other physiologic systems, a possibility of biomedical importance and of more general evolutionary and social interest as well.

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