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Review

The menopause and aging, a comparative perspective

Caleb E. Finch*

Davis School of Gerontology, and Department of Neurobiology, Dornsife College, 3715 McClintock Ave, University of Southern California, Los Angeles, CA 90089-0191, United States

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ABSTRACT

The neuroendocrinology of menopause is reviewed from a comparative perspective, with emphasis on laboratory rodent models. These changes are compared by the 2011 STRAW criteria (Stages of Reproductive Aging Workshop). Ovarian cell loss begins prenatally in all mammals studied, with exponential depletion of primary follicles and oocytes in association with loss of fecundity by midlife. Rodents and humans also share progressively increasing irregularity in ovulatory cycles and increasing fetal aneuploidy as oocyte depletion become imminent. Hypothalamic impairments of the estrogen-induced surge of pituitary gonadotrophins (luteinizing hormone, LH; follicle stimulating hormone, FSH) are prominent in middle-aged rodents, but sporadic in peri-menopausal women. In aging rodents, hypothalamic impairments of the LH surge have been experimentally associated with prolonged phases of sustained estradiol (E2) and very low progesterone (P4) ('unopposed estradiol'). Although peri-menopausal women also show hyper-estrogenic cycles, there is no indication for irreversible hypothalamic desensitization by E2. Ongoing cognitive assessments in clinical trials of estrogen therapy with and without P4 or other progestins may further inform about possible persisting effects of unopposed estrogens.This article is part of a Special Issue entitled 'Menopause'.

Contents

1. Introduction

First, ovarian senescence is reviewed from a comparative perspective across vertebrates. Then, the stages of menopause by the STRAW criteria (Stages of Reproductive Aging Workshop) are compared with laboratory rodent models. Past work from my lab in estradiol (E2)-driven rodent neuroendocrine is reviewed, and updated with recent findings that link impaired astrocyte neurotrophic activity to increased expression of estrogen receptor alpha (ERα). Species differences are important in neuroendocrine aging changes which are much less robust in menopausal women than in rodent models.

2. Ovarian senescence

2.1. Oocyte depletion and de novo oogenesis

Ovarian primary follicles and oocytes decline exponentially, starting by birth or before in humans, rodents, and all mammals examined (Fig. 1; Table 1) [1–3]. There is some evidence for

* Tel.: +1 213 369 7600; fax: +1 213 740 6581.
E-mail address: cefinch@usc.edu

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Table 1
Stages of ovarian aging in women and rodent models.

Ovarian aging, Stages defined by STRAW[a]	Women	Rodent models[b]
−5, early reproductive stages:Variable to regular cycles	15–20 y	2–3 mo
−4, peak fecundability Regular cycles	20–35 y	3–7 mo
−3b, late reproduction declining fecundability	30–50 y irregular cycles, short and long	7–12 mo, irregular lengthened cycles; rodents are "retired" as breeders
−2, early menopausal transition;	35–50 y elevated FSH; hypo- and hyperestrogenic cycles; increased anovulatory cycles	9–15 mo, acyclic (constant estrus, with unopposed estrogen; Fig. 3) and hypothalamic desensitization to E2 [48,54]
−1, late menopausal transition		Acyclic, anestrous, very low estrogens [56]
0, final menstrual period no fecundability	Amenorrhea, >2 mo; dwindling follicles	No exact equivalent to menopause; dwindling follicles
+1a,b early postmenopausal	Extinction of follicles; hot flushes, 2 y; increasing FSH and LH	Follicle depletion, 18–24 mo [3]; FSH & LH elevations equivalent to OVX if no pituitary tumors [56]
+1c	FSH elevations stabilize, 3–6 y	
+2, late postmenopausal	Urogenital atrophy	Uterine atrophy [56]

[a] Stages of Reproductive Aging Workshop (STRAW), 2011 revision [41].
[b] From longitudinal studies of lab rodents ([1,48–50]. Fig. 3 shows alternate trajectories of rodent reproductive senescence.

postnatal de novo oogenesis (neo-folliculogenesis) from Tilly and others [4,5]. However, as the ovarian stock dwindles, there is no evidence for a contribution of de novo oogenesis to active follicular pools. A surgical model of accelerated ovarian aging by hemi-ovariectomy (OVX) advanced the onset of fetal aneuploidy and acyclicity by about one month [6]. Acyclicity is predicted to begin at a threshold of 150 remaining oocytes [3]. As elegantly developed by Nelson and Felicio [7], the onset age of acyclicity can be predicted from the rate of ovarian oocyte loss, which is approximated by a single exponential; like the rate of radioactive decay and 'zeroeth order' chemical kinetics, the rate of oocyte loss is independent of the number remaining; also see [8]. The extreme 'radical ovarian resection' of removing 90–95% of the follicles in 5 months old mice accelerated the onset of ayclicity by 5 months, within the limits of the prediction [7]. These findings suggest that *de* novo oogenesis in mice to compensate for the excised primary follicles is minor after 5 months. Mathematical models of the human oocyte reserve are also consistent with minimal de novo oogenesis [9]. Nonetheless, the potential for recovering oogonial stem cells remains of great interest as women increasingly schedule pregnancies to later ages when natural fecundability is sharply dwindling.

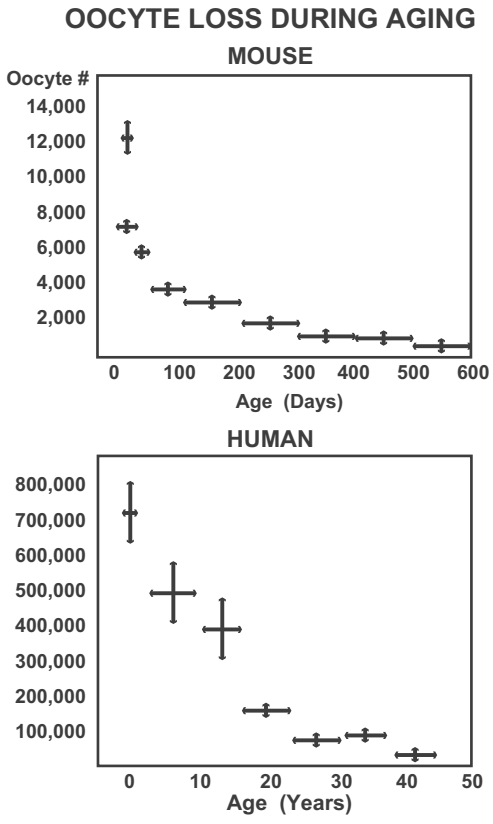

Fig. 1. Oocyte loss from birth thru midlife in mouse (British strain A) [108] and Caucasian women human [109]. Redrawn from Finch et al. [48] In both species, the stock of primary follicles and immature oocytes begins to decline exponentially before birth and becomes exhausted during midlife. Mean lifespans in 2010 are much greater than under Darwinian conditions before modern medicine and hygiene.

Although Zuckerman's [10] concept of finite pools of ovarian oocytes in humans and other mammals is considered the law of the land, the naked-mole rats (rodent family Bathyergidae) may prove to be an exception: these small subterranean species, now laboratory adapted, maintain reproduction to nearly the limit of their prodigious lifespans [11,12]. The current record for *Heterocephalus glaber*, exceeds 31 years in the lab colony of Rochelle Buffenstein (pers. comm.). Equally remarkable is the increase of litter size in the established breeders older than 15–20 years [11]. We hope for data on ovarian follicle populations by age.

Looking further into long-lived vertebrates, there are a few credible examples of fish and turtles that maintain reproduction into their later years [2,12]. Two species of rockfish (*Sebastes aleutianus*, rougheye rockfish and *S. alutus*, Pacific ocean perch) were examined for follicle counts of individuals of defined ages in a project that I organized [13]. Both fish species showed adult de novo oogenesis with annual crops of mature ova; *S. aleutianus* maintained follicle and oocyte numbers up to age 80 years. Further studies of these regularly harvested species could evaluate the viability of the oocytes by in vitro fertilization. Other shorter-lived fish show definitive ovarian senescence with definitive postreproductive phases in lab populations [2]. Thus during the last 500 million years of vertebrate evolution, ovarian senescence has arisen independently in different lineages.

Humans are unique among primates in a definitive post-menopausal phase of life that may have co-evolved with our exceptional longevity. The chimpanzee age at menopause at about 52 years observed in captivity is close to their maximum lifespan [14,15]. In natural populations, no postreproductive phase has been observed for chimpanzees, or for shorter lived monkeys, which also