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LETTER TO EDITOR

A (micro)environmental perspective on the evolution of female reproductive aging

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Aging is a natural process associated with a progressive decrease of cellular and tissue function. Such age-dependent disruption of organismal homeostasis is referred to as senescence. The dynamics of the aging process vary between different organs, with the female reproductive system being the most extreme case of this heterogeneity [1]. Indeed, the cessation of human female reproductive capacity occurs well before the end of expected lifespan. In an era when most human populations have come to benefit from substantial increases in average life expectancy [2], the early termination of female reproductive capacity remains an epidemiologically intriguing question and a clinically pertinent topic. In this issue of the Journal of Assisted Reproduction and Genetics, the problem of reproductive aging is comprehensively addressed under the auspices of human life history theory [3]. To further ease our readers into the burgeoning field of evolutionary medicine, the present commentary focuses on key Darwinian concepts at the heart of the early cessation of human ovarian function.

The origins of the ovarian lifespan effect can be approached from two main evolutionary viewpoints. The first postulates that natural selection favored the acceleration of female reproductive aging. Under this adaptive hypothesis, the aging effect largely resulted from the selection of traits that provide benefit at an early age but are associated with decreased functionality later in life. This process is known as antagonistic pleiotropy and is based on the concept that in resource-intensive processes, such as the female investment in reproduction, early benefits (when the likelihood of survival is higher) outweigh late costs [4]. The second main viewpoint postulates that the acceleration of female reproductive aging was not selected for, but rather it developed as a by-product of an environmentally dependent increase in life expectancy. Under this non-adaptive hypothesis, improved standards of living resulted in an increase in lifespan that was not accompanied by an equivalent extension of female reproductive capacity. A fundamental assumption of this postulate is that reproductive and non-reproductive (somatic) senescence can be uncoupled. Studies on nematodes have put forward the possibility that the evolutionarily conserved insulin/insulin-like growth factor-1 (IGF-1) pathway may serve as one of the mechanistic bases of this proposed uncoupling [5]. More specifically, data suggest that this signaling pathway regulates reproductive and somatic aging through largely distinct transcriptional targets. Yet, the extension of this mechanism to our species remains to be validated.

Are these two hypotheses mutually exclusive? Or can they be reconciled? Ecological data suggests the latter, as there is evidence supporting that both adaptive and non-adaptive mechanisms have contributed to the aging effect. Indeed, the non-adaptive component is illustrated by the observation that the controlled environment of captivity is sufficient to provide extended post-reproductive lifespan to animals that do not exhibit this trait in the wild [6]. Concurrently, the fact that a small number of mammalian species already display accelerated female reproductive aging (i.e., cessation of reproductive ability long before the average life expectancy) in their natural habitat [7] supports an adaptive basis to the process.

If selection was indeed one of the driving forces behind the aging effect, then what possible evolutionary benefits would be conferred by the early cessation of female reproductive capacity? Most likely increased survival of offspring. Indeed, post-reproductive lifespan provides an opportunity to channel investments previously allocated to reproduction into the extended support of genetically related children. This rationale forms the basis of what has been called "the grandmother hypothesis," which posits that the survival (and

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therefore the fecundity) of grandchildren is increased by post-reproductive familial assistance [8]. The key aspect of the grandmother hypothesis is that the benefit in increased offspring survival outweighs the cost of reproduction cessation, yet the exact nature of this trade-off remains unclear. Possible insight into this matter comes from the study of killer whales, a species that also displays early cessation of female reproductive capacity. In these cetaceans, it was observed that post-reproductively aged females act as leaders of collective movement, particularly under adverse natural conditions [9]. Such observation raises the possibility that the accumulation and sharing of knowledge to younger generations may be one of the fundamental bases of the grandmother effect. As for the grandmothers, benefits would accrue both from the enhanced reproductive success of their offspring and from a higher position in the social hierarchy—a status that would otherwise be difficult to attain as they are competing against younger, fertile rivals. In this regard, the concept of inter-generational conflict is another important aspect to take into consideration [10]. Under social structures based on food sharing, offspring from both younger and older mothers compete for the same resources. If younger mothers are more efficient competitors, this leaves the offspring from older mothers at a disadvantage. Again, observations in cetaceans seem to validate this concept: offspring of older mothers that are born into environments with inter-generational conflict face a higher hazard of mortality than those born from younger mothers [11]. Therefore, the restriction of reproductive capacity to younger generations diminishes the competition for resources among genetically related individuals. Taken together, the early cessation of female reproductive capacity was likely selected to ensure the prolonged nursing of offspring while simultaneously dampening the possibility of inter-generational reproductive conflict. Both mechanisms ultimately translate into increased survival of progeny, while reflecting the complex sociocultural aspects of human reproduction. The observation that women with prolonged post-reproductive lifespan have more grandchildren adds further support to this hypothesis [12].

But has the average female reproductive lifespan changed throughout history? The answer seems to be yes: epidemiological data support a secular trend toward an earlier age of menarche [13], and an increase in the average number of reproductive years has been recorded in a population-based cohort of women born in the twentieth century [14]. The fact that the start of female reproductive capacity can be clearly influenced by socioeconomic conditions suggests that its cessation may be delayed by anti-aging interventions. Since germ cell loss is a fundamental aspect of the aging process, most experimental approaches have focused on protecting oocytes from the effects of senescence and/or to regulate the dynamics of their recruitment and attrition. The aim behind both approaches is to prolong reproductive lifespan by a predominantly metabolic modulation of the post-natal ovarian microenvironment. In this regard, dietary supplementation with fatty acids, coenzyme Q10, or the short-term systemic delivery of rapamycin has been shown to extend ovarian function by decreasing oocyte recruitment [15]. Equally noteworthy is the observation that a high-fat diet critically impairs mouse oocyte quality by rendering these cells less competent to sustain post-fertilization development [16]. This evidence further illustrates the concept that nutrition can have a profound impact on the ovarian microenvironment and, consequently, on oocyte number and quality. The possibility that metabolic cues can also influence the size of the oocyte pool (determined during pre- and neonatal development) may provide new ways of extending ovarian lifespan. Indeed, experiments in insects have shown that ovary size is remarkably prone to developmental plasticity—a process by which developmental fate is affected by environmental conditions—and that the nutritional status of the developing organism has a profound effect on the number of germ cells in the adult [17].

In summary, a growing body of evidence supports the hypothesis that female reproductive aging has evolved in response to a series of genetic and environmental factors. Interventions in the ovarian (micro)environment may, therefore, influence the size and mobilization of the oocyte reserve. Accordingly, an environmental health perspective to reproductive aging may uncover new therapeutically targetable pathways to better understand, and ultimately prolong, female fertility.

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References

1. Walker LC, Herndon JG. Mosaic aging. Med Hypotheses. 2010;74:1048–51.
2. Ben-Haim MS, Kanfi Y, Mitchell SJ, Maoz N, Vaughan KL, Amariglio N, et al. Breaking the ceiling of human maximal life span. J Gerontol A Biol Sci Med Sci. 2018;73:1465–71.
3. Lubinsky M. Evolutionary justifications for human reproductive limitations. J Assist Reprod Genet. 2018;35:953–7.
4. Gaillard J-M, Lemaitre J-F. The Williams' legacy: a critical reappraisal of his nine predictions about the evolution of senescence. Evolution. 2017;71:2768–85.
5. Templeman NM, Luo S, Kaletsky R, Shi C, Ashraf J, Keyes W, et al. Insulin signaling regulates oocyte quality maintenance with age via cathepsin B activity. *Curr Biol*. 2018;28:753–760.e754.

6. Tidière M, Gaillard J-M, Berger V, Müller DWH, Bingaman Lackey L, Gimenez O, et al. Comparative analyses of longevity and senescence reveal variable survival benefits of living in zoos across mammals. Sci Rep. 2016;6:36361.
7. Ellis S, Franks DW, Nattrass S, Cant MA, Bradley DL, Giles D, et al. Postreproductive lifespans are rare in mammals. Ecol Evol. 2018;8:2482–94.
8. Hawkes K, O'Connell JF, Jones NG, Alvarez H, Charnov EL. Grandmothering, menopause, and the evolution of human life histories. Proc Natl Acad Sci U S A. 1998;95:1336–9.
9. Brent LJN, Franks DW, Foster EA, Balcomb KC, Cant MA, Croft DP. Ecological knowledge, leadership, and the evolution of menopause in killer whales. Curr Biol. 2015;25:746–50.
10. Cant MA, Johnstone RA. Reproductive conflict and the separation of reproductive generations in humans. Proc Natl Acad Sci U S A. 2008;105:5332–6.
11. Croft DP, Johnstone RA, Ellis S, Nattrass S, Franks DW, Brent LJN, et al. Reproductive conflict and the evolution of menopause in killer whales. Curr Biol. 2017;27:298–304.
12. Lahdenperä M, Lummaa V, Helle S, Tremblay M, Russell AF. Fitness benefits of prolonged post-reproductive lifespan in women. Nature. 2004;428:178–81.
13. Wyshak G, Frisch RE. Evidence for a secular trend in age of menarche. N Engl J Med. 1982;306:1033–5.
14. Nichols HB, Trentham-Dietz A, Hampton JM, Titus-Ernstoff L, Egan KM, Willett WC, et al. From menarche to menopause: trends among US women born from 1912 to 1969. Am J Epidemiol. 2006;164:1003–11.
15. Kallen A, Polotsky AJ, Johnson J. Untapped reserves: controlling primordial follicle growth activation. Trends Mol Med. 2018;24:319–31.
16. Han L, Ren C, Li L, Li X, Ge J, Wang H, et al. Embryonic defects induced by maternal obesity in mice derive from Stella insufficiency in oocytes. Nat Genet. 2018;50:432–42.
17. Mendes CC, Mirth CK. Stage-specific plasticity in ovary size is regulated by insulin/insulin-like growth factor and ecdysone signaling in Drosophila. Genetics. 2016;202:703–19.