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Invited Editorial

Menopause: why does fertility end before life?

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ABSTRACT

Menopause is associated with an ultimate cessation of child-bearing potential. Medical research on menopause focuses mostly on the underlying physiological changes associated with menopause. By contrast, evolutionary biologists are interested in understanding why women lose their potential to reproduce before the end of their lives. Evolution by natural selection predicts that the behaviors that we observe today are products of generations of selection on the genes that govern those behaviors. Since one would expect an individual reproducing throughout its life to produce more offspring than an individual stopping early, one would seldom expect genes for menopause to be selected for during our evolutionary past. This article discusses how menopause and prolonged lifespan might be explained by evolutionary theory, and highlights some angles for future research.

Menopause, or climacterium, is associated with reduced rates of ovulation and an ultimate cessation of child-bearing potential[1]. The proximate explanation for this change is a reduction in follicle number and ovarian function, while a consequence is reduced secretions of estrogens and progesterone. Medical research on menopause focuses mostly on the latter; the underlying endocrinological changes associated with menopause and how the 'negative' effects of menopause may be ameliorated, e.g. through hormone replacement therapies. By contrast, the question that interests evolutionary biologists is the former: why run out of eggs and lose reproductive potential before the end of life? Evolution by natural selection predicts that behaviors that we observe today are the products of generations of selection on the genes that govern those behaviors. Since one would expect an individual that is able to reproduce throughout its life to produce more offspring (and hence forward more genes to following generations) than an individual that stops early, one would seldom expect genes for menopause to be selected during our evolutionary past. Not surprisingly, true menopause is extremely rare in the animal kingdom, and virtually unique to humans (and at least one species of whale[2]). In short, human menopause with fertility ending before life is an enigma from an evolutionary viewpoint[3].

One set of evolutionary explanations for menopause suggests that the climacterium evolved as a consequence of intense reproductive investment early in life and/or 'to prevent' mothers from reproducing late in life, when the benefits of reproducing may be small and the costs large[3,4]. Reproductive investment may be particularly costly in humans, for offspring are born helpless

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and have a long period of dependence[5]. This high cost is exacerbated by short inter-birth intervals and resulting large numbers of dependent offspring typically nurtured simultaneously in humans. The benefits of reproducing late may also be small because pregnancies in old age have an elevated risk of miscarriage, the fetus of old mothers has a higher risk of being born dead[6], having a defect[7] or being born small[8]. In addition, late reproduction may be costly, for a mother that dies during or shortly after childbirth will not only jeopardize the life of her current child, but also those of earlier children which are still dependent on their mother for sustenance and protection[3,4]. Thus, menopause may have evolved because the costs of reproducing late in life out-weigh the benefits, and consequently genes that caused mothers to cease reproduction early were selected compared to those that allowed risky reproduction late in life[3,4]. Unfortunately, testing the hypothesis that women with menopause produce more surviving offspring than those without menopause is not feasible, since all women now experience menopause. However, examination of two other predictions is possible:

(1) Reproducing late in life does not add significantly to the number of surviving children already produced; and

(2) Menopause equals an early termination of reproduction.

It is on examination of these two predictions that some shortcomings of the above ideas about menopause become apparent.

First, it is now apparent that women reproducing late in life may produce more offspring than those that terminate reproduction early. These results are evident from a number of populations living in conditions of natural fertility and without access to health care[9]. For example, in the 18th and 19th centuries, Scandanavian Sami were reliant on reindeer herding and fishing for their livelihood and were without access to either medical care or contraception. Despite this, of all mothers surviving to menopause age, those that continued child-bearing at old age produced more surviving children in their lifetime than those that terminated reproduction earlier. Moreover, age at last reproduction explained 28% of the variance in offspring numbers, suggesting a key positive effect of age at last reproduction on evolutionary fitness. These results suggest that, although costs may be associated with late reproduction, these costs are smaller (not larger) than the benefits of reproducing late. One explanation for this may be that, in family-living species, the death of a mother may have a lower impact on offspring mortality than is often supposed because other individuals (husband, older offspring, grandparents, aunts/uncles, cousins) can subsume the role of the dead mother.

Second, it is true to say that women terminate reproduction early with respect to their life expectancy. However, it is interesting to note that the age at which humans terminate reproduction is consistent with the age of termination by other primates when differences in body size are accounted[10]. For example, in both chimpanzees and humans, reproduction declines to virtually zero at 45 years[11]. The difference is that, in chimps, mortality rates follow fertility so that, in the wild, less than 3% of adults are over 45 years[12], while, in humans, they do not, and 30% of adults may be above 45 years. In addition, the increased survivorship shown by women appears to be above and beyond what is required to ensure the survival of one's last offspring. For example, in humans, mothers deliver their last child when 40 years old on average. In order to ensure the survival of their last offspring, mothers may have to survive roughly 10 years after this age, but, in reality, they normally survive more than double this duration (if survived to 40 years), such that fully one-third of one's life is post-reproductive.

Problems such as these prompted Kristen Hawkes to suggest that lifespan rather than menopause is what has been under selection. In the Grandmother Hypothesis, Hawkes[13] suggests that, if mothers can increase the reproductive success of their offspring by helping with childcare, then a woman with genes for living beyond the decline in fertility may produce more grandchildren (and hence forward more genes to the following generation) than a woman that died before being able to help her offspring to reproduce. It is important to realize that initially women need not have lived long after their decline in fertility in order to help their offspring to reproduce, for a mother's decline in reproduction coincides with the commencement of reproduction of their first offspring. For example, women tend to begin reproducing at 20 years and end around 40 years, by which time their first offspring is 20 and will be beginning to reproduce.

There is now accumulating evidence to suggest that post-reproductive women can indeed have a significant and positive effect on their offspring's reproductive success. In rural Gambia, the pre-

sence of a grandmother improves the dietary condition of grandchildren and increases their survival chances[14]. Among the Hadza hunter-gatherers of Tanzania, variation in child weight is positively correlated with grandmother's foraging time[5], while, in historical populations of Germany[15] and Japan[16], the maternal grandmothers improved the survival of grandchildren. Although these studies provide compelling evidence in support of the Grandmother Hypothesis, they do not definitively answer whether female longevity is positively associated with the number of grandchildren that they forward to the following generation, i.e. they have not considered a strong correlate of evolutionary fitness.

Recently, Lahdenperä and colleagues[17] were able to investigate the fitness benefits (i.e. numbers of grandchildren produced) of living beyond one's reproductive capacity in farming/fishing communities of pre-modern (18th and 19th centuries) Finnish and Canadian people. These people experienced natural fertility and mortality conditions, lived without medical care and before more liberal economics and modern birth-control methods[18]. In addition, grandparent(s) were known to reside in the same house as at least one of their offspring, and nearby virtually all others. The study was based on large multi-generational demographic records, covering approximately 3000 women altogether and all their children and grandchildren. The results from this study showed that the longer a woman lived after menopause (age 50 years), the more grandchildren she forwarded to the following generation[17]. This effect equated to women having two extra grandchildren for every 10 years they survived beyond menopause. This relationship arose because, in the presence of a living mother, offspring reproduced earlier, more frequently and more successfully.

Longer-living women thus passed more genes to the following generation than those who had a shorter lifespan. Importantly, these results were general. First, grandmothers were beneficial to both their sons as well as their daughters. Second, the results were uninfluenced by social class, grandmothers being similarly important to peasant farmers as the land-owners themselves. Finally, parallel findings were observed from both study populations, Finland and Canada, despite their differing culturally, sociologically[17], ecologically and demographically. These results bring strong and general evidence in favor of the Grandmother Hypothesis, suggesting that increased human lifespan has been under positive selection. We believe that the prolonged post-reproductive lifespan of women observed today is the product of an evolutionary adaptation since, by helping their own offspring, females breed more successfully and increase their genetic contributions to the following generations.

Despite the evidence presented, many are sceptical of the Grandmother Hypothesis. This scepticism is based on at least five concerns, four of which are unfounded. First, it is often assumed that the large proportion of older people in a society today is a relatively recent phenomenon and a result of the steady increase in life expectancy over the past centuries. This is simply not true. Until recently, increases in life expectancy reflected reductions in infant mortality, and made little difference to the fraction of women past child-bearing age[19]. Even in historical human populations and traditional hunter-gatherer societies (characterizing living conditions more, when human traits evolved), 30% or more of women are usually beyond the age of 45 years, given that most who survive childhood live past their child-bearing years[19]. This large proportion of old, non-reproductive individuals in human populations marks a fundamental difference to our closest living primate relatives. Second, in humans, increasing longevity may be explained by the young keeping the old alive through care and protection. This may be true to a certain extent, and it would certainly benefit the young to keep the old alive if the old are beneficial. Nevertheless, energy tends to flow from old to young[20] and there is now no question that grandmothers benefit their offspring by allowing them to breed earlier, more frequently and more successfully[17]. Third, the Grandmother Hypothesis is assumed to be restricted to the passing of help from mother to daughter, and yet, in our closest living primate relatives, females (not males) tend to disperse away. How can the Grandmother Hypothesis be relevant if daughters were the dispersing sex in our ancestors? Two points are important: first, daughters too can be non-dispersive in traditional human societies; and, second, grandmothers may equally benefit sons as daughters.

Fourth, it has not been obvious how the Grandmother Hypothesis would explain protracted lifespans in men, and it has even been suggested that protracted lifespan in women is a epiphenomenon of selection for longevity in males[21]. This is exceedingly doubtful; it is never the case that positive selection for a characteristic in one sex produces a more extreme effect in the other. One obvious explanation that could account for protracted lifespan in men is a

grandfather effect. Although seldom considered, preliminary analyses in the Finns and Canadians suggest (Lahdenperä, unpublished) that grandfathers are able to improve the reproductive success of their offspring. Nevertheless, even if this does not turn out to be a general result, two other explanations are valid: first, genes inherited from a longer-living grandmother would pass to both daughters and sons, resulting in lengthening of female's as well as male's lifespan, and, second, men do not show obvious menopause and are capable of reproducing at advanced ages. So, even without any beneficial effects of men on the reproductive success of their offspring, male lifespan may have been similarly favored evolutionarily, but by different selective pressures to women[22].

Finally, an intriguing (but highly controversial[4]) implication of the Grandmother Hypothesis is that menopause may arise simply as a consequence of selection on prolonged lifespan. For example, if in mammals females are born with a finite number of eggs, and a threshold number is required to induce ovulation, it may be unsurprising that, when females live long enough, they will eventually run out. However, there are at least four reasons to suspect that menopause has been under selection[4]:

(1) Some mammals are capable of producing enough eggs to last until 60 years or more;

(2) There is now evidence from rodents that stem cells exist in the ovary and hence that follicles can be regenerated and eggs re-created after birth[23];

(3) Menopause in humans is to a degree 'self-induced'[4];

(4) The variation in onset of menopause is both variable and heritable.

Determining whether or not menopause is an epiphenomenon of increased lifespan will depend on an improved understanding of its proximate, physiological causes, such as: What is the minimum number of eggs required to induce ovulation? Does this vary with age? What causes the final 'self-induced' destruction of eggs[4] and why does it occur? Does it occur in all mammals? Can one induce menopause in other species if selection for longevity is selected artificially? And, more generally, what is the correlation between age at menopause and expected lifespan?

While the question of whether or not menopause is the product of natural selection remains contentious (but likely), there is little question that positive selection has acted on genes that increase lifespan. However, as indicated above, there is still considerable debate as to whether or not prolonged lifespan has been selected to ensure the survival of offspring (Mother Hypotheses) or to increase the reproductive success of those offspring (Grandmother Hypotheses). This debate is largely fuelled by semantics, for the difference is immaterial. In both cases the (grand)mother is attempting to secure her genetic dynasty by increasing the number of genes that she forwards into the following generation. We believe that women that carried genes for longevity were selected because of their ability to increase the survival and reproductive output of their children. We do not rule out the possibility that menopause itself is/was under selection, since shutting down one's reproductive system would allow women with low chances of reproducing successfully themselves to channel more resources into somatic maintenance and hence defer the onset of aging. Medical research aimed at increasing our understanding of, first, the onset of menopause at the physiological level (see questions above), second, the effects of sex hormone reductions on the rate of aging/senescence, and, third, the relationship between age at menopause and expected lifespan, will greatly increase our ability to make coherent arguments about the role of evolution on menopause.

Conflict of interest Nil.

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References

1. Pavelka MSM, Fedigan LM. Menopause: a comparative life history perspective. *Yearbook Phys Anthr* 1991;34:13–38

2. Marsh H, Kasuzya T. Changes in the ovaries of the short-finned pilot whale, *Globicephala macrorhynchus*, with age and reproductive

activity. In Perrin WF, Brownell RL, DeMaster DP, eds. *Reproduction in Whales, Dolphins and Porpoises*. Cambridge: Report of the International Whaling Commission, 1984:311–35
3. Williams GC. Pleiotropy, natural selection, and the evolution of senescence. *Evolution* 1957;11:398–411
4. Peccei JS. Menopause: adaptation or epiphenomenon? *Evol Anthr* 2001;10:43–57
5. Hawkes K, O'Connell JF, Blurton Jones NG. Hadza women's time allocation, offspring provisioning, and the evolution of long postmenopausal life spans. *Curr Anthr* 1997; 38:551–77
6. Wood JW. *Dynamics of Human Reproduction: Biology, Biometry, Demography*. New York: Aldine De Gruyter, 1994
7. Gaulden ME. Maternal age effect: the enigma of Down syndrome and other trisomic conditions. *Mutat Res* 1992;296:69–88
8. Jolly M, Sebire N, Harris J, Robinson S, Regan L. The risks associated with pregnancy in women aged 35 years or older. *Hum Reprod* 2000;15:2433–7
9. Helle S, Lummea V, Jokela J. Are reproductive and somatic senescence coupled in humans? Late, but not early, reproduction correlated with longevity in historical Sami women. *Proc R Soc Lond B* 2004; in press
10. Schultz AH. *The Life of Primates*. New York: Universe Books, 1969
11. Nishida T, Corp N, Hamai M, *et al*. Demography, female life history, and reproductive profiles among the chimpanzees of Mahale. *Am J Primatol* 2003;59:99–121
12. Hill K, Boesch C, Goodall J, *et al*. Mortality rates among wild chimpanzees. *J Hum Evol* 2001;40:437–50
13. Hawkes K. Grandmothers and the evolution of human longevity. *Am J Hum Biol* 2003;15:380–400
14. Sear R, Mace R, McGregor IA. Maternal grandmothers improve nutritional status and survival of children in rural Gambia. *Proc R Soc Lond* 2000;267:1641–7
15. Voland E, Beise J. Opposite effects of maternal and paternal grandmothers on infant survival in historical Krummhorn. *Behav Ecol Sociobiol* 2002;52:435–43
16. Jamison CS, Cornell LL, Jamison PL, *et al*. Are all grandmothers equal? A review and a preliminary test of the "grandmother hypothesis" in Tokugawa Japan. *Am J Phys Anthr* 2002; 119:67–76
17. Lahdenperä M, Lummaa V, Helle S, *et al*. Fitness benefits of prolonged post-reproductive lifespan in women. *Nature* 2004;428:178–81
18. Soininen AM. *Old Traditional Agriculture in Finland in the 18th and 19th Centuries*. Forssan kirjapaino Oy, 1974
19. Hawkes K. The grandmother effect. *Nature* 2004;428:128–9
20. Lee R. Rethinking the evolutionary theory of aging: transfers, not births, shape senescence in social species. *PNAS* 2003;100:9637–42
21. Marlowe F. The patriarch hypothesis – an alternative explanation of menopause. *Hum Nat* 2000;11:27–42
22. Hawkes K, Rogers AR, Charnov EL. The male's dilemma: increased offspring production is more paternity to steal. *Evol Ecol* 1995;9:1–16
23. Johnson J, Canning J, Kaneko T, *et al*. Germline stem cells and follicular renewal in the postnatal mammalian ovary. *Nature* 2004;428:145–50

COMMENTS FROM REVIEWER

Is biology destiny?

Thank you for the opportunity to review this very interesting editorial. I should state at the outset that my perspective is that of an historian of women and gender relations, with an interest in demographic history, and that I have no background in evolutionary biology or in medicine. Thus my views will necessarily come from a very different angle than those of other reviewers. We are increasingly urged to speak across disciplinary boundaries so this is an interesting challenge for me.

As it stands, and within its own paradigm, the editorial reads well and is logically and coherently argued. Taking the notion of the selection of the fittest as its benchmark, it makes a good case for the longevity of females for decades after menopause as linked to their support of their offspring and the enhancement of those descendents' life chances. Further, 'the grandmother hypothesis', that the longevity of females enables them to support their children, who in turn can produce more healthy grandchildren, makes sense within this perspective. Not surprisingly, this view sees biology as totally determining.

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