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A life for a (shorter) life: The reproduction–longevity trade-off

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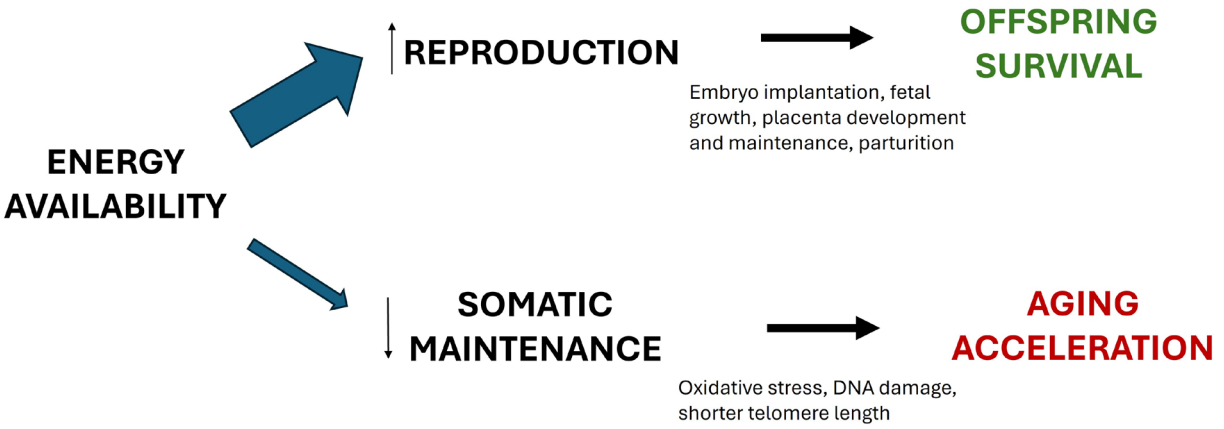

Fig. 1. Schematic of energy allocation during pregnancy. The mother experiences an energetic tradeoff that favors reproduction and minimizes somatic maintenance. This allocation strategy ensures offspring survival, but it accelerates maternal biological aging, resulting in a shorter lifespan.

Aging is inherent to every living organism, and it is associated with increased morbidity and mortality rates, negatively affecting reproductive fitness. But if natural selection favors traits that maximize reproductive rates, why do we age? One possible answer for this evolutionary paradox comes from traditional theories of aging, proposing that high fertility comes at the expense of longevity (1, 2). Notably, humans have a relatively long lifespan among mammals, but it is relatively short when compared to some reptiles, which can live for several hundred years, or plants, which can live up to a few millennia. Unlike other living organisms, most mammals give live births and provide care for their offspring, which incur significant energetic costs. According to the soma disposal theory of aging, energy allocation toward fecundity is an evolutionary adaptation to maximize reproductive fitness, while keeping the body's maintenance and repair costs to a minimum (1). Ryan et al. (3) found evidence for this theory by conducting both cross-sectional and longitudinal analyses among a population in the Philippines. The authors reported that pregnancy was associated with accelerated aging among Philippine women. This finding aligns with the soma disposal theory of aging, which predicts that somatic defects will accumulate over an individual's lifetime through inefficient repair, decreased proofreading capacity of DNA polymerases, cell damage due to free radicals, and cross-linked proteins that slow down cell function (1). Increased somatic maintenance and repair is considered energetically costly, and it would result in a shift in resource allocation away from reproduction. Conversely, when reproduction is prioritized, there is less energy available for somatic maintenance, which accelerates aging processes but maximizes offspring survival chances, ultimately resulting in increased fitness (Fig. 1).

Pregnancy and lactation demand extra energy for the growth and development of the infant. Studies in humans estimate that gestation costs approximately 300 kcal/d, and lactation demands an additional 500 kcal/d to the mother [reviewed by Kominiarek and Rajan (4)]. Ryan et al. (3) expand these short-term costs of female reproduction to long-term costs illustrated by a reduction in their longevity. The authors also reported that young women who experienced more pregnancies had a stronger aging pace, with each additional pregnancy accelerating aging by ~2.6 mo on average. This result increases our understanding of mechanisms mediating life history strategies. According to r/K selection theory, r-selected species are characterized by faster development, high reproductive rates at earlier ages, but a shorter lifespan than K-selected species. Typically, r-strategists have evolved in unpredictable environments and thus have low chances of surviving to old age. In contrast, K-strategists are adapted to predictable environments, where females reach sexual maturity at a relatively later age but have a relatively longer lifespan (5). The trade-off between reproduction and somatic maintenance might be the key mechanism underlying the evolution of these divergent life history strategies. Ryan et al. (3) estimated that each pregnancy incurs an average of 0.65% increase in all-cause mortality risk. This effect would be stronger in species in which females' age at first birth is as early as a few months or days postnatal. Even stronger if they give

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birth to multiple infants in every pregnancy. Naturally, in unpredictable environments, energetic investments in a more efficient somatic repair would be deemed useless if survival chances are low. Therefore, the variation in the timing and rates of fertility that determine mammalian life history traits appear to be mediated by shifts in energetic allocation due to selection pressures. Interestingly, Ryan et al. (3) found that the number of pregnancies men fathered did not affect their biological age. This finding is expected when we consider sex differences in energetic costs associated with pregnancy. Yet, data from the World Health Organization show that Filipino men live approximately 6.2 y less than Filipino women (6). If only women's lifespan is affected by fecundity, how do they tend to live longer than men? Do men have any comparable costs from reproduction on their lifespan? If not, are there any different mechanisms that mediate aging processes in men?

Ryan et al. add pregnancy history as a factor to account for lifespan variation among women.

Biological aging refers to the gradual deterioration of molecular and cellular mechanisms that regulate physiological functions. These include stem cell exhaustion, inflammation, mitochondrial dysfunction, telomere attrition, and loss of proteostasis (7). Based on these mechanisms, numerous biomarkers of aging (e.g., telomere length, DNA damage, hormones, cytokines) have been developed to estimate biological age, allowing us to calculate age acceleration based on its difference from chronological age. More recently, several DNA methylation patterns, known as epigenetic clocks, have shown promising results in predicting biological age. They are based on multiple sites associated with mutations, inflammation, telomere length, DNA damage, or lifestyle (e.g., smoking pack years) and have been associated with morbidity, mortality, and higher risks of developing age-related diseases [reviewed by Ryan (8)]. The link between aging and pregnancy is likely a result of inflammatory pathways, which play a central role in gestation to ensure successful outcomes. This includes proinflammatory mechanisms to enable implantation, anti-inflammatory state to prevent fetal rejection, and a second proinflammatory state to promote parturition (9). These inflammatory states increase susceptibility to oxidative stress, which can cause DNA damage (10). One study reported that women with inadequate weight gain during gestation had shorter telomere lengths than those with adequate weight gain (11). Moreover, studies have shown that the DNA methylation pattern changes after pregnancy (12) and that young mothers have shorter telomere lengths than women who became mothers at later ages (13). Although men do not experience aging effects from fathering offspring, sex differences in epigenetic clocks have shown that men are biologically older than women, supporting demographic data on longevity (14). One study following a cohort of twins from Finland examined four epigenetic clocks and found that sex differences in aging are stronger in older individuals and are mediated by lifestyle factors such as BMI and smoking (14). However, as those factors are limited to our modern society, comparative studies using our closest living relatives can help us understand the evolutionary mechanisms underpinning sex-dependent longevity.

While the costs of reproduction in females are centered around gestation and lactation, male energetic costs vary by social systems. In polygamous societies, male–male competition for female access has driven the evolution of male adaptive traits that increase their reproductive fitness through direct competition (e.g., antlers, larger canines) or by female choice (e.g., bright colors). These traits have been correlated with high dominance rank, which is often accompanied by high testosterone and glucocorticoid (GC) levels, hormones that indicate high energetic costs (15). Interestingly, one study reported that dominant baboons have more offspring but a shorter lifespan than subordinate males (16), suggesting that reproductive advantages among males also come at the cost of longevity in these species. Female dominance has also been positively associated with GC levels, but one recent study found that their GC to dehydroepiandrosterone–sulfate (DHEAS) ratio is lower compared to subordinate females (17). DHEAS is an adrenal androgen involved in stress regulation by antagonizing GC effects to help restore allostasis, but it also functions as a reservoir of sex steroids. A high GC to DHEAS ratio is therefore considered an index of prolonged stress, which is characteristic of conditions that involve high energetic demands. The low GC:DHEAS ratio among dominant females suggests that the benefits of dominance exceed the costs. This contrast between males and females illustrates sex differences in reproductive strategies within polygamous societies. While males compete for female access, females compete for food resources to maximize their fitness, which may offset the costs of social dominance.

If social dominance mediates sex differences in longevity, how is aging regulated in nonpolygamous societies? Experimental studies suggest that sex differences in longevity are hormonally mediated. One study in sheep found that castration decelerated epigenetic aging and that androgen-sensitive CpG sites are hypomethylated with aging in males but remain stable in females and in castrated males (18). Moreover, studies in mice have demonstrated a resistant effect of estrogen to oxidative damage, suggesting that mechanisms inherent to female physiology may have evolved adaptations to minimize DNA damage, whereas testosterone seems to have the opposite effect (19). Therefore, even in the absence of male–male competition, sex differences in reproductive physiology appear to account for lifespan variation between males and females.

As for the factors that affect aging in our modern society, socioeconomic status, chronic stress, smoking, diet, and exercise have been the leading candidates to explain individual variation in longevity (20). Ryan et al. (3) add pregnancy history as a factor to account for lifespan variation among women. It is important to note, as Ryan et al. (3) suggested, that this variable can interact with the lifestyle factors aforementioned. Considering the energetic tradeoff between reproduction and somatic maintenance, we expect that the effect of pregnancy on aging will be mitigated in women with access to abundant food resources and health care. Similarly, we expect that postpartum factors and

decisions such as breastfeeding duration, childcare support system, and duration of maternal leave will influence the long-term impact of pregnancy on women. This is central to understanding how to minimize the aging effect among planning and expecting mothers and whether current antiaging treatments would be effective based on reproductive history.

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