The quest for biomarkers linking ovarian aging and longevity

> Our lives are but specks of dust falling through the fingers of time. Like sands of the hourglass…
>
> – Socrates

The ovaries steadily age, like "specks of dust falling through the fingers of time." A once-robust pool of primordial follicles dwindles, a critical threshold of follicular loss is met, and a chapter closes in the lifespan of the ovary. However, with the aging of the ovaries, another hourglass turns: one that measures the remaining days of one's life.

Ovarian aging has dogmatically been considered inevitable and predestined: an unpleasant but accepted nuisance. Perhaps it was a less urgent issue in centuries past, when many women never reached—or did not live much past—the age of menopause. The ovaries of the 21st century, however, are facing a far different fate. With the age of menopause largely unchanged over the past century but lifespan decades longer, women are spending a significant portion of their lives in menopause. Putting aside the obvious impact of menopause on fertility, menopause and its associated endocrine dysfunction impacts all organ systems. Menopause is accompanied by significant morbidity, including cardiovascular disease, an increased incidence of cancer, cognitive decline, declining bone and sexual health, among countless other organ system impairments. For all people with ovaries, the age of menopause is an important predictor of one's overall health given the morbidity that follows in the postmenopausal years. Beyond morbidity, however, lies the ultimate cost: the age of menopause is inextricably linked to mortality.

Epidemiological and laboratory-based studies indisputably link the timing of menopause with lifespan. A landmark Dutch study examined a cohort of 12,134 women and showed a decrease in the age-adjusted mortality rate of 2% for every 1-year increase in the age of menopause (1). Large population-based cohort studies consistently link the age of menopause to lifespan. One therefore infers that identifying biomarkers to predict the age of menopause, and thus potentially predicting one's lifespan, would be of tremendous interest and value.

Antimüllerian hormone (AMH), a serum hormone produced in the ovary by growing follicles that reflects the remaining pool of primordial follicles, is the most clinically useful marker of ovarian reserve. With limitations and caveats, AMH has the power to provide a window into one's reproductive potential. A 14-year longitudinal study found that AMH is a strong predictor of time to menopause among late reproductive-age women, and numerous studies have reported strong associations between AMH and time to natural menopause (2). This relationship, which becomes clearer with measurement of multiple AMH time points, provides a promising biomarker for reproductive aging.

A number of biomarkers for systemic aging and longevity have emerged, with myriad data investigating leukocyte telomere length, mitochondrial DNA copy number, and epigenetic age acceleration. The AgeAccel tool uses methylomic data to correlate one's DNA methylation-predicted age with chronological age as a predictor of epigenetic aging. (3). Intriguingly, in the analyses of stored blood, saliva, and buccal epithelium from 4 studies, including the Women's Health Initiative, increased epigenetic age acceleration in blood was significantly associated with an earlier age of menopause and longer time since menopause (3). Consistent, compelling evidence suggests that menopause accelerates epigenetic aging, providing an attractive target to better understand both ovarian aging and longevity.

Coupling the relationship between AMH and time to menopause and the relationship between menopause and longevity, it stands to reason that the dots can be connected between the markers of ovarian reserve and longevity. It is through this lens that Kim et al. (4) investigated the relationship between premenopausal reproductive age, measured by serum AMH, and leukocyte aging markers (4). The investigators performed a secondary analysis of the Coronary Artery Risk Development in Young Adults (CARDIA) study, a population-based prospective cohort study that performed periodic screenings at study years 15, 20, and 25. Analysis included premenopausal women with AMH measurements at CARDIA examination year 15, along with leukocyte telomere length at year 15 or 25, mitochondrial DNA copy number at year 15 or 25, or methylation profiling to assess epigenetic aging at year 15 or 20. The investigators performed linear regression models to evaluate for cross-sectional associations between aging biomarkers and AMH and investigated whether AMH was associated with steeper declines in telomere length, mitochondrial DNA copy number, or epigenetic age acceleration after adjusting for age, race, and smoking.

The investigators found that AMH was correlated with chronologic age, as expected, but was not independently associated with leukocyte telomere length, mitochondrial DNA copy number, or intrinsic epigenetic age acceleration. Their findings echo those of other studies that have inconsistently identified associations between ovarian aging and leukocyte aging markers. One report identified a high correlation between leukocyte mitochondrial DNA copy number and follicular mitochondrial DNA copy number; however, correlations with AMH were not evaluated. There has been a significant interest, and meaningful work done, investigating the relationship between telomere length and ovarian aging and between epigenetic aging and ovarian aging. The current study and others suggest that either the epigenome in leukocytes is not representative of that of ovarian follicles and granulosa cells or no true relationship exists. Antimüllerian hormone may simply not be the ideal biomarker to reflect ovarian aging as a predictor of systemic aging; however, it is too soon to draw that conclusion.

The question posed in this study requires further investigation. A single time point analysis of AMH at a late

reproductive age may be insufficient to identify an association, and it remains possible that associations between biomarkers of ovarian reserve and aging may be stronger at younger ages and over multiple time points or at peak AMH. While using data from the CARDIA study was a resourceful tool, the available data did not include gonadotoxic environmental exposures, such as radiation or chemotherapy that could negatively impact AMH. This is all to say that while the findings of this study were unrevealing, the biological plausibility remains.

Although this particular question remains unanswered, the investigators shed light on the importance of synergizing the study of ovarian aging and systemic aging. Predictive biomarkers or not, menopause and lifespan are inextricably linked. The markers assessed by Kim et al. (4) represent only 3 proposed mechanisms of aging—namely, telomere attrition, mitochondrial dysfunction, and epigenetic aging. Additional widely accepted hallmarks of aging include altered intercellular communication, genomic instability, loss of proteostasis, cellular senescence, stem cell exhaustion, and, in particular, deregulated nutrient sensing. Investigating these hallmarks may offer important windows into not only systemic aging but also ovarian aging. My group is particularly interested in the role of the phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (mTOR) pathway and its role in both physiologic and accelerated ovarian aging. The mTOR pathway is a central regulator of aging, lifespan, autophagy and cellular senescence, and mTOR dysregulation contributes to myriad benign and malignant disease processes. Mammalian target of rapamycin activation also plays a critical role in primordial follicle activation and depletion of the primordial follicle pool, with mTOR inhibition contributing to primordial follicle quiescence and maintenance of the primordial follicle pool (5). Understanding that mTOR is a key central regulator of systemic aging and is critical to maintenance of the primordial follicle pool, it reasons that this pathway provides an important link between both ovarian aging and lifespan. Other hallmarks of aging, including genomic instability and senescence, are under active investigation to understand their roles in both ovarian aging and systemic aging.

Reproductive health, ovarian aging, and menopause, and the critical roles they play in systemic health and longevity, have long been underestimated. The ovary holds tremendous potential as a tool to understand aging. While there may not yet be an established link between AMH and markers of longevity, the question is timely and urgent: can markers of ovarian aging predict lifespan? If the age of menopause can be predicted, can it be modified? If the age of menopause can be modified, can lifespan—and most importantly health span—be modified? Perhaps the study of ovarian aging will reveal keys to understanding improved health span and healthy longevity.

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https://doi.org/10.1016/j.fertnstert.2022.05.016

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