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Guest Editorial

Geroscience Approaches to Women's Health in an Aging World

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The U.S. population is aging. By 2034, for the first time in U.S. history there will be more people over the age of 65 years old than under the age of 18. This means that 77.0 million people will be over the age of 65 years, half of which are women (United States Census Bureau, 2019) (1). This trend is not unique to the United States, as the global population is also experiencing unprecedented changes in its age structure due to longer life expectancies and decreasing birth rates. In 2020, the United Nations Department of Economic and Social Affairs reported 727 million people worldwide at or over the age of 65 years and projected that in the next 3 decades this age group will increase from 9% of the total population to representing approximately 16.0% in 2050 (2).

Focusing on women's aging processes will be critically important as in most areas of the world women live longer than men, and so comprise the majority of older persons, especially at more advanced ages. As a result, many conditions related to reproductive aging contribute to significant health care costs including menopausal symptoms and its associated comorbidity risks, cancers of the ovaries, uterus, breast, and vulvar region, urinary incontinence, pelvic floor disorders as well as fertility preservation. Indeed, along with shifts in the aging population is the concomitant decrease in birth rates. The decline in U.S. birth rates has occurred gradually over many decades with births below replacement level since 1971 (3) and recently, the Center for Disease Control National Center for Health Statistics reported that the United States hit a record low with another 4% drop in birth rates in 2020 from 2019 (4). These trends, which are occurring worldwide are contributing to lifestyle, socioeconomic influences, and other environmental changes leading women to have children at later ages. For example, in 1970 the average age of women in the United States when their first child was born was 21 years old for mothers and 27 years of age for fathers, but by 2017 these averages rose to 27 and 31 years of age for mothers and fathers, respectively (5,6). Most importantly, between 2017 and 2019, almost half of all births in the United States were from women past the age of 30 years including 3.46% born by mothers over the age of 40 years (6). Thus, a geroscience approach to understanding how the female reproductive system ages is critical in the need to develop treatments that significantly affect a woman's health, fertility, and quality of life for this growing population of aging women.

In women, signs of normal aging in the reproductive system begin in their 30s resulting in gradual declines in fecundity from 30 to 35 years of age followed by more rapid declines by 37 years old. This is much earlier compared to men whose reproductive capabilities decline around 45 years of age, as demonstrated in studies of older men with younger partners showing increased risks of miscarriage and mental health issues in their progeny. The decline in female reproductive organs is associated with declines in hormone levels, reduced ovulation, and dysregulated menstrual cycles. While menopause defined by the cessation of menstruation occurs on average for most women around the age of 51 years old, many women experience early menopause between the ages of 41 and 45 years while about 1% of women experience premature menopause before the age of 40 years. Menopause for which there are no effective treatments significantly affects women's health lending to increased risk of osteoporosis, cardiovascular disease, stroke, urinary incontinence, and other conditions covered in this issue that significantly affect quality of life. For example, in this issue Labandeira-García and colleagues (7) show in animal models how estrogen regulates the renin–angiotension system in the gut and its potential impact in menopause-associated increases in age-related disorders involving gut motility, permeability, and inflammation. To date, an important contributor to these afflictions, preservation of steroidogenic functions of the ovaries and other tissues and optimizing hormone therapies to maximize their benefit to risk ratio have been met with limited or no success.

Understanding the gaps in the basic mechanisms that control aging in these tissues will provide important targets for therapeutic strategies to counter reproductive aging and its impacts on the aging population. The following articles will discuss how the aging reproductive system intersects with reproductive fitness and overall health. While these tissues which include the ovaries, oviducts, uterus, vagina, and vulvar region have been well-studied and appreciated for their importance in the health of young women, the aging of these tissues has been primarily focused on pathways associated with disease, like cancer and menopause while aging is a major risk factor for these afflictions. As a result, there are fundamental gaps in our understanding of the pathways that control healthy aging. Identification of the mechanisms underlying the aging reproductive

system has the potential to provide interventions or treatments for age-related decline and promote a healthier life span. For example, it is known that genitourinary afflictions caused by menopause result from effects of low estrogen on the female genitourinary tract, including the vagina, labia, urethra, and bladder. While it was known that vaginal microbiota, particularly *Lactobacillus* spp., are beneficial to the female genital tract, in this issue Shardell and colleagues (8) show that their abundance declines with age in women from 35 to 60 years old, and this decrease in microbiota is associated with vulvar-vaginal atrophy and dryness and sexual dysfunction along with an overall self-reported quality of life suggesting a potential avenue for novel treatments.

To understand aging in the female reproductive system it is also necessary to understand that these tissues are among the first in the body to age. For example, functional decline has been well-documented to begin in the ovary of a woman after the age of 30. This is compared to most other tissues which begin to show decline in function at or well after 40 years of age. In addition to age-related loss in tissue function, increases in cellular senescence and inflammation and perturbations in proteostasis, DNA repair and metabolism, all hallmarks of aging, occur in the ovary as well. For example, Llarena and Hine review in this issue (9) how multiple aging pathways, including those involved in metabolism and nutrient sensing such as PI3K/PTEN/AKT/FOXO3, TSC/mTOR, growth hormone/IGF-1, H2S, and sirtuins, converge in the mammalian ovary to regulate the primordial follicle pool. Dhahbi et al (10) also demonstrate how using the Ames dwarf mouse which is a well-established model for delayed aging exhibits a unique set of small noncoding RNA that may help regulate the younger ovarian phenotype found in these mice.

Importantly, aging of the ovary and associated neuroendocrine system affects many organ systems outside the reproductive system, and the ability of women to live longer than men continue to raise questions as to the relationships between the ability to bear children, parity, and female health span, answers to which currently remain elusive. Research as often found a U- or J-shaped association between parity and mortality. This suggests that multiple pregnancies, childbirth, and lactation stresses the body after a certain parity level. Here, Orr et al (11) investigated the Irish Longitudinal Study on Ageing (TILDA) to test whether parity is associated with mortality in women living in Ireland aged 50 years or older (born between 1931 and 1950) and found that in contrast to previous population studies, higher parity was associated with lower risk of mortality in this population, even after adjustment for early life and socioeconomic circumstances. Animal studies have also shown that the effects of aging can be reversed by replacing old gonads with young gonads in animals increasing health span (12,13). In this issue, Schneider, Masternak and colleagues (14) review further evidence that show females increased longevity is associated with delayed ovarian aging.

In summary, the primary papers and reviews in this issue of JGBS illustrate changes brought about by aging in reproductive tissue and underscore the importance of understanding how the female reproductive system ages. This collection also highlights the deficits in our understanding of how women age. The effect of reproductive aging is especially significant as life expectancies potentially rise, and men and women can expect to spend a greater proportion of their life span in hormonal decline. It is also interesting to speculate about whether aging may be for the first time in world history, a risk factor that can affect the health of future generations as more couples delay having children to later ages. Progress in this area of biomedical research will require a multifaceted, integrative geroscience approach to sustain healthier aging in women. This will be essential under the current environment to maintain a sustainable age distribution for our global populations.

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Conflict of Interest

The author declares that there is no conflict of interest.

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