the unspoken truth

REPRODUCTIVE LONGEVITY AND EQUALITY AFFECTS US ALL

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Introduction

The dominant narrative in the area of reproductive longevity is that fertility is limited to a finite period during adulthood which is significantly shorter for women than men. Did you know that women's reproductive organs are considered geriatric in their early 30s when their fertility begins to decline drastically? Let that sink in for a moment. By the age of 40, women only have a five percent chance of becoming pregnant in any month, yet children born today have a projected life expectancy of nearly 100 years. Soon women will live more of their life after menopause than before menopause.

Did you know?

Women who go through **menopause later** tend to **live longer**, as do their **male siblings**.

Ovaries show signs of aging **decades before** other tissues. They are the '**canary in the coal mine**' for aging.

Menopause sets off a cascade of **negative health effects** in women's bodies that impact bone, cognitive, cardiovascular, and immune function.

We can no longer accept that women must complete their families (if they choose to have biological children) before the age of 40, nor that a woman's overall health declines precipitously at menopause in midlife. The complex web of decisions imposed by these limitations—whether to prioritize career or family—adds enormous stress to women's lives and bodies which can lead to even earlier menopause and fertility complications.

> **Ovaries show signs of aging decades before other tissues.**

Beyond reproduction, the end of fertility sets off a cascade of negative health effects in a woman's body. As a society, every aspect of a woman's life is influenced by the fact that her reproductive capacity is limited—overall health, family planning, career decisions. Despite its profound impact on women's health and well-being, **female reproductive aging** is an understudied topic—but why? Women's health, reproductive longevity and equality are all inextricably linked.

Current State of Women's Reproductive Longevity

Consider a scenario where women are not constrained in their reproductive choices by a limited and immutable biological clock and could instead choose a time that is right for them to start their families: a world where women are not subject to the detrimental health effects of reduced reproductive hormone levels. The implications for social, economic and personal empowerment from that freedom of choice and freedom from health risks would be extraordinary. By extending their reproductive span, we seek to empower women with more control over their lives and at the same time delay the onset of age-related diseases. We want to ensure that one day women will have parity and options in their reproductive choices.

Females have all the eggs they will ever produce while still in the womb—7 million eggs at 26 weeks of gestation; 1 million at birth; 300,000 at puberty. At that point, eggs start dying off at a rate of 1,000 a month.[1]

By the time women reach childbearing age, they only have one percent of the original number of eggs left. Imagine if we could increase that to just 2%, it would be game-changing for women. Ten percent of women are infertile by the time they turn 35, and just five years later, at the age of 40, women have only a 5% chance of becoming pregnant in any given month.[2] Women who become pregnant in their mid-30s are classified by the medical community as "geriatric mothers."

Why it Matters...

On a societal level, reproductive inequality negatively impacts women's health, family planning, and career development.

Understanding the limits on mammalian female reproductive capacity will provide important clues about aging in other tissues.

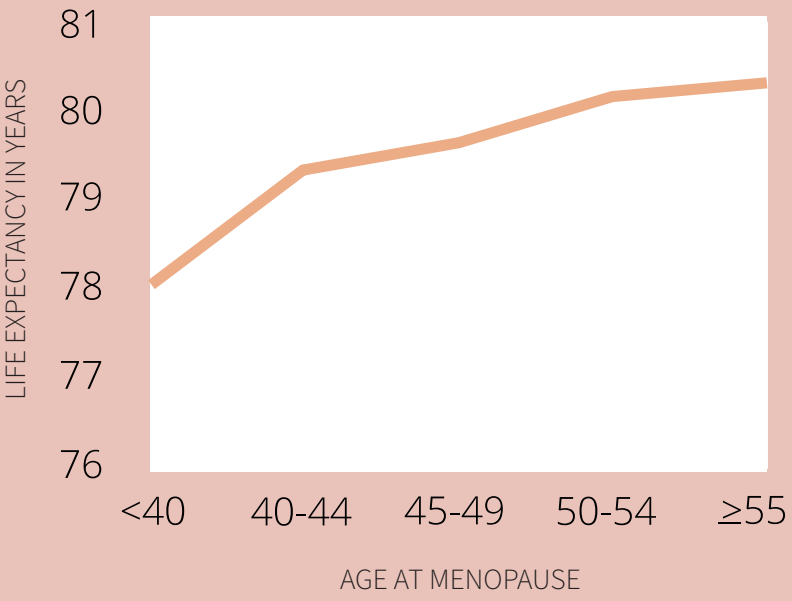
1. MerckManuals. <https://www.merckmanuals.com/home/women-s-health-issues/biology-of-the-female-reproductive-system/female-internal-genital-organs>
2. Broekmans, F. J. *et al. Endocr Rev* **30**, 465 (2009)

Extended Fertility and Longevity in Women

Moreover, the age at which a woman reaches menopause is a strong indicator of lifespan: Women who go through early menopause have a higher morbidity risk, while women who go through menopause later live longer, as do their brothers.[3-6] Why is that? Understanding how and why the ovary ages prematurely will have direct implications for understanding aging in the rest of the body.

The science behind menopause is fascinating, but woefully incomplete. We humans are in the extreme minority—very few species go through menopause.[7] Human females universally cease to cycle at an average age of 50, while closely related female chimpanzees cease to cycle very close to the age at death.[8] The question of why males can produce sperm throughout their lives, but women are unable to make eggs after the initial production in utero remains poorly understood. This is a potential area for therapeutic intervention.

Figure 1 Extended fertility correlates with longevity in women



Several studies demonstrate that later menopause correlates with increased longevity.

Women with natural menopause early have increased risk of mortality compared with those who have natural menopause later.

3. Shadyab, A. H. *et al. Menopause* **24**, 35 (2017)
4. Ossewaarde, M. E. *et al. Epidemiology* **16**, 556 (2005)
5. Malek, A. M. *et al. Prev Med Rep* **15**, 100955 (2019)
6. Smith, K. R. *et al. J Gerontol A Biol Sci Med Sci* **64**, 740 (2009)
7. Ellis, S. *et al. Sci Rep* **8**, 12833 (2018)
8. Alberts, S. C. *et al. PNAS* **110**, 13440-13445 (2013)

Menopause's profound negative effect on women's health

Menopause, even in healthy females, has an extreme negative impact on women's bodies and quality of life—increasing risk of cognitive decline, insomnia, depression, heart disease, stroke, osteoporosis, weight gain and arthritis, to name a few.[2]

Long before menopause, there is a strong connection between reproductive function and women's overall health. If there is underlying dysfunction in reproductive organs, even in young women, this profoundly affects other parts of the body. For instance, women with polycystic ovarian syndrome are prone to metabolic diseases such as diabetes and cardiovascular issues later in life,[9] and studies have shown that this can be passed on to their children, both sons and daughters.[10, 11]

The downstream consequences are clear, but why human females undergo a precipitous decline in fertility at midlife and what sets it in motion are a mystery. We need to understand why humans are different, and in doing so, how we might intervene. What is the underlying science behind this?

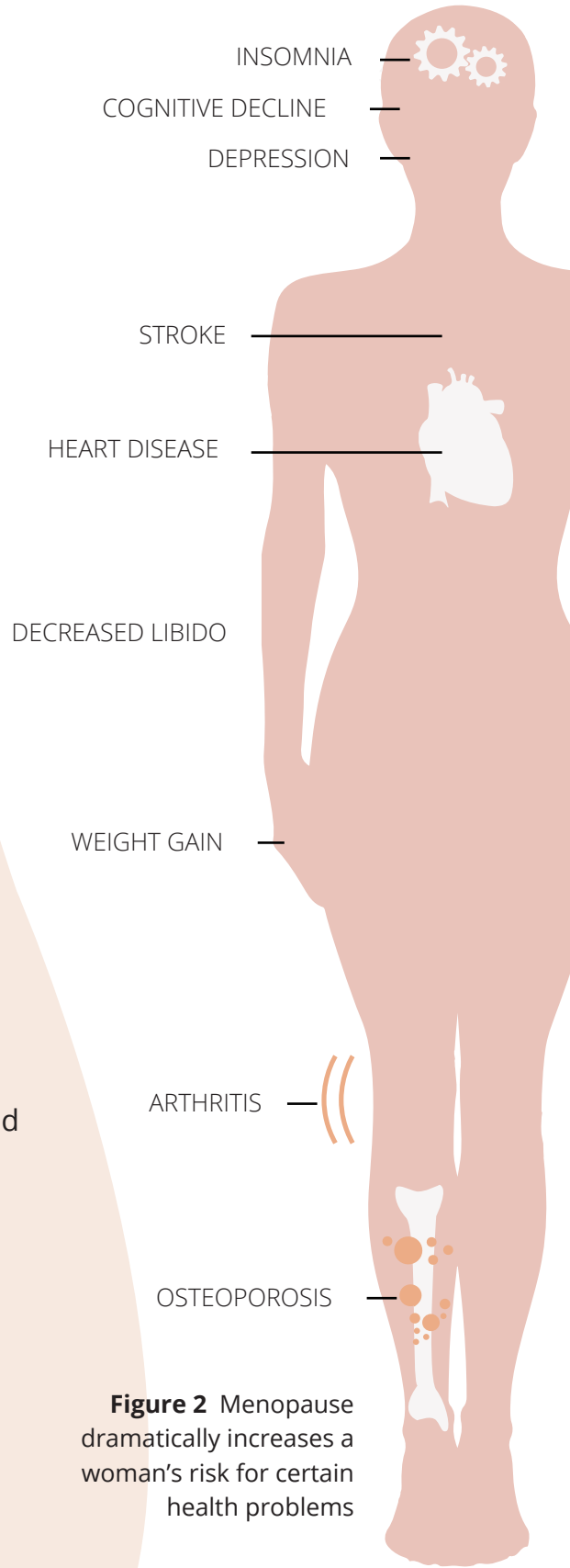


Figure 2 Menopause dramatically increases a woman's risk for certain health problems

9. Anagnostis, P. *et al. Metabolism* **86**, 33 (2018)
10. Torchen, L. C. *et al. J Clin Endocrinol Metab* **101**, 2069 (2016)
11. Torchen, L. C. *et al. Fertil Steril* **106**, 50 (2016)

THE GLOBAL CONSORTIUM FOR REPRODUCTIVE LONGEVITY & EQUALITY

The Global Consortium for Reproductive Longevity and Equality (GCRLE) is advancing research to better understand the underlying causes of female reproductive aging.

To address these issues and gain a better understanding of female reproductive system aging, a global collaborative Consortium dedicated to facilitating research for female reproductive longevity and equality was launched at the Buck Institute for Research on Aging in 2019.

Through funding, collaboration, and innovation, we are accelerating the pace of discovery and informing the path to intervention. We believe we can profoundly alter the societal balance toward equality for women by defining what leads to menopause and developing interventions to slow or reverse it for greater quality of life.

GCRLE's mandate is to advance knowledge in the field of female reproductive aging and accelerate the development of strategies to prevent or delay ovarian aging. We are building the field to understand the basic biological mechanisms that trigger female reproductive senescence, from the earliest stages through to menopause, and ultimately leverage this understanding to intervene in ovarian aging and balance the scales.

> **We are attracting the world's best and brightest researchers to focus their efforts on understanding female reproductive senescence and fostering an intellectual ecosystem designed to accelerate collaboration.**

There really is no existing field for this—we are building it! We are structuring a collaborative network platform to enable knowledge sharing between experts from different disciplines and regions of the world. The Consortium is an innovation hub like no other that enables interactions between researchers in like and disparate scientific fields who might not normally communicate or work together—this is what is needed to move the field forward. It supports a quickly growing knowledge base through a shared information portal for not only researchers but the public at large.

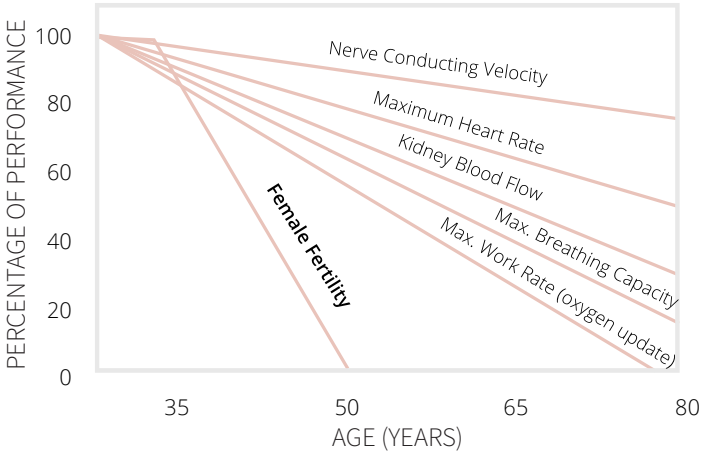
> **We are building a first-of-its-kind Reproductive Biology Hub at the Buck Institute to provide experimental support and training for studies that require expertise in ovarian biology.**

This core facility will be accessible to any lab in the world, with priority to members of the Consortium. By providing researchers from outside the field with the resources to plan and execute experiments using ovarian tissue, we lower the barrier to entry to grow the research.

IT and big data are essential to advancing the field. Thus, we are building a bioinformatics platform that will provide analytic tools for multi-omics projects to investigators who are part of the Consortium. To accelerate the discovery process, the bioinformatics core will also compile and organize large datasets generated by the consortium to be made available to Consortium scientists first and later to the scientific community at large.

Given the multifactorial nature of ovarian aging, charting a new path requires interdisciplinary cooperation between investigators from inside and outside this area of science. We are building a sustainable, impactful, and diverse research ecosystem to support the field by funding innovative, bold ideas in areas that are deemed unpopular, high-risk, or out-of-scope for government funding. We can no longer wait to advance this field. The time is now! We welcome and encourage creativity in research. As with any ecosystem, we require all stakeholders to advance the field and welcome industry, academic, philanthropic and government partners to join us.

Figure 3 Functional Decline with Age



12. Stenson, A. L. *et al. J Womens Health (Larchmt)* **19** (2010)
13. Yen, C. F. *et al. Gynecol Minim Invasive Ther* **8**, 4 (2019)

Female reproductive aging is a global issue and women's health concerns cross international borders. At the same time, there are unique challenges to exploring these topics, particularly in the context of cultures where women may not be empowered.[12] There are genetic differences in phenotypes that may hold clues about broader mechanisms of aging, for example endometriosis affects more women in Asia than anyplace else in the world.[13]

Through the GCRLE, we are building an ecosystem that encompasses every scientist, in every country, who has an interest in this important field. This will be accomplished by building a hub and spoke network architecture while empowering female scientists worldwide to contribute to this emerging field.

Our goal is to create opportunities for interaction and collaboration that cross cultural and physical divides to remove barriers to progress and push the field forward. We are pioneering a movement that will have major societal impact.

> **Our mission is to positively impact the lives of women throughout the world. We intend to change the narrative around female reproductive health and equality with this global initiative to influence the culture of the way we do science.**

The GCRLE is enabling research around female reproductive aging to go further, faster, and on a larger scale. Join us!

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visit our website www.GCRLE.org
or contact us at info@GCRLE.org.

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