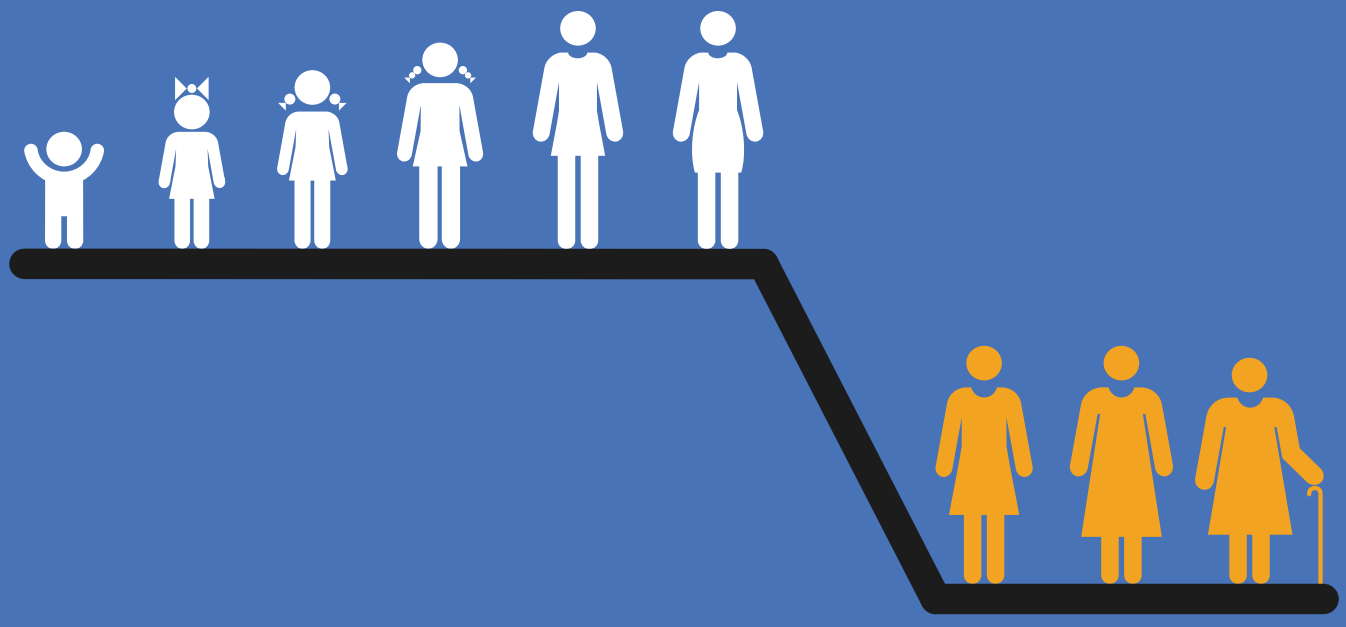
LongevityTechnology

Delaying the menopause to increase women's healthspan:

Ovarian longevity



This report is written in two sections.

- **The first is a deep dive for scientists into the pathways and interventions that could deepen knowledge for a start-up or scientist interested in the space and looking for an overall view into the background of ovarian aging;**

- **Part 2 is for potential investors explaining the current methods for fertility and menopause management and why tackling ovarian longevity is a positive destination for investment capital.**

Women's life expectancy has gone-up by 30 years but the onset of menopause has only been pushed-out by 3 to 4 years.

Executive summary

Ovarian longevity, the disconnect with women's longevity, and why it matters.

- Ovarian aging is the natural decline in the quality and the quantity of eggs (oocytes) that eventually results in infertility and menopause. Interestingly, ovaries are one of the earliest-aging organs and ovarian aging is considered the pacemaker of female body aging as it drives the aging of multiple organs of the body.

- This report considers 'Ovarian longevity' the potential to delay menopause to better align with the increasing healthspan of women, to consequently increase the size of the child-bearing window and improve fertility rates.

- This increase reap huge benefits for women's careers, healthspans and longevity, the health of their children, and the global economy.

- Ovarian aging is an issue for two important reasons: Firstly, menopause is associated with a health decline for females which means women could spend a large proportion of their lifespans in poor health and, secondly, ovarian aging is associated with a pressure on females to reproduce before they reach the average age of infertility.

- During menopause, the loss of estrogen due to ovarian failure, increases several health risks for women including cardiovascular disease, skeletal fragility and Alzheimer's. This means that a woman may spend a large period of her life in poor health – a recent NHS study of UK data concluded that women may live for 34% of their lives in poor health in comparison with 26% for men.

- For many women, as career opportunities and choices have improved, particularly in the developed world, more are choosing to wait longer before having children. However, although advances in education, health, diet and sanitation have increased women's life expectancy by up to 30 years in recent decades, the average age of onset of menopause has only increased by 3 to 4 years. Relative to lifespan, the preferred window for childbirth is therefore both shrinking and increasingly fraught with difficulties.

- Lower fertility rates also mean reduced average family sizes and therefore, populations in many countries are declining. The World Bank has reported that the global average total fertility rate, which needs to be above 2.1 for a population to grow, had almost halved from its 1960 rate of 4.7 to only 2.4 in 2018. Most of the developed world is already below 2.0 and falling. The continuation of this trend will heap further pressure on shrinking younger workforces to support an increasingly aging population.

- While many may look to social funding and social welfare programmes, flexible working and educating young women about the impacts of delaying motherhood, we at Longevity.Technology are looking to ovarian longevity. Instead of papering over the cracks of declining fertility and menopause effects, we are investigating how we can shift the paradigm and prevent the effects of ovarian aging before they happen.

- To date, there have been two key areas of focus in terms of dealing with this issue – improving fertility through assisted reproductive technologies (e.g. high cost and low success rate IVF programmes) and ameliorating the effects of the menopause, through hormone replacement therapy. Both are multi-billion dollar industries but treat consequences instead of focusing on prevention. A technique that prevents ovarian aging will cover both industries and could also impact the life and healthspan of women, pulling in the longevity industry on top.

Foreword

Aging is a public health pandemic and the major risk factor for most chronic diseases in the developed world (cancer, heart disease, neurodegenerative disease, etc). Although aging has long been appreciated as a risk factor, modern medicine has largely ignored it as a therapeutic target. That's changing. Thanks to basic science discoveries we now know that biological aging is malleable and if we figure out how it works then we can exploit that knowledge to reduce overall disease risk. As we make progress in extending healthy longevity, if we don't address reproductive longevity gender inequality is going to get worse, not better. This is because menopause makes a woman's body age faster. Beyond reproduction, the end of fertility sets off a cascade of negative health effects in a woman's body. As the average age of menopause has remained unchanged while overall lifespan has increased, a girl born today can expect to spend more of her life after menopause than before it. This is simply unacceptable.

On a societal level, every aspect of a woman's life is influenced by the fact that her reproductive capacity is limited and directly impacts decisions about overall health, career, and family planning. From the moment a woman goes through puberty, whether she wants to have children or not, every decision she makes will be overshadowed by the fact that she will undergo this reproductive decline in midlife. Relative to their lifespan, women are forced to make life-changing reproductive decisions in an increasingly narrow window of their lives. Menopause, with its associated health risks, hits just when most women are reaching the pinnacle of their careers. Men don't have these concerns - this is truly an issue of equity! Whether or not a woman wants to have biological children, her health, reproductive span, and equality are inextricably linked. If we are to ensure that increasing healthy longevity benefits everyone equally, we must also aim to extend female reproductive longevity.

Over the past decades, as more women have prioritized education and career, delaying childbearing has become a broad pattern among women almost everywhere in the developed world. Yet reproductive aging will impact every single female on the planet who lives to adulthood. The decline in egg quality and quantity has significant clinical consequences including infertility, miscarriages, and birth defects. Unfortunately, many women face an unpleasant surprise - that their ovaries age at over twice the rate of tissue in the rest of the body and are considered geriatric by their mid 30s - when they try to get pregnant. Girls are born with their one and only lifetime supply of eggs and when they run out menopause happens. Why can men can produce sperm throughout their lives, while women are unable to make eggs after the initial production in utero? We simply don't know the answer, and we need more basic scientific research to figure this out!

I want to CANCEL MENOPAUSE. It's not a biological imperative – humans are highly unusual as one of the few species that experience menopause. A few years ago, with the visionary support of the Bia-Echo Foundation, I founded a moonshot effort to extend female reproductive span at the Buck Institute for Research on Aging called the Global Consortium for Reproductive Longevity & Equality (GCRLE). Our goal is to extend female reproductive span - we want to figure out what leads to reproductive decline in women and develop interventions to slow or reverse it. Unlike the healthy longevity field, which has seen a decade of growth and increasing awareness, the field of reproductive longevity is unfortunately still in its earliest stages. That can change; but we will need concerted, collaborative, and ambitious efforts to accelerate our knowledge. In essence, we need to build an entire scientific research field from the ground up.

The GCRLE's mission is to facilitate & accelerate translating basic scientific discoveries from the lab into useful products and therapies to impact women's lives. To accomplish this lofty goal, we are attracting the most creative scientific minds to work in the field through funding, resources, and collaborative networks. We are cultivating relationships with other organizations and funders on a global scale to strengthen outcomes - in essence we are building an ecosystem. The Consortium is an innovation hub that supports a quickly growing knowledge base, to build a sustainable, impactful, research field. Most importantly, we are forming the connections- between fellow scientists and with non-scientists- to create the intellectual ecosystem that is necessary for accelerated innovation.

Consider a world where women are not constrained in their reproductive choices, where they are not subject to the detrimental health effects of menopause in mid-life. The social, economic, and personal empowerment resulting from that freedom would have extraordinary implications for every woman's life. The economic costs of infertility and menopause are staggering, and the menopause market is more than $14 Bn and growing. Beyond women, understanding how and why ovaries age prematurely will have direct implications for understand aging in the rest of the body. This research is imperative for every person on the planet. The GCRLE is pioneering a new movement, one that will positively impact the lives of women around the world.

This in-depth report on ovarian longevity from Longevity.Technology's market intelligence unit provides key insights for the nascent menopause market and highlights important considerations for scientists, developers, and investors. I invite you to read it and learn more about this important area of aging research.

Jennifer Garrison, PhD

Founder & Director, Global Consortium for Reproductive Longevity & Equality
Assistant Professor, Buck Institute for Research on Aging

Global Consortium for Reproductive Longevity & Equality

The Global Consortium for Reproductive Longevity & Equality is dreaming big. In 2019 the Center for Reproductive Longevity & Equality (CRLE) opened at the Buck Institute and was the first facility to focus solely on reproductive longevity and equality as it relates to aging. To strengthen and broaden its reach, the Global Consortium for Reproductive Longevity and Equality (GCRLE) is pioneering a new movement to advance the science focused on female reproductive aging. Launched in 2020 at the Buck Institute and generously funded by the Bia-Echo foundation, this international collaborative Consortium is dedicated to facilitating key scientific discoveries and accelerating translation of those insights into diagnostics, products, and therapeutics to improve women's lives.

Reproductive longevity is about far more than fertility or menopause and its accompanying mortality risk. It involves a woman's entire life experience, her career, her family, and most importantly, her health and well-being – it is about equality. This initiative, by focusing research on understanding how and why women go through reproductive decline in mid-life, has the potential to dramatically and significantly improve the health and welfare of women worldwide. Through funding, collaboration, and innovation, the GCRLE is accelerating the pace of discovery to inform the path to effective intervention. It believes 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.

Many of the same biological processes that deteriorate with age throughout the body also act in the ovaries, which age more rapidly than any other human tissue. This means that this research has implications for everyone: in addition to the overall societal benefits of increased equity in life planning, understanding the limits on reproductive capacity will provide important clues about the effects of aging in other parts of human biology. Women who go through menopause relatively late, for example, also tend to live longer, as do their male siblings. Research into women's reproductive longevity may have a profound impact on our scientific and medical knowledge far beyond the field's boundaries.

The downstream consequences are clear, but why women undergo a precipitous decline in fertility at midlife and what sets it in motion remain a mystery. Despite its profound impact on health and fertility, female reproductive aging is an understudied topic. Until we discover the causal factors that drive ovarian aging, everything we use to treat infertility and menopause will simply be a bandaid. The GRCLE's goal is to build this field from the ground up 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 and balance the inequities women face managing family, career and health decisions.

The GCRLE's mission is to build an ecosystem that encompasses every scientist interested in the field to enable the research to go further, faster, and on a larger scale. To further its mission, in 2020 the GCRLE announced the first inaugural recipients of annual GCRLE Grant Awards. The 23 recipients comprise a global group who share a vision of advancing research to better understand the underlying causes of female reproductive aging. Grantees were selected by a Scientific Advisory Council composed of leaders in the fields of Aging and Reproductive Biology and range from early career scientists to established scholars in the field. This stellar cohort of researchers are the vanguard of our mission; they have already begun laying the foundations for entirely new scientific avenues of discovery. A Bioinformatics/AI core

and a first-of-its-kind Reproductive Biology Hub facility has been built at the Buck Institute to provide support for these and all future studies requiring expertise in ovarian biology.

Some of the cutting-edge research GCRLE funded includes:

- Creating better animal models of menopause to study how it occurs in humans
- Defining a 'clock' for female reproductive decline, so that a woman can accurately know where she is along her individual reproductive span trajectory
- Generating a picture of the differences between young and aged oocytes that we can use to understand fertility decline
- Testing pharmaceuticals and diets that could help delay ovarian aging

GCRLE are implementing novel, innovative operating ideas that force interactions and networks between people who might not normally communicate or work together. That means getting scientists to share data, ideas, and projects in different ways; fostering collaborations and dialogue between industry, funders, biotech and academic scientists, and clinicians that go beyond traditional models; and galvanizing and organizing non-scientist leaders who will serve as ambassadors to highlight GCRLE's efforts to bring much needed attention to this issue. Donate to the GCRLE here to support our vision for catalyzing true progress in extending female reproductive longevity that translates into gains in the healthy aging space. Together we can offer women more hope for their reproductive future but also to empower all aspects of their well-being.

Part 1: For the scientist looking for deeper knowledge about ovarian longevity.

A deep dive into the science and pathways of ovarian longevity, how it relates to female longevity and the interventions that could be translated into products to delay ovarian aging.

What is ovarian aging?

- Ovarian aging is the natural decline in the quality and the quantity of eggs (oocytes) that eventually results in infertility and menopause.
- Quantity and quality are highly variable between individuals. “Quantity of eggs left” can be used as a biomarker for the age of the ovary.
- Quality decline is poorly understood but could be due to the accumulation of inflammation and damage in the body with age.
- The rate and age that fertility naturally decline at vary widely between women.
- Preventing and/or delaying the reduction in both quality and number of eggs is important for both female health and fertility.

Ovarian reserve – Quantity

Ovarian aging is one of the etiological factors of infertility, meaning that it is one the main contributors, as well as the driver to the onset of menopause. To assess the “age” of the ovary, it is most common to look at the number of eggs left in the “ovarian reserve”. To fully understand this, we must first understand how the ovarian reserve is established and how it becomes diminished as women age.

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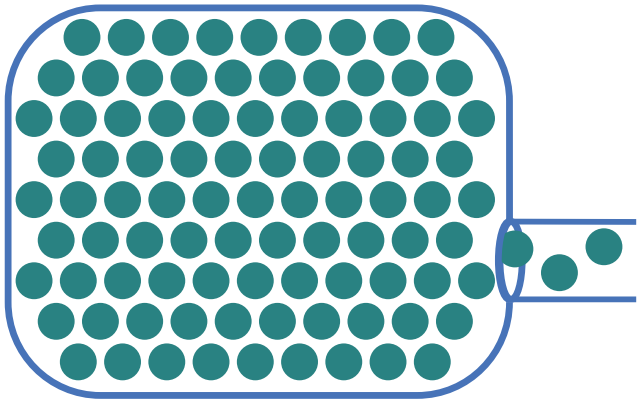
Ovarian reserve refers to the number of viable oocytes (potential ova/eggs) available at any time in a women’s lifetime. Due to the lack of germline stem cells, female ovarian reserve cannot be replenished, and the number that determines it is not straightforward as it is dependent on (1) the pre-established ovarian reserve (PreOR) and (2) the number of follicles shuttled into the dynamic ovarian reserve (DOR) during each menstrual cycle.

Side note: Before beginning to describe ovarian aging, it must be stated that recent studies have shown the sizes of the PreOR can vary vastly between individuals (more than 20-fold individual variation in follicle numbers have been reported at birth as well as puberty) and the number of follicles shuttled into the DOR is also specific to an individual (Monniaux, et al., 2014). Therefore, in the following description, we are using the range of numbers that are provided as textbook, but keep in mind that these could vary widely per individual by a factor of +/- 20x.



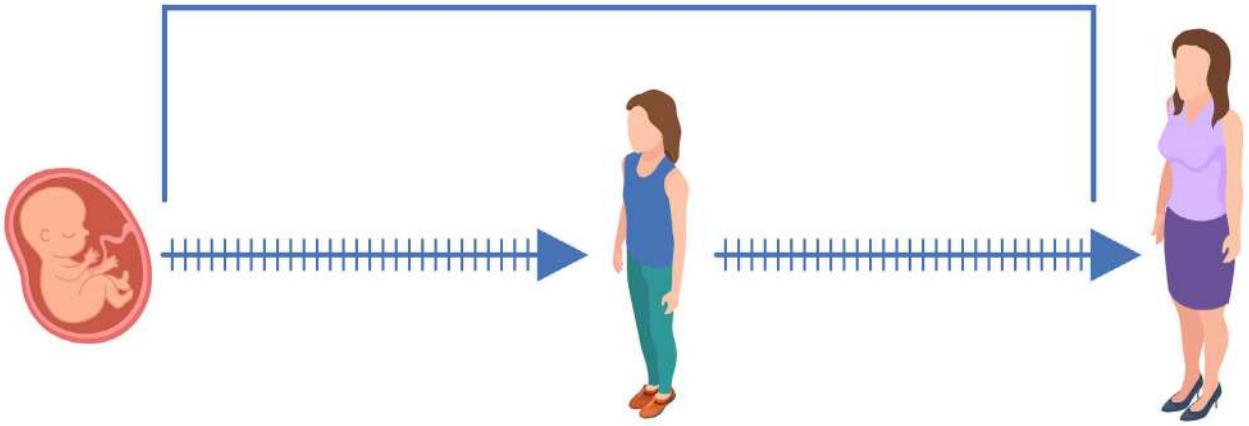
Pre- established ovarian reserve:

- 1-2 million primordial folicles
- Established in third trimester in-utero (through oogenesis)
- Paused until puberty

Figure 1. The pre-established ovarian reserve.

The PreOR is described as a pool of 1-2 million primordial follicles – oocytes surrounded by thin layers of granulosa cells – that is established in the third trimester during foetal development, in a process called oogenesis, and is left on pause, waiting for puberty (Figure 1). However, the PreOR degenerates during this hiatus, due to insufficient gonadotrophin hormone, and by the time of the first menarche (period) a female only has around 350-500,000 primordial follicles left (Figure 2). So at the start of a woman's fertility, she could already be 65-75% down on the number of eggs with which she was born.

Insufficient gonadotrophin hormones causes Atresia



PreOR established

1 - 2 million
Primordial follicles

First Menarche

300,000 - 500,000
Primordial follicles

Figure 2. The pre-established ovarian reserve.

From this point, it is a numbers game; during each menstrual cycle, a significant number of primordial follicles (thought to be around 1000) are activated to continue growing, in a process called folliculogenesis, developing into early growing follicles and, once they acquire an antral cavity, become small antral follicles (SAFs). It is these SAFs that make up the DOR (Figure 3).

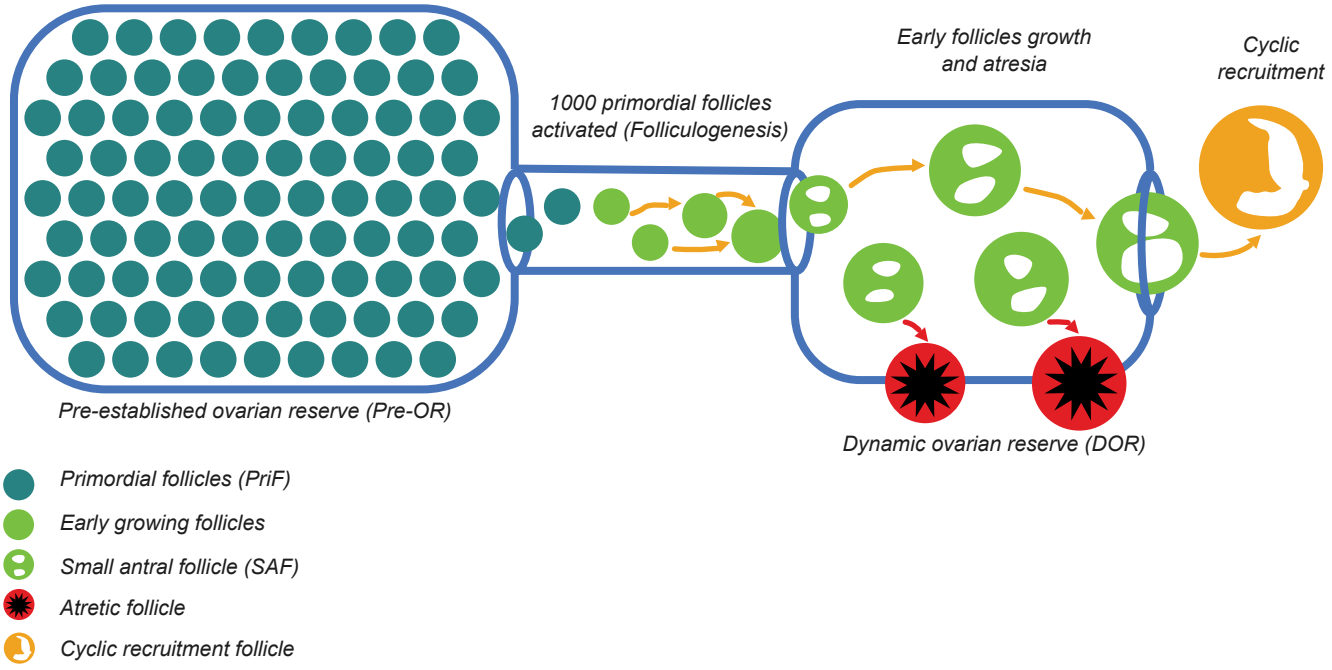


Figure 3. The Dynamic ovarian reserve (DOR) adapted from (Yang, et al., 2021).

The whittling down continues at the SAF stage, where most follicles undergo atretic degeneration (a process called atresia) and are discarded, whereas a few of them, under the influence of gonadotrophin (GTD) stimulation, reach the preovulatory stage of a Graafian follicle. The dominant Graafian follicle ovulates to release the mature oocyte for fertilisation, whereas the remaining theca and granulosa cells undergo transformation to become the corpus luteum, the mass of cells responsible to produce the hormone progesterone during early pregnancy. The number of primordial follicles to undergo the full development until ovulation is approximately 500 in a woman's lifetime (Figure 4). So ultimately, from the 1-2 million primordial follicles a woman is born with she will only produce 500 eggs that are ready for fertilisation.

Quantity and quality are highly variable between individuals. "Quantity of eggs left" can be used as a biomarker for the age of the ovary.

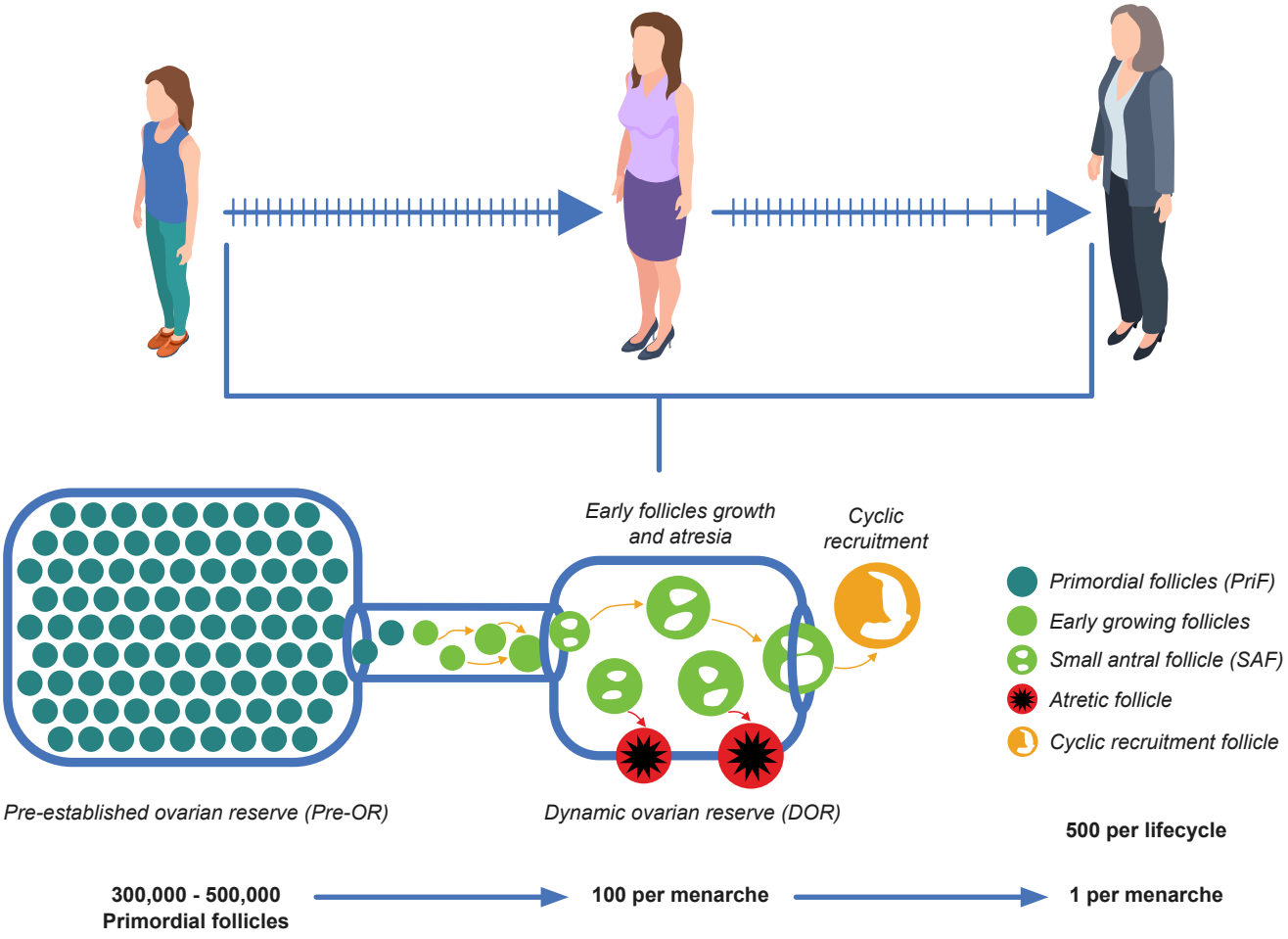


Figure 4. Each menstrual cycle results in one Graafian follicle for cyclic recruitment, resulting in 500 from a pool of 300,000-500,000 in a lifetime.

The dynamic relationship between the PreOR and the DOR

So clearly there is a functional, and dynamic, relationship between the PreOR and the DOR: the dormant primordial follicles in the PreOR are recruited into the DOR in a continuous manner, so the DOR remains relatively stable while the PreOr continues to decrease.

However, contributing to even further depletion of the ovarian reserve is the number of SAFs in the DOR that are eliminated via atresia. As the number of ovulated eggs per estrous cycle is fixed, a larger DOR pool means that more SAFs will be eliminated, and more primordial follicles will then have to be activated from PreOR to replenish the loss of DOR. Such a vicious cycle eventually leads to meaningless exhaustion of ovarian follicle reserve (Figure 5).

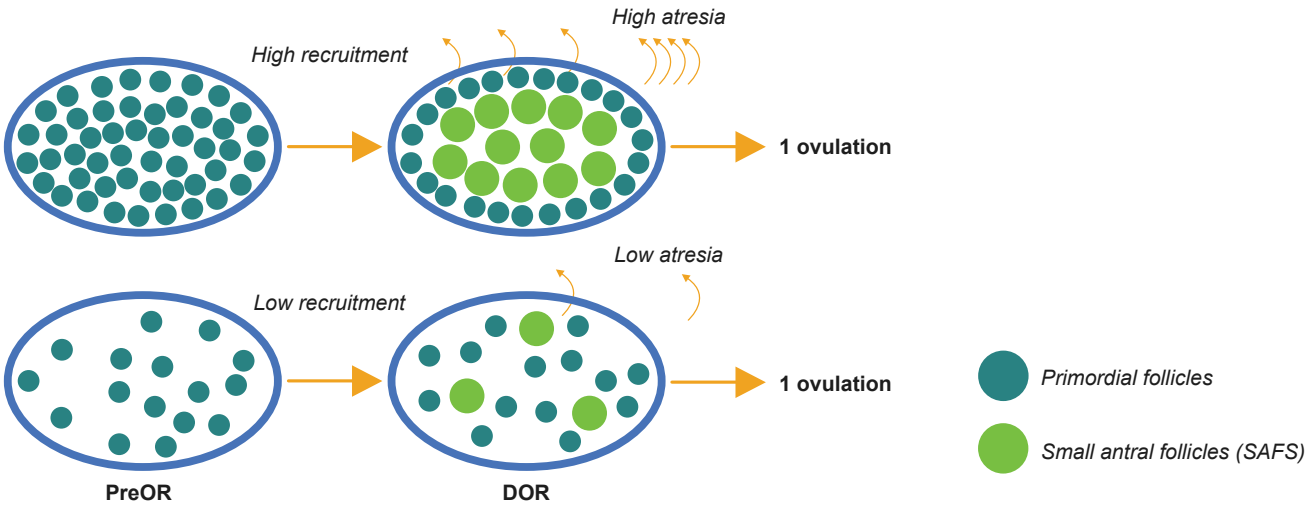


Figure 5. The relationship between the PreOR and the DOR

The knock-on effect of a diminishing PreOR is, ultimately, that there are fewer primordial follicles to recruit and thus, as we age, the pool of the dynamic ovarian reserve (SAFs) also begins to decrease. As a result, the number of SAFs available at any given time-point in a woman's life can be used as a biological marker of her ovarian age. Menopause is the final step in the process referred to as ovarian aging. The age-related decrease in follicle numbers causes the onset of cycle irregularity and the final cessation of menses.

Quality matters

Female fertility is not just about the quantity of oocytes; quality of the oocyte is critical for fertilisation and subsequent embryo development. The parallel decay in oocyte quality contributes to the gradual decline in fertility and the final occurrence of natural sterility: as women get older it becomes increasingly challenging to conceive.

Aged oocytes display chromosomal abnormalities and cellular organelle dysfunction which can increase the likelihood of spontaneous miscarriage and abnormalities in offspring (Igarashi, Takahashi, & Nagase, 2015). Therefore, quality is key, and, with age, the numerical changes detailed earlier are accompanied by changes in the quality of the follicles. However, the mechanisms by which aging impacts quality is more complicated and currently poorly understood.

Quality decline is poorly understood but could be due to the accumulation of inflammation and damage in the body with age.

One explanation is that there is an accumulation of damage in resting follicles/oocytes causing diminished quality overtime. In addition, the “limited pool theory” suggests the altered hormonal environment brought about by the quantitatively diminished DOR affects oocyte development and results in a higher incidence of abnormalities in the remaining oocytes. These two explanations are not mutually exclusive and there could be overlap. If the limited pool theory is correct, then it would suggest young woman with diminished dynamic ovarian reserve would also have a significant decrease in oocyte quality.

However, over the past decade there has been mounting evidence that the DOR does not impact chances of spontaneous conception or cause an increased risk of foetal abnormalities in naturally conceived pregnancies by women with lower ovarian reserve (Ata, Seyhan, & Seli, 2019). This would suggest that quantitative decline in ovarian reserve may not necessarily be accompanied by a qualitative decline and the accumulating damage theory of aging may be more at play for oocyte quality. Studies have shown that the level of reactive oxygen species (ROS) and inflammatory factors significantly increase in the ovary during the function decline period (Lim & Luderer, 2011). Further research into diminishing quality with age needs to be established (Ata, Seyhan, & Seli, 2019).

However, from the current research, the damage to resting follicles/oocytes with age seems the most likely explanation for reduced quality.

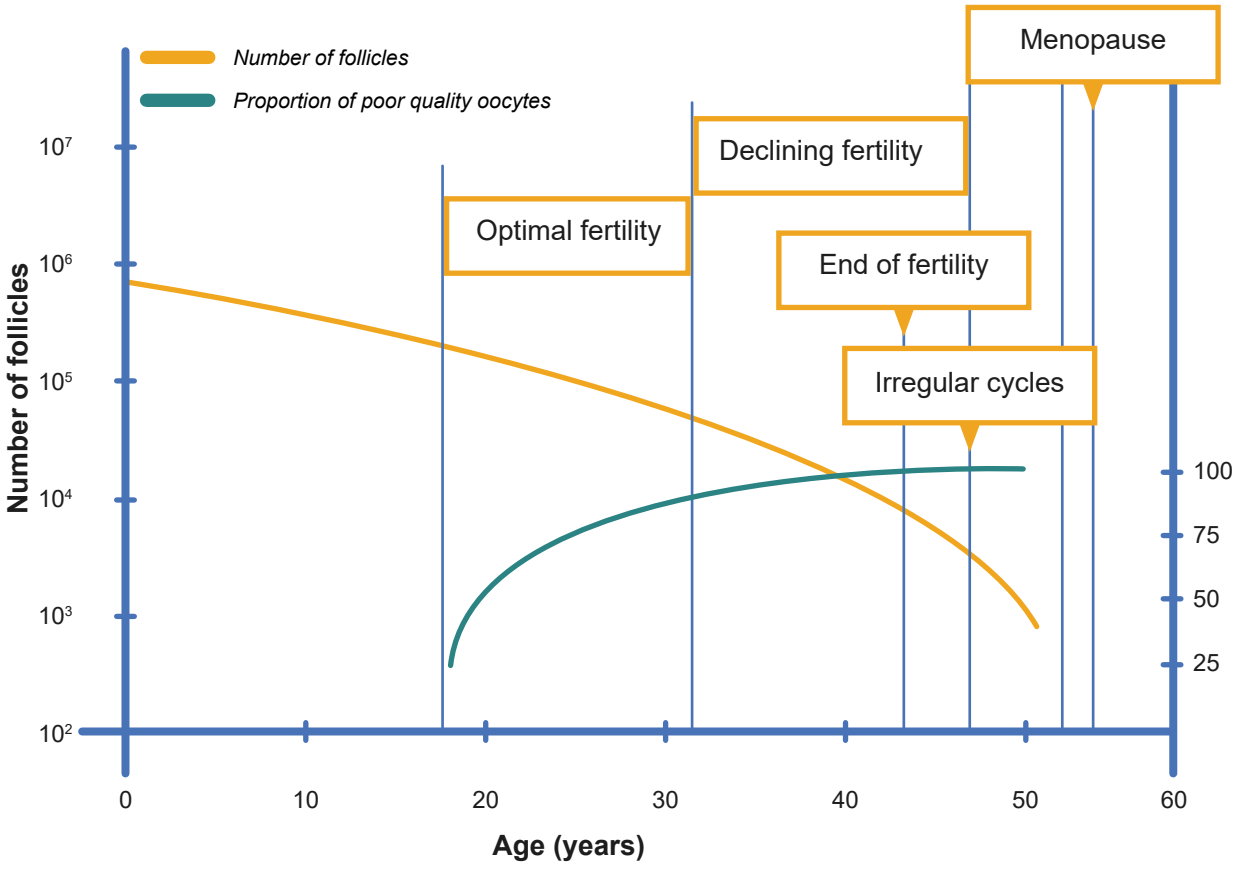


Figure 5. Proportion of poor-quality oocytes increases with age

Regulation of quality and quantity

The rate and age that fertility naturally decline varies widely between women. The size of both reserves appears to be highly variable between individuals of similar age, but the equilibrium size of the dynamic reserve in adults seems to be specific to each individual.

Regulation of quantity

The dynamics of both follicular reserves appears to result from the fine tuning of regulations involving two main pathways, (1) the PI3K-AKT and (2) the BMP/AMH/SMAD pathways. Mutations in genes encoding the ligands, receptors or signalling effectors of these pathways can accelerate or modulate the exhaustion rate of the ovarian reserves, causing premature ovarian insufficiency (POI) or increase in reproductive longevity, respectively (Monniaux, et al., 2014).

Increased activation of primordial follicles can be driven by:

- Augmented PI3K and mTOR activity (activated by phosphorylation it causes follicular activation and growth)
- FMR1 premutation
- SIRT1 and SIRT3 deficiencies (probably due to loss of mTOR inhibition)

Suppression of follicular activation can be driven by:

- FOXO3a, TSC1 and TSC2 activation (deactivated by phosphorylation)
- Anti-Müllerian hormone (AMH) prevents PreOR depletion by reducing phosphorylation and maintaining activation of FOXO3a, a downstream component of the PI3K/PTEN/AKT pathway that helps to maintain the dormancy of primordial follicles
- Potentially through hydrogen sulfide (H_2S) production and signalling (more research required)
- Elevated activity of SIRT1

It is interesting to note that many of these terms will already be familiar to those within the field of longevity science.

Regulation of quality

The mature mammalian oocyte is highly enriched in mitochondria and contains a larger mitochondrial DNA (mtDNA) copy number than any other cell type. Furthermore, mtDNA copy number is increased dramatically during oocyte maturation, going from approximately 100 in primordial follicles to over 100,000 in mature oocytes. However, with age mtDNA can be compromised through reactive oxygen species (ROS) or by induced damage or improper mtDNA replication and repair. This starts a loop where compromised cellular energy production then further propagates ROS production. It is likely that the accumulation of mtDNA mutations through ROS-induced mtDNA damage or impaired mtDNA repair is part of a complex series of mechanisms that contribute to ovarian longevity (Llarena & Christopher, 2020).

Evidence for mitochondria and ROS influence on quality:

- Increased levels of ROS in human follicular fluid can predict impaired embryo development and embryo arrest in in vitro fertilisation cycles
- Homozygous knock-in mice that cannot proofread mtDNA accumulate mtDNA mutations 2-5 times more than wild-type (WT). These mice have reduced fertility in comparison to WT – this effect is so profound that knockin mice cannot become pregnant after 20 weeks
- In humans, females with the same proof-reading deficiency undergo menopause before the age of 35

There also seems to be a role for sirtuins to regulate quality of oocytes (Llarena & Christopher, 2020). The following findings could show that SIRTS are required for meiotic spindle assembly, oocyte development and chromosome segregating during meiosis:

- Aging-related decreases in ovarian SIRT1 expression negatively influence chromatic compaction and can impair oocyte development.
- SIRT2 knockdown can impair spindle organisation and lead to chromosome misalignment,
- SIRT3 over-expression reduces spindle defects and chromosome misalignment in mouse oocytes.

Preventing and/or delaying the reduction in both quality and number of eggs is important for both female health and fertility.

Why does ovarian longevity matter - longer living ovaries, longer healthier life?

"Out of 34 currently living supercentenarians, 33 are women"

- The ovary is the earliest aging organ in females and is considered the "pacemaker" of female body aging, its dysfunction drives the aging of multiple other organs in the body
- Lifespan has increased for women worldwide, but this has not been accompanied by an equivalent increase in healthspan
- Ovarian state, and its direct link to estrogen levels, can influence the health of all phases of life and could be a main determinant of female lifespan

Ovarian longevity and healthspan

The withdrawal of estrogen due to ovarian failure (menopause) has systemic effects on the body, including increased risk of cardiovascular disease, skeletal fragility, genitourinary and vasomotor (constriction of blood vessel) symptoms.

This phenomenon is more pertinent in the modern world than ever before. Due to education, sanitation, diet and health advances, women's life expectancy has been prolonged as much as 30 years in recent decades; but the onset of menopause has only been pushed-out by 3-4 years. This means that a woman may spend a large period of her later life in poor health – a recent piloted objective-wide NHS study of data concluded that women may live for 34% of her life in poor health in comparison to 26% for males.

So, what is the difference between the sexes? Decline in sex steroid hormones (estrogen and testosterone) accompanies several age-associated pathologies which may influence human healthspan in both sexes. However, a key difference is that the rate of decline differs greatly between the sexes, and this could be due to the relatively early menopause, in terms of lifespan, experienced in females.

> The ovary is the earliest aging organ in females and is considered the "pacemaker" of female body aging its dysfunction drives the aging of multiple other organs in the body.

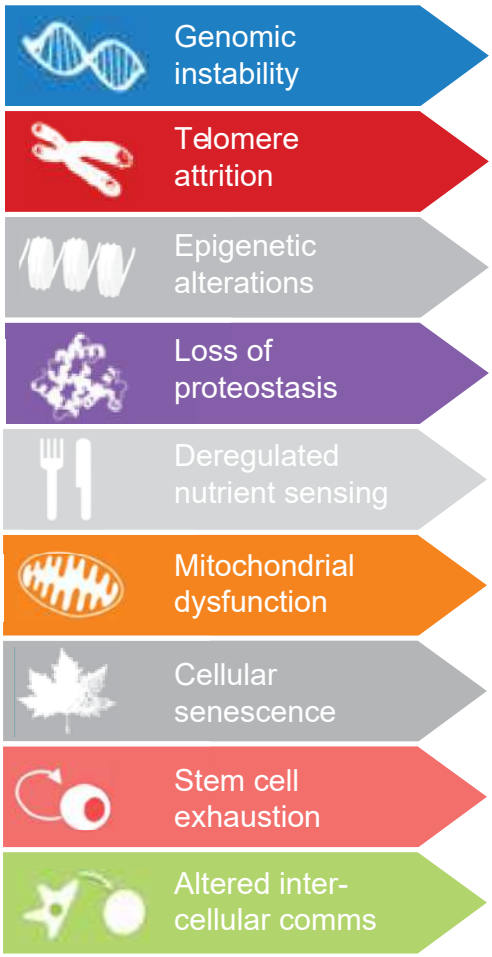
The major consequences of menopause are thought to be related primarily to estrogen deficiency:

- Estrogen has important metabolic effects in most major organ systems
- It normalises the vaginal and urethral environment, positively influences arterial blood flow, and thus could prevent plaque build-up, has a positive impact on blood serum lipid profile, reduces rates of diabetes, helps to prevent bone loss (and may restore lost bone) and maintains neuronal health in the central nervous system and spine by promoting growth and mitigating inflammation (Langer, Hodis, Lobo, & Allison, 2021)
- Consistently, the risks of hypertension and developing Alzheimer's disease, two major causes of death in females, are remarkably inversely correlated with estrogen production

Important actions of estrogens are mediated by estrogen receptors which are in several tissues including the uterus, bone, breast, white adipose tissue, liver, and muscle. During the first year of menopause, women lose on average 80% per year of their estrogens. Delaying ovarian decline could potentially delay the onset of disease that is associated with a decline in estrogen production. For example, cardioprotective benefits, cognitive behaviour, and immune and renal functions can be positively restored by re-establishment of active ovarian function in aged female mice (Peterson, Parkinson, & Mason, 2016). Futher supporting this hypothesis is estrogen deprivation in healthy women younger than 50 years undergoing bilateral oophorectomy (removal of both ovaries and fallopian tubes) has been shown to accelerate the development of diseases related to aging, including coronary artery disease, cardiac arrhythmias, stroke, dementia and osteoporosis.

> Ovarian state, and its direct link to estrogen levels, can influence the health of all phases of life and could be a main determinant of female lifespan.

Interestingly, a re-review in 2018 (Sehll & Ganz, 2018) related estrogen to the hallmarks of aging, further shining a light on how menopause and the related decline of estrogen could drive the aging of other organs (Figure 6).



Rodent cancer models demonstrate that estrogen signaling enhances genomic instability, promotes cell cycle entry, induces micronuclei, and increases DNA damagein cancer cells.

Limiting estrogen could accelerate aging via telomere shortening as sex hormones act on the TERT gene increasing telomerase activity.

Estrogen might mediate this stress response that occurs when unfolded proteins accumulate in the endoplasmic reticulum, suggesting that protein destabilization may mediate the effects of estrogen blockade on accelerated aging.

Estrogens exert direct and indirect effects on mitochondrial function in a variety of tissues. Estrogens have cell-specific effects on many physiologic endpoints, including regulation of mitochondrial biogenesis and activity.

Multiple animal studies have shown a role of estrogen in stimulating stem cell division, in hematopoietic stem cells, embroyonal stem cells, and mesenchymal stem cells.

Animal and cellulat studies have demonstrated a role for estrogen signaling in promoting intracellular communication, suggesting that reducing estrogen might lead to dysregulation of this communication and contribute to accelerated aging.

Figure 6. The connection of estrogen to the other hallmarks of aging, suggesting ways that menopause could contribute to the aging of multiple other organs - reviewed in depth in (Sehll & Ganz, 2018).

Ovarian longevity and lifespan

Although aging is thought to be standard, there is mounting evidence that suggests there are differences in aging and longevity phenotypes between the sexes. In over 54 countries, analysis has revealed that female life expectancy is above that of males. Out of 34 currently living supercentenarians (>110 years of age), 33 are women (Adams, 2019). For the NIA Interventions Testing Program (ITP), female individuals consistently outlive males at 3 independent sites, suggesting human female advantage may be repeated in mice in controlled conditions.

Lifespan has increased for women worldwide, but this has not been accompanied by an equivalent increase in healthspan.

Despite research efforts in this field for over a century, the relationship between female fertility and longevity remains a mystery. There are two longevity theories that would suggest female fertility is inversely related to lifespan due to metabolic trade-off between reproduction and longevity (Qiao, et al., 2021):

1. The disposable soma theory suggests that aging is a dynamic process with two aspects: random damage and repair of tissue in the process of life. The human body is affected by a variety of external and internal damages; aging is accompanied by accumulated damage and continuous repair. When the repair cannot make up for the damage due to the energy shortage caused by growth and reproduction, the body will eventually die.

2. The antagonistic pleiotropy theory suggests that some genes have multple functions, some of which are beneficial to growth and reproduction and some of which are not, some of which are beneficial to growth and reproduction and some of which are not. Evolutionary selection of mutated genes helps people grow and reproduce when they are young, but these genes lead people to age with time because the main function has been achieved, i.e., passing genetic information on to the next generation.

In the literature, the research is conflicting. For example, a study that looked at the relationship between longevity and reproductive stress, using a historical data set from the British aristocracy, found that those who died first tended to have their first child at a younger age and those who died at oldest age had their first child at an older age. Further, when only including women who had reached menopause (>60), female longevity was negatively correlated with number of children given birth to and positively correlated with age of first childbirth (Figure 7). This research suggests human life histories involve a trade-off between longevity and reproduction (Westendorp & Kirkwood, 1998). More current studies have mirrored these findings, showing a negative relationship between female fertility and lifespan due to the high energy expenditure in female reproduction (Samuli, Virpi, & Jukka, 2005) (Hurt, Ronsmans, & Thomas, 2006) (Gagnon, 2016). However, other studies have found no significant relationship between female fertility and lifespan (16, 17).

A recent cross-sectional study investigated the relationship further by looking at female fertility and longevity in China's oldest populations. By comparing centenarian women with women aged 80-99 years, it was found that those who were over the age of 100 had significantly lower number of children and a higher initial childbearing age and last childbearing age. Furthermore, blood serum analysis looked at the difference in estrogen and testosterone in centenarians versus women aged 80-99 years. Multivariate logistic regression showed that testosterone levels were positively associated, and estrogen levels were negatively associated, with women 80-99 years when centenarian women were considered as reference, suggesting estrogen levels are positively associated, and testosterone negatively associated, with longevity. This study again emphasised that less and late childbearing might be a significant factor of longevity, and successful aging might be promoted by reducing and delaying female childbearing (Qiao, et al., 2021). However, this is only one study and there has been other studies that have shown opposite results. The relationship between the number of children given birth to, age of mother at first childbirth, and reproductive span/fertility is complex.

Longevity alternatives that should be garnering attention

After extensive research, it seems there are a range of unexplored therapeutic possibilities for targeting ovarian longevity that are already being investigated by those targeting longevity for tackling aging in general. Furthermore, future methods that are being developed for longevity research could also be applied.

Supplementation with already available supplements/repurposed drugs

For example, the free radical theory of aging suggests that when our bodies age a lot of damage can be attributed to the increasing level of reactive oxygen species (ROS) and the decrease in oxidative defence system related enzymes. The levels of oxidative stress caused by elevated levels of intracellular ROS is one of the most significant contributors to cellular senescence and aging in mammals. People supplementing for longevity have been using antioxidant supplements such as curcumin, co-enzyme Q10 and N-acetyl-L-cysteine (NAC) to help alleviate oxidative stress within their bodies. It could be that oxidative stress is a leading driver in the ovarian aging process as it is thought to promote the development of other aging-related aetiologies, such as telomere shortening, mitochondrial dysfunction, apoptosis, and inflammation.

To date, several studies have shown that the accumulation of ROS in the ovaries deteriorates oocyte quality, induces granulosa cell (GC) apoptosis, and accelerates degeneration of the corpus luteum. The level of intra-ovarian ROS has been confirmed to be positively correlated with female age, which also makes the female germline particularly vulnerable to the cumulative effects of chronic oxidative stress (Yang, et al., 2021). Therefore, alleviating oxidative stress in the ovaries has the potential to be an important entry point for maintaining ovarian longevity.

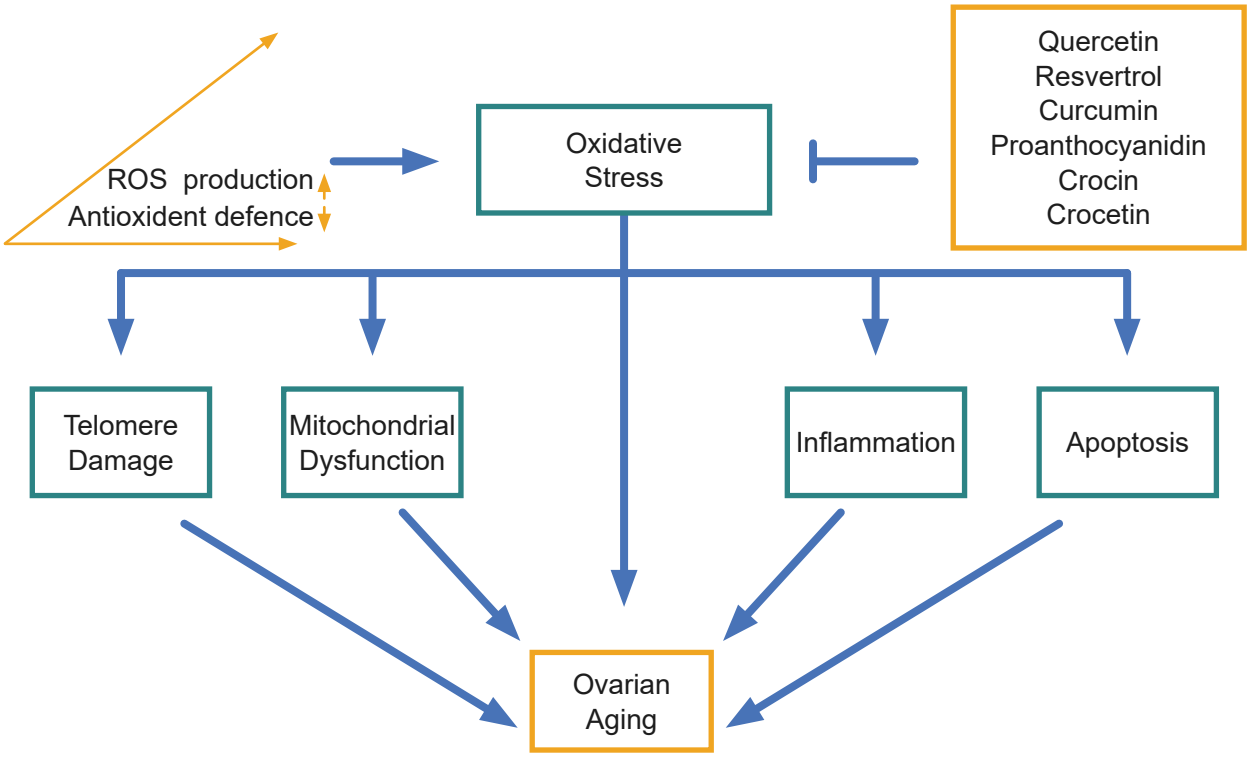


Figure 11. Oxidative stress is a driver for other etiologies of ovarian aging and could be prevented by supplementation with antioxidants (Yang, et al., 2021).

The possibilities of Melatonin

One antioxidant in particular, melatonin (MLT), seems to be of promise in both aging and ovarian longevity. MLT is a natural hormone that is produced by the pineal gland (located in your brain) and helps control the sleep cycle. It is also a direct antioxidant and a modulator of systems protecting against oxidative stress. It has been shown that MLT levels decline with age and as such some view MLT as the “fountain of youth” (Bowles, 2017). Furthermore, studies have demonstrated that less exposure to sunlight can delay reproductive aging, which is thought to be related to MLT. There is a lot of data emerging showing the possibilities of MLT in preventing ovarian aging (35 science publications as of 2021). Even though the mechanism underlying the anti-aging effect of MLT in the human ovary still needs to be fully explained, the administration of MLT, lacking serious side-effects and providing additional benefits to patients treated with it, is clearly indicated in women with age-related ovarian decay (Tesarik, Galán-Lázaro, & M, 2021).

Mitochondrial rejuvenation

Another longevity intervention that is being studied is mitochondrial rejuvenation – boosting mitochondrial health has been largely studied in longevity research and mitochondrial dysfunction is one of the nine hallmarks of aging. As stated in section 3, oocyte quality can be impacted by mitochondrial quality as there are large amounts of mitochondria in mature oocytes. Mitochondria are the energy (ATP) producers of the cell, but as we age ATP production declines. One of the reasons for this is the decline in the ATP cofactor NAD+, that mitochondria use to generate ATP. In the context of female fertility, after age 30, NAD+ levels were found to be an important factor contributing to the success of in vitro fertilisation (IVF). Additionally, SIRT1, a NAD+ precursor molecule, is critical to ovarian function and fertility and without it animals are sterile. Scientists from Australia and Harvard demonstrated that NAD+ supplementation can be used as an effective and non-invasive strategy to restore and maintain female fertility during aging. Therefore, it may be of consequence to supplement with NAD+ boosters such as NR, NMN and nicotinamide, although further research needs to be established in this field.

Caloric restriction and its mimetics

Caloric restriction (CR) is a dietary intervention that is generally considered to prolong the maximum lifespan and delay age-related alternations in a range of species. CR restricts the energy intake and induces undernutrition without malnutrition – this is called caloric restriction with optimal nutrition (CRON). Recently it was suggested that the CR longevity effect could be due to energy resource being relocated from reproduction to somatic maintenance. Experiments in mice have shown that adult-onset CR can delay ovarian aging through the maintenance of the PreOR and good egg quality.

However, a recent review has shown that CR can have both positive and negative impact on female reproduction and that there are differences between rodents and humans. For example, CR in rodents simultaneously increases reproductive capacity and prolongs fertility lifespan. In contrast, CR advances menopause onset in women. Furthermore, CR can be hard to implement as a strategy in everyday life. Therefore, instead of implementing CR in everyday life, CR mimetics such as resveratrol, rapamycin and metformin, that act on similar pathways, could be an alternative. Resveratrol and metformin are thought to delay the ovarian aging process by inducing the expression of SIRT1 and reducing oxidative damage (Qin,

et al., 2019). Rapamycin targets mTOR and may suppress activation of the PreOR – however, suppressing mTOR may hinder oocyte meiotic maturation which could limit the use of mTOR-suppressing drugs for fertility-related diseases (Yu, 2019) (Figure 12).

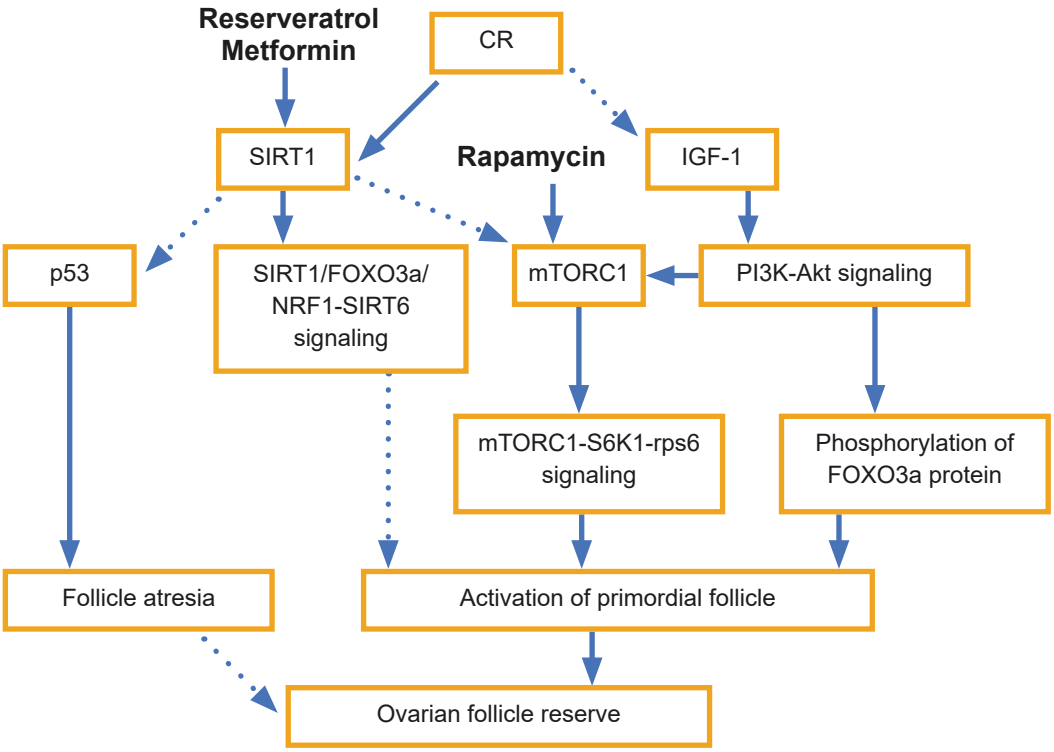


Figure 12. Metformin, resveratrol and rapamycin could act as caloric restriction mimetics by targeting the same pathways.

‘Future longevity research that could be applied in the future’

Platelet-rich plasma

There are also new methods in longevity that are still in the experimental phase that could also be applied to ovarian longevity. Platelet-rich plasma (PRP), a plasma fraction of peripheral blood with a high concentration of platelets, has been implemented in regenerative medicine in the last decade. There are various factors in PRP that are important for follicular growth and maturation and initial reports have demonstrated intraovarian injection of PRP improved hormonal profile and increased the number of retrieved oocytes in patients with diminished ovarian reserve. There are several other studies that have reported the intraovarian injection of PRP has resulted in healthy live births. However, there needs to be further evaluation for this novel approach (Vo, Tanaka, & Kawamura, 2021).

Stem cell treatments

Stem cell treatment could be another method to be investigated and evaluated for its therapeutic effects in animal models of degenerative disease that could be applied too. There are few reports to date that look at the effects of stem cells in reproductive diseases however it is thought that stem cell transplantation improves ovarian function in premature ovarian failure models as their exosomes have positive effects in increasing the expression of related hormone, preventing granulosa cell apoptosis, and regulating ovarian hormones. Further studies are required to evaluate their therapeutic mechanism of action and to ensure legal regulations with safety (NA & Kim, 2020).

Targeting molecules

Molecular targets could also be used in the treatment of ovarian aging – for example, bioinformatic analysis identified differentially expressed genes when comparing ovarian expression data from young and old mice. The biological functions of these genes were primarily in the immune response regulation, cell-cell adhesion, and phagosome pathways. Specific antibodies proteins encoded by the genes were more highly expressed in the ovaries of old mice than young mice. These genes could be targeted in therapies however, the analysis and verification were performed in mice models (Ma, et al., 2020).

Very recently, a new study, published in nature, scanned the genes of around 200,000 women near the age of menopause and discovered 290 genetic variants that could help predict and prevent early menopause and infertility. Many of the genetic variants identified were involved in processes that respond to DNA damage. Using the identified variants, the authors produced a risk score to see if they could predict which woman who have premature ovarian insufficiency – although a weak predictor, the risk score identified women who started menopause by 40 better than smoking status.

The two DNA-repair genes with the strongest association to menopause timing was CHEK1 and CHEK2. Women who lacked a CHEK2 protein had a delayed menopause, around 3-3.5 years after those with a normal working protein. In mice verification studies, females without the CHEK2 gene have more eggs than normal mice when older, and those with an extra copy of CHEK1 seemed to have more eggs in the PreOR after birth. Targeting DNA-repair genes could have unwanted consequences, however, the study is the first that could lead to genetic therapeutics to extend fertility and delay menopause in women. In the short-term, these findings could allow women to make more informed decisions about when they will reach menopause, and depending on the outcome, avoid costly IVF treatments (Ruth, et al., 2021).

Table of supplements and their evidence for efficacy for ovarian aging in pre-clinical models

Intervention	Dose/ concentration	Age of intiation	Organism/ cell type	Outcome	References
Vitamin C	N/A	N/A	NMRI mice	Total volume of ovary, coretx, medulla and corpus luteum were significantly increased in vitamin C group in comaprison to the controls. Vitain C could compensate undesirable efects of ovarian aging in mouse model.	Abdollahifar MA, Azad N, Sajadi E, Shams Mofarahe Z, Zare F, Moradi A, Rezaee F, Gholamin M, Abdi S. Vitamin C restores ovarian follicular reservation in a mouse model of aging. Anat Cell Biol. 2019 Jun;52(2):196-203. doi: 10.5115/acb.2019.52.2.196. Epub 2019 Jun 30. PMID: 31338237; PMCID: PMC6624328.
Vitamin E	100mg/kg/day	3-4 months old	NMRI mice	D-gal impaired the estrous cycle, also degenerative changes occur in the ovarian follicles and damage to the uterus and ovarian tissue occurs. In D-gal group, the level of sex hormones ($p = 0.03$) and the total antioxidant capacity ($p = 0.002$) decreased, while the level of malondialdehyde and gonadotropins increased ($p = 0.03$). Myricertin at lower doses and vitamin E ameliorated the D-gal effects. Myricertin performed better than vitamin E.	Omidi M, Ahangarpour A, Ali Mard S, Khorsandi L. The effects of myricitrin and vitamin E against reproductive changes induced by D-galactose as an aging model in female mice: An experimental study. Int J Reprod Biomed. 2019 Dec 26;17(11):789-798. doi: 10.18502/ijrm.v17i10.5486. PMID: 31911961; PMCID: PMC6906854.
Myricertin	5, 10 and 20mg/ kg/day	3-4 months old	NMRI mice	D-gal impaired the estrous cycle, also degenerative changes occur in the ovarian follicles and damage to the uterus and ovarian tissue occurs. In D-gal group, the level of sex hormones ($p = 0.03$) and the total antioxidant capacity ($p = 0.002$) decreased, while the level of malondialdehyde and gonadotropins increased ($p = 0.03$). Myricitrin at lower doses and vitamin E ameliorated the D-gal effects.	Omidi M, Ahangarpour A, Ali Mard S, Khorsandi L. The effects of myricitrin and vitamin E against reproductive changes induced by D-galactose as an aging model in female mice: An experimental study. Int J Reprod Biomed. 2019 Dec 26;17(11):789-798. doi: 10.18502/ijrm.v17i10.5486. PMID: 31911961; PMCID: PMC6906854.
N-acetyl-L-cysteine (NAC)	0.1mM for a year	1-1.5 months old	Female Kunming mice	Mice treated with a long-term low concentration (0.1 mM) of NAC had increased litter sizes at the ages of 7-10 months compared with age-matched controls without NAC treatment. NAC also increased the quality of the oocytes from these older mice. Moreover, the expression of sirtuins was increased, telomerase activity was higher and telomere length was longer in the ovaries of mice treated with NAC compared with those of the control group.	Liu J, Liu M, Ye X, Liu K, Huang J, Wang L, Ji G, Liu N, Tang X, Baltz JM, Keefe DL, Liu L. Delay in oocyte aging in mice by the antioxidant N-acetyl-L-cysteine (NAC). Hum Reprod. 2012 May;27(5):1411-20. doi: 10.1093/humrep/des019. Epub 2012 Feb 21. PMID: 22357770.

Intervention	Dose/ concentration	Age of intiation	Organism/ cell type	Outcome	References
Curcumin	long term treatement with 100mg/kg	N/A	Single oocytes from primordial and primary follicles	Long-term treatment with 100 mg/kg curcumin improved the ovarian reserve indicators of AMH, FSH, and estradiol in aging mice. Mechanistic studies show that curcumin can affect the translocation of FOXO3, thereby inhibiting the PTEN-AKT-FOXO3a pathway and protecting primordial follicles from overactivation. These results suggest that curcumin is a potential drug for the treatment of POI patients and for fertility preservation.	Lv Y, Cao RC, Liu HB, Su XW, Lu G, Ma JL, Chan WY. Single-Oocyte Gene Expression Suggests That Curcumin Can Protect the Ovarian Reserve by Regulating the PTEN-AKT-FOXO3a Pathway. Int J Mol Sci. 2021 Jun 18;22(12):6570. doi: 10.3390/ijms22126570. PMID: 34207376; PMCID: PMC8235657.
Nictoinamide Riboside	400mg/kg/day	8 months	C57/BL6 mice	Ovarian NAD+ levels decrease with aging whereas supplementing nicotinamide riboside increased ovarian NAD+ levels in mice. NR supplementation increased ovulatory potential, oocyte quantity and quality, and increased live birth rate in aging mice. NR supplementation improved ovarian mitochondrial functions.	Yang Q, Cong L, Wang Y, Luo X, Li H, Wang H, Zhu J, Dai S, Jin H, Yao G, Shi S, Hsueh AJ, Sun Y. Increasing ovarian NAD+ levels improve mitochondrial functions and reverse ovarian aging. Free Radic Biol Med. 2020 Aug 20;156:1-10. doi: 10.1016/j.freeradbiomed.2020.05.003. Epub 2020 May 31. Erratum in: Free Radic Biol Med. 2021 Apr 23;: PMID: 32492457.
Co-enzyme Q10	22mg/kg three times a week	9 months		Diminished expression of the enzymes responsible for CoQ production, Pdss2 and Coq6, was observed in oocytes of older females in both mouse and human. The age-related decline in oocyte quality and quantity could be reversed by the administration of CoQ10. Ovarian reserve in the oocyte-specific Pdss2-deficient animals was diminished, leading to premature ovarian failure which could be prevented by maternal dietary administration of CoQ10.	Ben-Meir, A., Burstein, E., Borrego-Alvarez, A., Chong, J., Wong, E., Yavorska, T., Naranian, T., Chi, M., Wang, Y., Bentov, Y., Alexis, J., Meriano, J., Sung, H. K., Gasser, D. L., Moley, K. H., Hekimi, S., Casper, R. F., & Jurisicova, A. (2015). Coenzyme Q10 restores oocyte mitochondrial function and fertility during reproductive aging. Aging cell, 14(5), 887–895. https://doi.org/10.1111/acel.12368.
Catalpol	5mg/kg/day	14 months	Sprague Dawley (SD) Rats	Catalpol works on the sex organs by nourishing ovarian tissues and improving both the quality and quantity of follicles, thus leading to rebalanced E2 and P4 levels in aged rats so that catalpol has a direct in vivo antiaging effect on the rat ovarian system.	Min Wei, Ye Lu, Daniel Liu, Wenwen Ru, Ovarian Failure-Resistant Effects of Catalpol in Aged Female Rats, Biological and Pharmaceutical Bulletin, 2014, Volume 37, Issue 9, Pages 1444-1449.

Intervention	Dose/ concentration	Age of intiation	Organism/ cell type	Outcome	References
Genistein	N/A	12-15 months	SD Rats	Results indicated that genistein and resveratrol can increase the ovarian follicular reserve and prolong the ovarian lifespan in rats, and their positive effects may be not only due to their intervention in the transition from primordial to primary follicle, but also due to the inhibiting effect on follicular atresia.	Chen ZG, Luo LL, Xu JJ, Zhuang XL, Kong XX, Fu YC. Effects of plant polyphenols on ovarian follicular reserve in aging rats. Biochem Cell Biol. 2010 Aug;88(4):737-45. doi: 10.1139/O10-012. PMID: 20651847.
Mogroside V	100mM	N/A	Cumulus-oocyte complexes	Supplementation with MV protected oocytes from the LPS-mediated reduction in the meiotic maturation rate and the subsequent blastocyst formation rate. MV alleviated the abnormalities in spindle formation and chromosome alignment, decrease in α-tubulin acetylation levels, the disruption of actin polymerization, and the reductions in mitochondrial contents and lipid droplet contents caused by LPS exposure.	Yan K, Cui K, Nie J, Zhang H, Sui L, Zhang H, Yang X, Xu CL, Liang X. Mogroside V Protects Porcine Oocytes From Lipopolysaccharide-Induced Meiotic Defects. Front Cell Dev Biol. 2021 Mar 2;9:639691. doi: 10.3389/fcell.2021.639691. PMID: 33763421; PMCID: PMC7982822.
Proanthocyandin	5 μg/mL for 72 h	N/A	D-gal induced cultured ovarian tissue	GSPE could maintain the homeostasis between cell proliferation and apoptosis in the D-gal-induced and natural aging ovaries, as well as alleviate D-gal-induced nucleus chromatin condensation in the ovarian granulosa cells. In conclusion, GSPE treatment can effectively prevent the ovarian aging process in hens by reducing oxidative stress.	Liu X, Lin X, Mi Y, Li J, Zhang C. Grape Seed Proanthocyanidin Extract Prevents Ovarian Aging by Inhibiting Oxidative Stress in the Hens. Oxid Med Cell Longev. 2018 Jan 9;2018:9390810. doi: 10.1155/2018/9390810. PMID: 29541349; PMCID: PMC5818927.
Quercetin	Three doses: 12.5mg/kg 25mg/kg 50mg/ kg for 90 days	12 months	Menopausal SD rats	Although no significant changes were detected in the serum levels of T-AOC, SOD, GSH, GSH-PX, and GST between the quercetin and control groups, the mRNA and protein expression levels of the oxidative stress-related genes SOD-1, CAT and GSS in menopausal rat ovaries were increased by low-dose quercetin. Quercetin increased the antioxidant capacity of the ovary by upregulating the expression of some oxidative stress-related genes both in vivo and in vitro.	Wang, J., Qian, X., Gao, Q., Lv, C., Xu, J., Jin, H., & Zhu, H. (2018). Quercetin increases the antioxidant capacity of the ovary in menopausal rats and in ovarian granulosa cell culture in vitro. Journal of ovarian research, 11(1), 51. https://doi.org/10.1186/s13048-018-0421-0

Intervention	Dose/ concentration	Age of intiation	Organism/ cell type	Outcome	References
Fructus corni	1.11g/kg daily for 24 days	16 months	IRC Mice	Aging mice had restored number of growing follicles and corpus luteum in ovary after PFC treatment. PFC restored estradiol and progesterone levels but reduced LH and FSH levels. PFC regulated ovarian function-associated hormone levels in aging mice.	Wang, Y., Wu, J. Z., Li, Y., & Qi, X. (2019). Polysaccharides of Fructus corni Improve Ovarian Function in Mice with Aging-Associated Perimenopause Symptoms. Evidence-based complementary and alternative medicine : eCAM, 2019, 2089586. https://doi.org/10.1155/2019/2089586
Melatonin	15 mg kg−1	11 months	KM-strain mice	injections of MLT to mice during the follicle activation phase can reduce the number of activated follicles by inhibiting the PI3K-AKT-FOXO3 pathway; during the early follicle growth phase, MLT administration suppressed follicle growth and atresia, and multiple pathways involved in folliculogenesis, including PI3K-AKT, were suppressed; MLT deficiency in mice increased follicle activation and atresia, and eventually accelerated age-related fertility decline.	Yang, C., Liu, Q., Chen, Y., Wang, X., Ran, Z., Fang, F., Xiong, J., Liu, G., Li, X., Yang, L., & He, C. (2021). Melatonin delays ovarian aging in mice by slowing down the exhaustion of ovarian reserve. Communications biology, 4(1), 534. https://doi.org/10.1038/s42003-021-02042-z

Part 2: For the investor looking to ovarian longevity as an opportunity.

Understanding the growing women's health market:

The alternatives to tackling ovarian longevity and why tackling ovarian longevity covers three markets

Why fertility is the future

- For many women, having children is still a key priority, but as career opportunities and choices have improved for women, particularly in the developed world, more are choosing to wait longer before having children
- Although women are living longer, the average age of menopause has not increased to the same extent. The window for childbirth is therefore shrinking proportionally to lifespan.
- Lower fertility rates also mean reduced average family sizes and therefore, populations in many countries are declining
- The continuation of this trend will heap further pressure on shrinking younger workforces to support the inevitable growing tsunami of retirees as lifespan for men and women increases
- The pool of women looking to extend their fertility is increasing and will produce a large target market
- Traditionally the female fertility industry has been dominated by large clinics offering similar treatments at similar price points. There are a number of bottlenecks in fertility services including access, cost of treatment and lack of digitisation and automation within the most basic procedures. Lengthy, expensive, and sometimes distressingly ineffective experiences are the norm
- There could be a range of possibilities for targeting ovarian longevity, and some are already being used by those interested in longevity for tackling aging in general

If there was an intervention that could extend fertility, delay menopause, and extend longevity it has massive potential from an investment standpoint

"It's one of nature's great inequities," Dagan Wells, Professor of Reproductive Medicine at the University of Oxford, on the progressive decline in female fertility from the age of 35 years onward.

As the ovarian age of a woman increases her ability to produce offspring decreases. The consequence of advancing maternal age not only puts a woman at risk during natural and assisted conception, but also impacts the outcomes of the pregnancy: ectopic pregnancy, spontaneous abortion, foetal chromosomal abnormalities, congenital anomalies, placenta previa and abruption and preeclampsia are all correlated to advance maternal age and recent evidence increasingly points toward an independent association between maternal age and cerebral palsy, neurocognitive and psychiatric disorders (Correa-de-Araujo & Yoon, 2021) (Balasch & Gratacós, 2012).

So, the tough choice faced by many women is: have babies early to avoid complications but put your career on hold or focus on a dependent-free career and lifestyle but if you want to have children later – things could get complicated.

For many women, having children is still a key priority, but as career opportunities and choices have improved for women, particularly in the developed world, more are choosing to wait longer before having children.

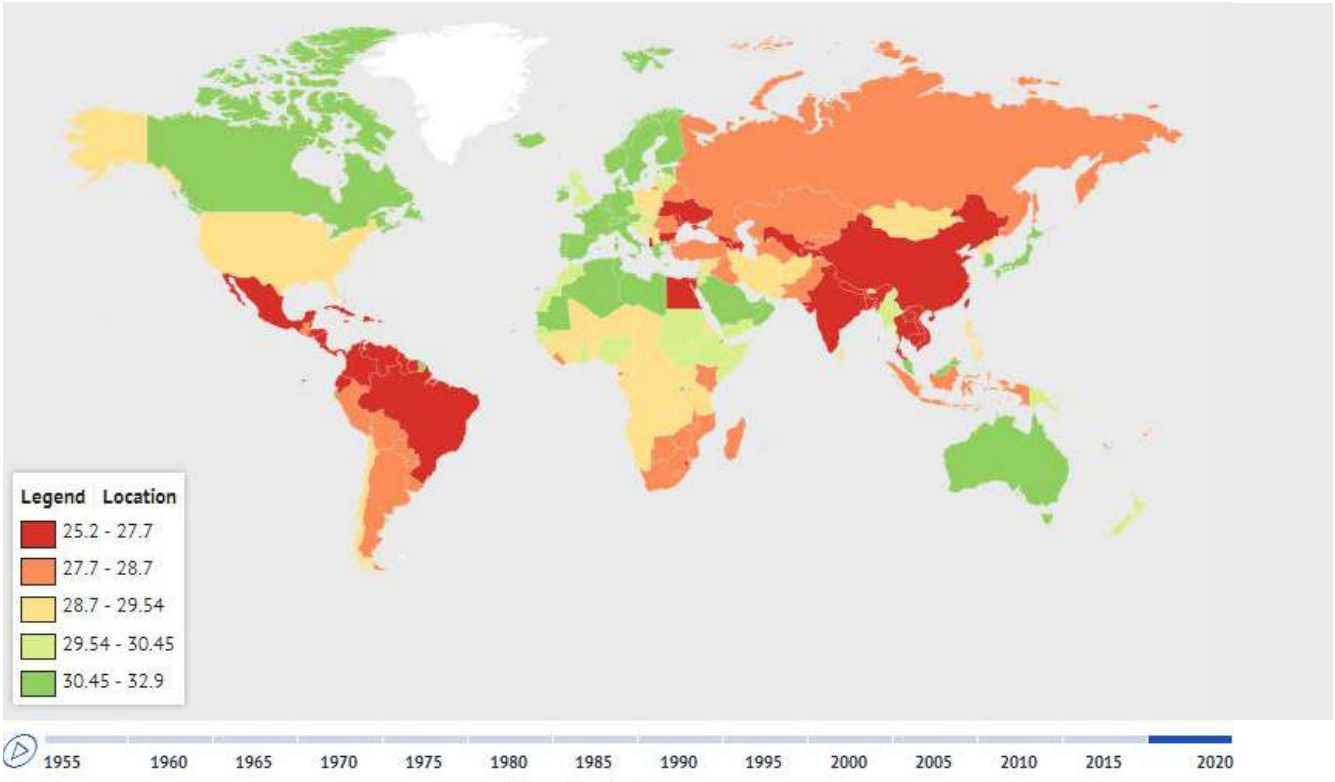


Figure 8. World map of the mean age of childbearing (years). Libya is the top country by age of childbearing in the world. As of 2020, age of childbearing in Libya was 32.82 years. The top 5 countries for later-life pregnancy also include Republic of Korea, Hong Kong, Saudi Arabia, and Djibouti (World Data Atlas, 2020).

Even with the risks, in modern societies, the proportion of females that are delaying childbearing beyond the age of 35 years has rapidly surged in recent decades. By 2018, the number of women having their first child after age 35 had increased nearly 10-fold since 1970. Even though the average age of first-time mothers in America has risen from 21 to 26, this is still a younger age than the average women in any other developed nation, where average age of 'first births' for new mothers is aged 31 (Figure 8).

Although women are living longer, the average age of menopause has not increased to the same extent. The window for childbirth is therefore both shrinking proportionally to lifespan.

This delay in childbearing is giving rise to what is being described as "declining birth rates". For example, the US birth rate has declined for six years and 19%, in total, since 2007 and, in 2020, Australia recorded its first population decline since the First World War (Bricker, 2021). The most significant decrease in birth rates is in countries where employment is growing, but this does not necessarily mean that motherhood is dropping overall. The total percentage of women who are mothers has risen, partly due to older women, college educated women and unmarried women being more likely to have a baby than they would have been: 86 per cent of American women aged 40 to 44 have children (Filipovic, 2021). This reflects that motherhood is not on the decline so much as motherhood is delayed, and the number of families with just one or two children is climbing.

Lower fertility rates also mean reduced average family sizes and, therefore, populations in many countries are declining.

What the data truly reflects is that fertility rates (the number of children born alive to women of that age during the year as a proportion of the average annual population of women of the same age) are falling below replacement rates: for a country to naturally replace its population, its fertility needs to be at least 2.1 but many countries are falling far below that (Figure 9). The World Bank has reported that the global average total fertility rate had almost halved from its 1960 rate of 4.7 to only 2.4 in 2018. Consequently, many countries are experiencing population declines. This means China could lose between 600 and 700 million people from its population (1.386 billion) by 2100 (Bricker, 2021).

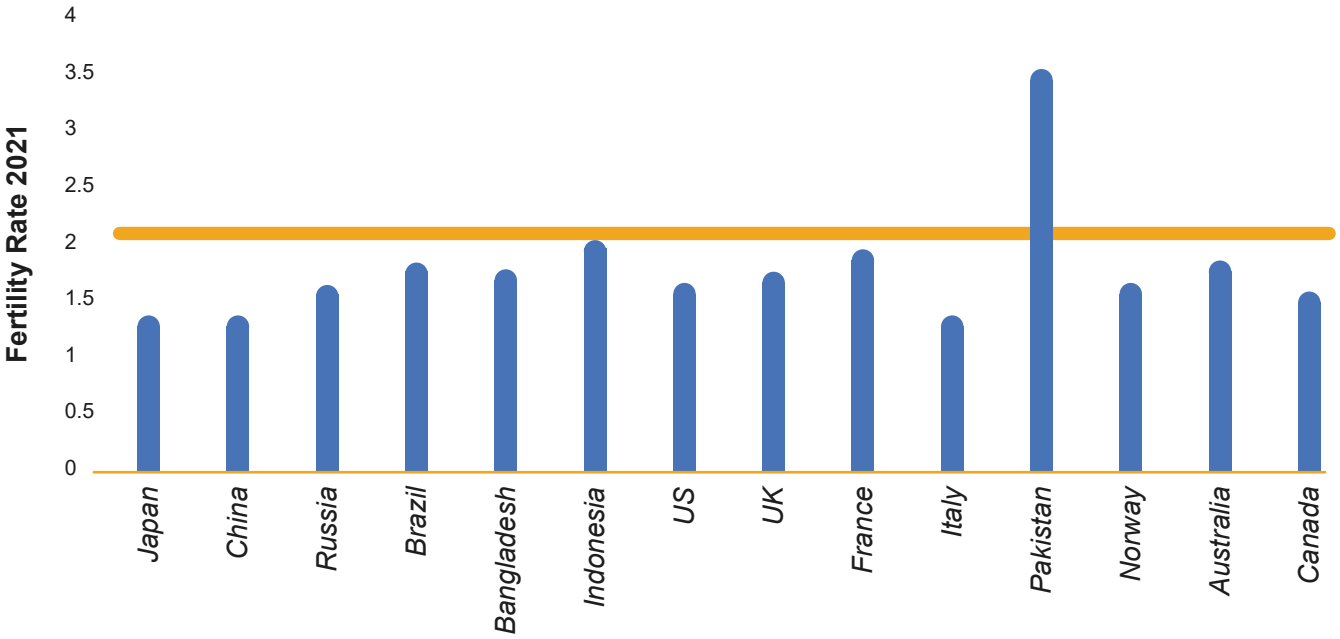


Figure 9. Fertility rate in various countries is dropping below the population replacement rate of 2.1

But why should we care about fertility rates and population decline? Fewer people are good for the climate, but the economic consequences could be severe. In the 1960s, there were six people of working age for every retired person. Today, the ratio is three-to-one. By 2035, it will be two-to-one (Bricker, 2021) (Figure 10).

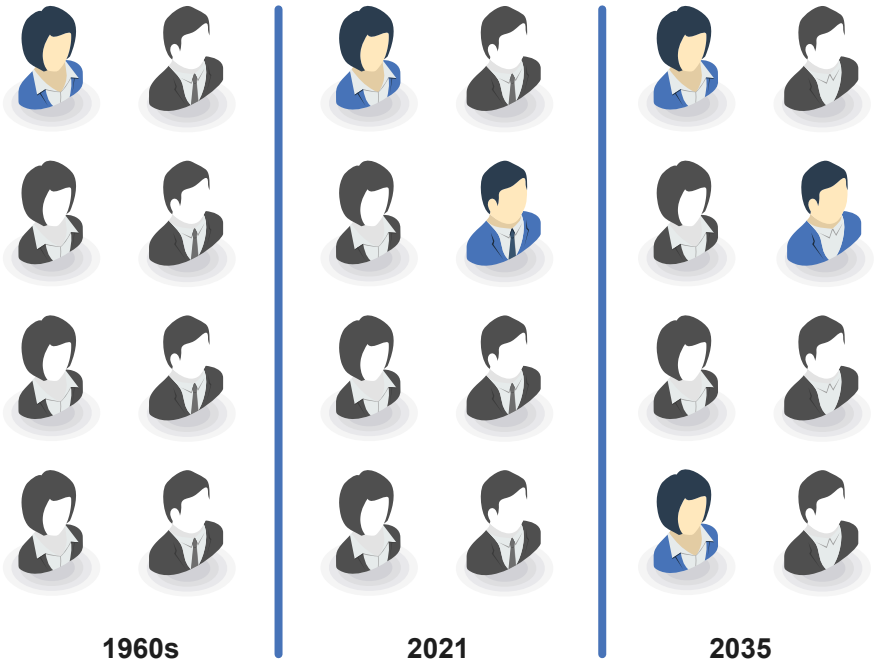


Figure 10. Proportion of retired persons (blue) to working persons (black) in the 1960s, today and predicted for 2035.

Fertility rates declining, coupled with the enhanced lifespan due to modern sanitation and medicine, means the silver tsunami is on most nations doorsteps. Imagine a world where the number of 'pensioners' vastly dominates the number of young workers. Here are just some of the potential consequences if fertility decline remains (International Strategic Analysis, 2019):

- **Fewer workers:** as birth rates fall, working age populations eventually fall as well. This leads to labour shortages in countries where working-age populations are in decline
- **Fewer consumers:** lower birth rates and a falling working age population also means fewer consumers to generate growth on domestic markets, leaving countries with low birth rates more exposed to external shock
- **Older populations:** unless older segments of the population become economically productive, they will remain as a cost base to the economy. A shrinking working age population is unsustainable and could threaten many leading economies
- **Wealthy markets are in decline:** places with the world's lowest birth rates are found in wealthier countries. This is causing a greater concentration of wealth in small segments of these countries' populations, as opportunities for growth become more concentrated
- **Educators and policymakers in decline:** Fewer young people will inevitably cause school and colleges to close due to declining student recruitment and enrolment. One projection suggests there will 10% fewer college students in 2054 than today

So why are women choosing to delay childbirth?

For many women, reconsidering motherhood is not due to hardship or unmet desire, but rather a new landscape of opportunity. Countries where women have abundant opportunity to pursue higher education, live independently, make choices regarding contraception and work, tend to have a higher average of age of first birth and lower birth rates overall (Filipovic, 2021). Below is an overview of the reasons as to why women are beginning to delay motherhood (Oberhauser, 2021) (Sager, 2021) (Survey statistics taken from "Becoming a mother – understanding women's choices today" British Pregnancy Advisory Service, 2015).

- **Higher education levels**: women with higher education levels, especially unmarried women, tend to put off childbearing until their early 30s. US education department estimates show that, fifty years ago, 58% of U.S college graduate were men. Today 56% are women
- **Careers**: 70% of women surveyed in the British Pregnancy Advisory Service (BPAS) report believed that combining work with childcare would be difficult and 79% feel the responsibilities of caring for children still largely fall to women. With more women moving into traditionally male-dominated industries and a rise in female entrepreneurs over the past decade, women's representation in the workforce is steadily increasing and many are not prepared to give up the careers that they have fought for
- **Finances**: financial cost is a very relevant factor for delaying parenthood. In general, the price of all necessities in the world will keep increasing, including the budget to raise children starting from labouring budget to education rates
- **Relationship freedom**: 82% of women in the BPAS report classed "being in the right relationship" as one of the most important factors for starting a family
- **Reproductive contraception**: the US federal regulators' approval of birth control in the 1960s expanded reproductive freedom for women. For the first time women had a greater control of sex for reproduction. These days there are over 12 female contraceptive methods and 84% of women in the

UK are using some type of female contraceptive.

- **Rise in fertility treatments**: advances in fertility treatments have made it more feasible for women to have children later in their lifetime. The average chance of taking home a baby with each in vitro fertilisation cycle (IVF) is 30%. As of 2021, 33% of Americans have turned to fertility treatments or know someone who has. However, when surveyed in the BPAS report, fewer than one in ten women said the fact that IVF was available made them less concerned about delaying having children

Although the concerns about the economic impacts of lower birth rates are valid, the importance of giving a woman the option for finding love, respect, a career and a full life can be argued far greater. To curb any of the above reasons for delaying motherhood is essentially taking a step backwards for women's rights. Given that a growing global population of wealthier people living longer is basically unsustainable, longer-term answers come down to finding more innovative ways of dealing with the problem. While many may look to social funding social welfare programs, flexible working and educating young women about the impacts of delaying motherhood, we at Longevity.Technology are looking to ovarian longevity.

Not only can delaying the aging of ovaries promote fertility but it may also enhance healthspan and lifespan for over 50% of the world's population.

As stated previously in this report menopause and time of first childbirth may also have an impact on lifespan and healthspan. The earlier you hit menopause could decrease lifespan and healthspan. Certain changes due to hormonal imbalances include weight gain, fatigue, memory decline, low libido and muscle loss. The average age of starting perimenopause amongst women is around 45 to 50 years of age. With women's average lifespan already increased, there is a growing population of older women creating a huge target market for extension of quality-of-life post-menopause. Delaying ovarian aging could postpone menopause and shorten the period of a women's life spent post-menopause. It could also delay women having children, which could potentially extend their lifespan.

The pool of women looking to extend their fertility and enhance their healthspans is increasing and will produce a large target market.

Ovarian aging is treated as two separate issues: infertility and menopause. But should it be? Couldn't you tackle both markets at once?

Currently, ovarian aging is still looked at as two separate issues, the first being fertility and the second being menopause and its related symptoms / increased disease risk. Both are treated instead of prevented. Fertility is tackled using assisted reproductive technologies, whereas hormone replacement therapy is the current method for treatment of menopause. Ovarian tissue cryopreservation could be a new anti-aging treatment of the future where women's own ovarian tissue is taken at a young age and later used to postpone menopause and prevent troublesome symptoms and diseases that come with menopause.

"Nobody wants IVF. They want a baby." Claire Tomkins, Future Family

Assisted conception is when medical interventions are used to aid conceiving. There are multiple different methods that people can use if they are having issues when conceiving and the choice will be dependent on that couple and the factors preventing the unity of sperm and egg. The assisted reproductive technologies discussed here are oocyte cryopreservation and embryo cryopreservation, which are the most applicable and common methods in terms of delaying fertility.

Over 1.1 million in vitro fertilisation (IVF) treatment cycles have taken place since the first IVF treatment baby, Louise Brown, born 40 years ago. Most IVF cycles use fresh oocytes, meaning that the oocytes are taken from the women/donor and combined with a partners/donors sperm in a laboratory dish to create an embryo. The resulting embryos are then transplanted back into the womb. Although IVF can help address infertility in younger women, it cannot reverse the effects of age – particularly in women over 40. Age is one of the main predictors of IVF outcomes. Live birth rates after IVF decrease from 46.8% in women under 35 to 3.1% after the age of 42 (Llarena & Hine, Reproductive Longevity and Aging: Geroscience Approaches to Maintain Long-Term Ovarian Fitness, 2020) (Figure 11).

If there was an intervention that could extend fertility, delay menopause, and extend longevity it has massive potential from an investment standpoint.

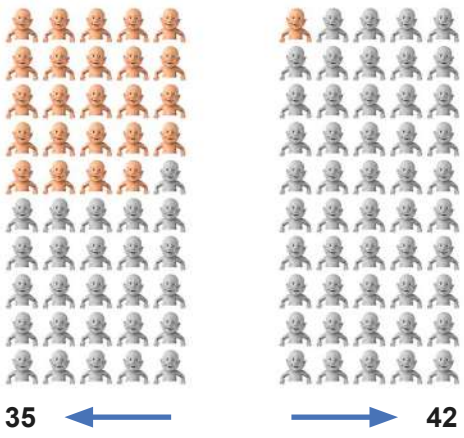


Figure 11. Live birth rates after IVF decrease from 46.8% in women under 35 to 3.1% after the age of 42

Furthermore, fresh oocytes and subsequent IVF is not a solution to age-related fertility decline because it cannot reverse the oocyte degeneration that occurs with increasing age. However, oocytes can be collected and then frozen, in a method called “oocyte cryopreservation”. In fertility preservation, oocyte cryopreservation is called “social egg freezing” and is typically offered to women under 38 years of age who want the option of having healthy, genetically-related children later. Using this method reduces the risk of having children with the associated chromosomal abnormalities.

It is estimated that the survival rate of oocytes after vitrification (freezing method) is 90-97%, the fertilisation rate is 71-79% and the implantation rate is 17-41%. Clinical pregnancy rates have been estimated between 4-12% per oocyte (Petropanagos, Cattapan, Baylis, & Leader, 2015). However, these data are collected from oocytes obtained from women less than 30 years of age and clinical pregnancy rates decline with advanced maternal age at the time of freezing. Furthermore, live birth rate is 2-12% for women under 38 years of age (Petropanagos, Cattapan, Baylis, & Leader, 2015). Although the number of people using this treatment is growing, the numbers are still small, making up around 1.5% of all fertility cycles carried out across the UK in 2016 (Human Fertilisation and Embryology Authority, 2016).

Alternatively, oocytes can be collected, IVF performed, and the resulting embryo can be frozen in “embryo cryopreservation”. However, the use of male-partner/donor sperm to create embryos introduces several ethical, moral and legal concerns. For example, regarding the destiny of “orphan” embryos in case of death or separation. Women may find themselves in the situation of possessing no reproductive chances except for frozen embryos generated from an ex-partners sperm. Oocyte cryopreservation gives women reproductive autonomy and therefore oocyte cryopreservation is being promoted as the gold standard in female onco-fertility preservation (Rienzi & Ubaldi, 2015).

Furthermore, the costs of social oocyte cryopreservation are significant. Not only do you need to pay for oocyte stimulation, which may need to be repeated multiple times, but there are also the fees of storage to consider (Table 1). In Canada the estimated storage fees is between $300 and $500 per year and thus the longer you want to freeze your oocytes, the higher the cost (Petropanagos, Cattapan, Baylis, & Leader, 2015). This becomes more complicated with the fact the younger you freeze your oocytes the better. A lot of health insurance programs do not currently cover social oocyte preservation or for IVF.

Table 1. Costs of oocyte freezing in different countries

Country	Cost per cycle treatment	Annual storage fees
UK	£3,500-£4,500	£200 - £360
USA	$15,000-$20,000	$500-$600
Canada	$5000-$10,000	$300-$500
Australia	$4000-$7000	$400-$500

There is a huge market in fertility preservation; it is estimated that the total market is about $4.3 billion for oocyte freezing and $2.7 billion for IVF and this will continue to grow as the number of women wanting to delay fertility becomes larger. However, social oocyte cryopreservation comes with risks and financial costs to the individual. Some companies are beginning to cover some of the IVF costs such as medication, consultation and the IVF costs themselves. Tech companies like Pinterest, Spotify, Slack and Facebook offer the best IVF coverage. However, these methods **do nothing for delaying menopause, and thus have no contribution to healthspan.**

Tackling ovarian aging could have the potential to make IVF and oocyte cryopreservation a more redundant market. If you can delay the aging of the ovary, to extend the quality and quantity of oocytes into later life, females who want to have children at a later age (40s) might not need to think about these current treatments (unless there are other medical reasons for in play).

Hormone replacement therapy for menopause

Hormone replacement therapy (HRT) supplements women with hormones that are lost during the menopausal transition. The main aim of HRT is to relieve the symptoms that are associated with menopause by mimicking the hormones estrogen and progesterone created by the human ovary.

Clinically, HRT is initiated near the start of menopause, and as it turns out the age of starting HRT is critical in determining benefit/risk. HRT use in women dropped between 2002 and 2008 due to a publication by Women's Health Initiative (WHI) trial that had non-significant findings for increased breast cancer and cardiovascular heart disease when using conjugated equine estrogen + medroxyprogesterone acetate. This led to the US Food and Drug Administration (FDA) placing a black box warning on all HRT regimens in 2002 and, combined with the press that the trial received, caused a significant drop in HRT use.

However, in the trial, the WHI enrolled primarily women well beyond menopause (mean age 63 years, mean time since menopause 12 years), with only 30% of the cohort <60 years of age. Since these findings, it has become clear that the time since menopause that HRT was initiated is as an important co-founding factor that was not considered when the WHI was designed. There is robust evidence that estrogen is a highly effective treatment for menopausal vasomotor symptoms and the genitourinary syndrome of menopause. Further, if initiated within 10 years of menopause, HRT is effective in reducing all-cause mortality, can prevent coronary heart disease (dependent on treatment regimen), reduce fracture risk, and could protect against dementia. Even so, the FDA's decision remains unchanged despite the emergence of data that contradicts the initial trials findings.

However, replacement of hormones does nothing for fertility only potentially for the extension of lifespan/healthspan.

According to the studies conducted by the North American Menopause Society around one million women in the US are currently opting for hormone replacement therapy and the number is expected to reach about 2.5 million in the near future. The increasing number of women who are about to reach menopause, along with the wide menopausal window of 40 to 55 years, is expected to lead the HRT market.

If ovarian aging can be delayed, then a knock-on effect will be that hormones do not need to be replaced, as they will continue to occur in their monthly cycle. This could extend the menopause window above 55 years and stop women from needing HRT until much later in life.

Ovarian tissue cryopreservation -a current treatment for fertility and hormone replacement?

So is there any treatment that can do both? There is a treatment that has been used for the last twenty years that could tackle both fertility and hormone replacement theory in one, called ovarian tissue cryopreservation (OTC) (Figure 12). OTC is the process where the ovarian tissue is removed, sliced and then cryopreserved. Once thawed the ovarian tissue can be grafted back into the patient either in the pelvic cavity (orthotopic site) or in regions such as the forearm or abdominal wall (heterotopic sites). The cortical region of the ovary, which contains over 90% of the follicular reserve, is what is used for cryopreservation and thus hundreds of primordial follicles can be preserved at once, significantly increasing future chances of pregnancy (Vuković, Kasum, Orešković, Čehić, & Jelena Raguž, 2019). OTC is currently considered as a method of fertility preservation which is advancing rapidly.

OTC for fertility preservation

OTC is not a new procedure. It was first designed to allow young women that were at risk of idiopathic ovarian insufficiency, due to cancer treatments, to maintain their reproductive potential. It is currently the only fertility preservation method for prepuberal cancer patients and, as it does not require ovarian stimulation, treatment does not have to be delayed for retrieval of oocytes and embryos from multiple cycles like in egg freezing. The average number of eggs that are procured at one time is 8-12. In OTC thousands of eggs can be stored within a single sample of tissue. A further plus for fertility, is that in vitro fertilisation can be avoided because ovarian tissue placed back in the pelvic cavity can allow spontaneous pregnancies to occur if the fallopian tubes are still present and functional. To date, 130 babies have been born using this method, and half have been conceived by natural conception (Vuković, Kasum, Orešković, Čehić, & Jelena Raguž, 2019).

OTC for hormone replacement therapy

What is also interesting about this method is that it is also thought to restore ovarian endocrine function; the tissue grafts are said to create hormones in physiological concentration and under hypothalamus-pituitary-ovary feedback, producing lower and safer levels of estrogen in comparison to HRT. If this is the case, not only will estrogen be restored, but also androgen production, which could improve a woman's sexual function, genitourinary syndrome of menopause and decreased libido. After orthotopic reimplantation, ovarian endocrine function is restored in more than 95% of patients with a duration of ovarian activity of 4-5 years (can reach 7 years depending on the follicular density). If the goal of OTC is only for hormone replacement therapy, the ovarian slices

After orthotopic reimplantation, ovarian endocrine function is restored in more than 95% of patients with a duration of ovarian activity of 4-5 years.

can also be put in at a heterotic graft site such as the abdomen, forearm, breast tissue, rectus muscle and subperitoneal tissue. This would also offer less invasive surgery, closer monitoring, and prevention of pregnancy at an older age. Heterotopic grafts could also mean the procedure could be repeated every 4-5 years after the duration of ovarian activity comes to an end.

OTC is still classed as an experimental procedure, even though it is expected that The American Society for Reproductive Medicine will soon lift its experimental designation of ovarian tissue freezing. However, there are some limiting factors that must be considered. For example, the age of the patient is important as there must be a remaining ovarian reserve when the ovarian cortical is removed. This would be a decision that most women would have to make at a younger age, and it is not a guarantee that a woman at the age of 25 would be willing to have a surgical procedure to avoid menopausal symptoms a quarter of a century later.

Furthermore, as at least two surgical procedures need to be performed, the costs of removal, freezing, and “top-ups” could surmount. In places where medical care is covered, there would have to be significant evidence that the cost benefits of delaying menopause outweigh those of menopausal symptoms and disease risk. Currently, whether the amount of hormone that the slices produce can eliminate menopausal symptoms and risk of disease remains in the “unknown” bracket, with some experimental procedures in rats showing the endocrine function is less than that of rats with intact ovaries (Vuković, Kasum, Orešković, Čehić, & Jelena Raguž, 2019). There is also the chance of complications arising from ischemia, since ovarian tissue graft is an avascular graft, which could cause the loss of many follicles and lead to a

decrease in the graft longevity.

Currently, there is a company in the UK offering the procedure called ProFaM (Fertility Preservation and Menopause Delay). The fees for the removal procedure range from £2890 (in opportunistic cases, where patient is already undergoing surgery) to £6000 (exclusive surgery). However, storage fees for are not stated on the website. Furthermore, there may be additional costs for each round of surgery. These prices may also change dependent on the patient circumstance and chosen hospital site. Patients must be under the age of 35 for fertility treatment and under the age of 40 for menopausal treatment as a “general” rule, however, “a few” ovarian reserve tests are

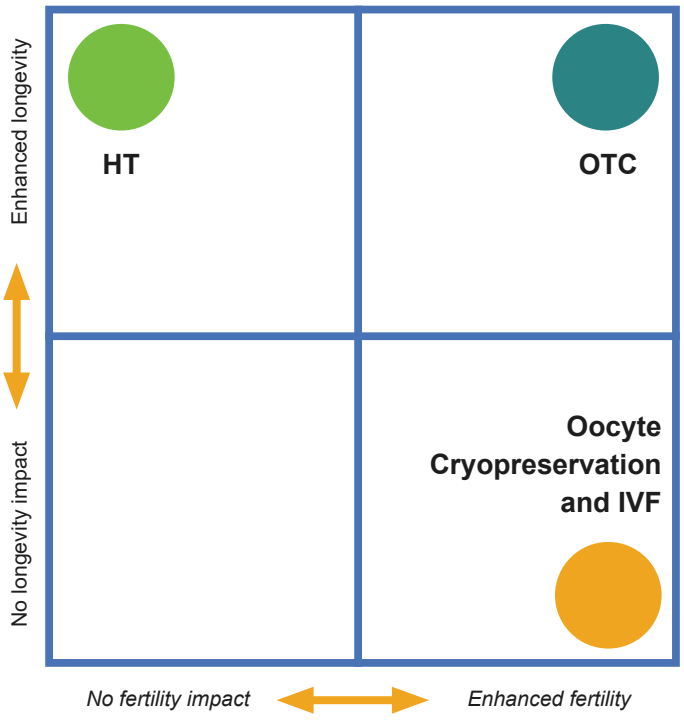


Figure 12. Comparison of Ovarian tissue cryopreservation, hormone therapy and oocyte cryopreservation in terms of longevity and fertility impact.

Tackling ovarian longevity: from an investment standpoint

There are three markets that should be considered when looking at ovarian longevity from an investment standpoint:

1. Fertility preservation market: the global fertility market size was valued at $33.1 billion in 2020. This is predicted to reach $47.9 billion by 2030 (Precedence Research, 2021).
2. The global menopause market: the global menopause market size was valued at $14.7 billion in 2020 and is expected to reach $22.7 billion by 2028 (Grand View Research, 2021).
3. The longevity market: the market is already worth $110 billion and analysts at Bank of America have estimated the industry that extends life is set to be worth at least $600 billion by 2025 (Newman, 2019).

There could be a range of possibilities for targeting ovarian longevity, and some are already being used by those interested in longevity for tackling aging in general.

Traditionally the female fertility industry has been dominated by large clinics offering similar treatments at similar price points. There are number of bottlenecks in fertility services including access, cost of treatment and lack of digitisation and automation within the most basic procedures. Lengthy, expensive, and sometimes potentially ineffective experiences are the norm.

The interest in the scientific community into ovarian longevity is growing exponentially, with 784 out of 1946 articles on Pubmed, about ovarian longevity, published in the last three years. Interest is not only growing in the scientific community – a $6 million gift from a Silicon Valley-connected, tech-focused lawyer, entrepreneur and philanthropist will fund a new centre at the Buck Institute for Aging Research to focus on ways to boost fertility and women's health overall.

Aiding ovarian longevity falls into all three of these markets: if there was an intervention that could extend fertility, delay menopause, and extend longevity it has massive potential from an investment standpoint.

The Longevity.Technology Survey

At longevity.technology, we conducted a survey of 1000 females in the UK population and analysed the results of those between the ages of 18-44 (457 respondents). When questioned whether they would take an intervention to delay menopause and extend fertility, 32% chose a method (methods included; take a supplement, take a prescribed drug, freeze my eggs, remove an ovary, undergo HRT). This percentage, when extrapolated, corresponds to 3.6 million women in the UK population and 20 million in the US (between the ages of 18-44). We predict these numbers to grow even higher as females begin to understand the impact of menopause on the aging process and how they could manipulate their own fertility in a safe and effective manner.

% of woman (18-44) that will take an intervention to delay menopause and extend fertility

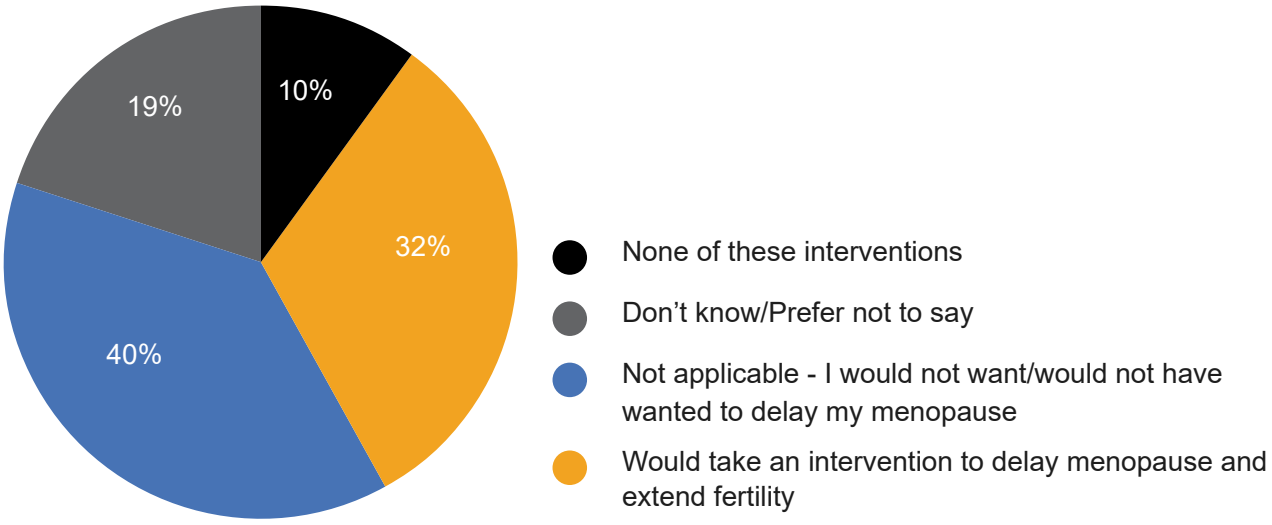
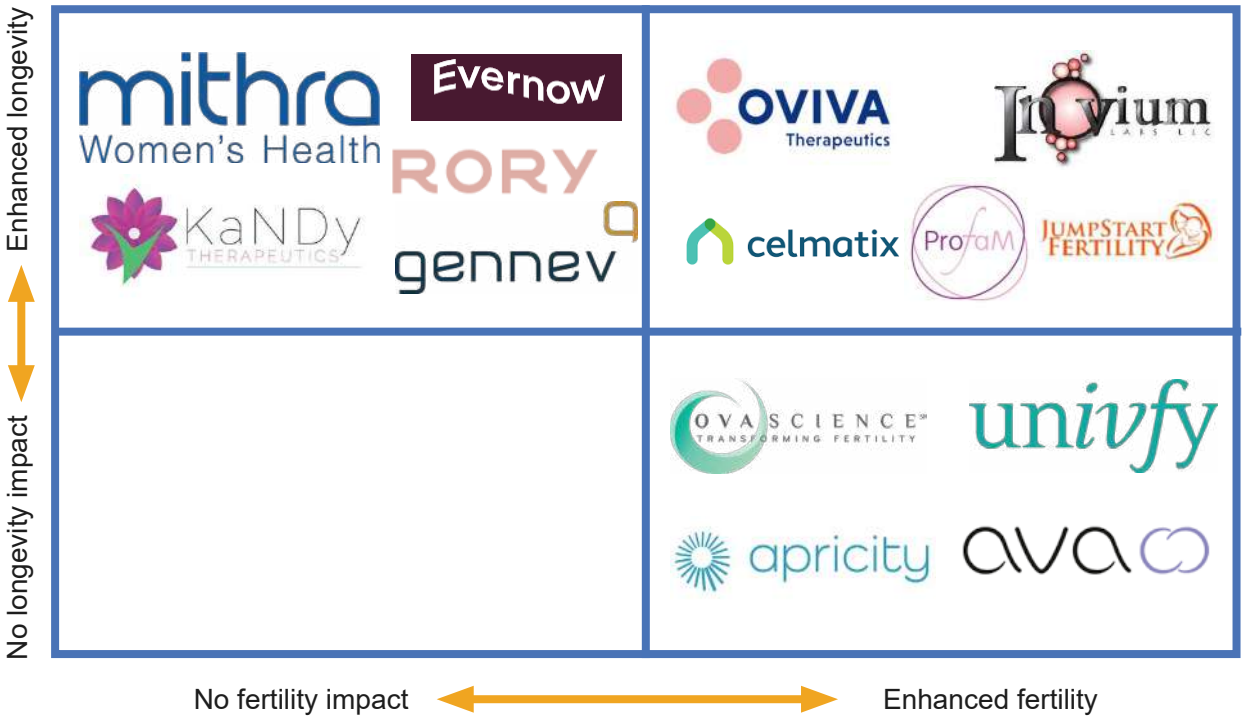


Figure 13. Results from YouGov poll, conducted by Longevity.Technology, asking women aged 18-44 if they would take an intervention to delay menopause and extend their fertility.

Clearly, there is a growing market and a longevity company that can produce clinically sound data to prove its intervention can delay the ovarian aging process has a lot to gain. There are several companies in the field of ovarian longevity at the moment, but we expect this to grow as the longevity industry continues to accelerate, and women's health and fertility markets boom. IP-rich tech companies in this space require patient capital and extended time horizons and investing in a field as specific and emotive as fertility will require domain expertise to understand the science behind the field (for more background into the science, please refer to section 2 of this report). However, we at Longevity.Technology believe this is an opportunity to watch out for.

Femtech Companies 2021



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