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Biological Clock and Reproductive Longevity: Molecular Insights into Ovarian Aging and the Role of Physical Activity

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ABSTRACT

Introduction. The "biological clock" remains the primary determinant of female reproductive potential, as fertility is strictly limited by a finite pool of oocytes. In modern society, including professional athletes, the trend toward delayed childbearing has increased the clinical relevance of age-related fertility decline. This review explores the molecular foundations of ovarian aging and the impact of lifestyle on reproductive longevity.

Materials and Methods. A narrative review was conducted using PubMed and Google Scholar, focusing on clinical guidelines (ASRM, ESHRE) and recent research regarding oocyte depletion, biomarkers (AMH, AFC), and the influence of physical activity and psychosocial stress on fertility outcomes.

Literature Review. Reproductive aging is driven by oxidative stress, mitochondrial dysfunction (reduced ATP production), and degradation of cohesin proteins, leading to increased embryonic aneuploidy and miscarriage rates. While AMH and AFC are reliable for assessing follicle quantity, they remain limited in predicting oocyte quality or spontaneous conception. In active populations, extreme physical exertion and psychological pressure can modulate the ovarian microenvironment, potentially affecting reproductive success and long-term quality of life.

Summary and Conclusions. Despite advancements in ART, female age remains the most critical predictor of fertility. To optimize reproductive longevity, it is essential to integrate early fertility education and individualized counseling into the routine medical care of active women.

Keywords:female fertility; female fertility; reproductive aging; ovarian reserve; oocyte quality; assisted reproductive technology; oocyte cryopreservation

1. Introduction

Delayed motherhood has become increasingly common in developed countries due to educational, professional, and socioeconomic factors [1]. This demographic shift has important medical consequences, as female fertility is biologically time-limited and declines with age. Infertility affects a significant proportion of the global population and represents a major public health concern [1]. The decline in fertility begins gradually in the early thirties and becomes more pronounced after the age of 35 [2]. Advanced maternal age is associated with reduced fecundity, increased time to conception, and higher rates of miscarriage and chromosomal abnormalities [3]. These factors affect both natural conception and assisted reproductive technologies [1,2]. Importantly, demographic data indicate that the average age at first childbirth has been steadily increasing across many European countries, which further contributes to the growing prevalence of age-related infertility. This trend highlights the discrepancy between social reproductive planning and biological reproductive capacity [4,5]. In addition, many women overestimate the effectiveness of assisted reproductive technologies and underestimate the impact of age on oocyte quality, which may delay seeking medical advice [6]. As a result, a significant proportion of patients present at advanced reproductive age, when therapeutic options are more limited and less effective. The aim of this review is to summarize current knowledge regarding the impact of female age on fertility, including underlying biological mechanisms, diagnostic tools, and available therapeutic strategies.

2. Research materials and methods

This study was conducted as a narrative review. Literature was identified through searches in PubMed and Google Scholar using keywords such as “female age fertility,” “ovarian aging,” “oocyte quality,” and “fertility preservation.” Priority was given to publications from the last 5–10 years, including systematic reviews, meta-analyses, and clinical guidelines issued by international organizations such as ASRM and ESHRE [1,7,8,9,10]. Studies were selected based on relevance, scientific quality, and applicability to clinical practice.

3. Literature Review

3.1. Physiology of Female Fertility

Female reproductive capacity is determined by a finite pool of oocytes established during fetal life. At approximately 20 weeks of gestation, the female fetus possesses 6 to 7 million germ cells. This number decreases to roughly 1 to 2 million at birth and continues to decline to

approximately 300,000–400,000 by the onset of puberty. This ovarian reserve declines progressively due to follicular atresia, leading to reduced fertility over time.

The biological limitation explains why the reproductive lifespan is considerably shorter than the overall lifespan and why fertility preservation has become an increasingly relevant clinical issue. The rate of follicular depletion is not linear and accelerates with age, particularly after the mid thirties, which explains the rapid decline in fertility observed during this period. It is estimated that when the count of primordial follicles drops below a critical threshold (approximately 1,000), menopause occurs, typically around the age of 50–51 [11,12]. Individual variability in the rate of ovarian aging has also been described, suggesting that genetic and environmental factors may influence the reproductive lifespan and the age of menopause [13].

3.2. Impact of Age on Fertility

Female fertility begins to decline after the age of 30 and decreases more rapidly after 35 [2]. This decline is associated with reduced probability of conception and increased risk of infertility [5]. In clinical practice, this means that even women with regular menstrual cycles may experience reduced reproductive efficiency once age-related changes in oocyte quality begin to dominate.

Advanced maternal age is also associated with higher rates of miscarriage, largely due to chromosomal abnormalities. The majority of early pregnancy losses are attributed to aneuploidy, with incidence increasing significantly with age [3,14].

In addition, the likelihood of obtaining euploid embryos decreases with advancing maternal age, which significantly affects both natural conception and outcomes of assisted reproductive technologies [14]. This decline in embryo competence is one of the main limiting factors in reproductive success in older women. Age is a critical factor influencing outcomes in assisted reproductive technologies, with declining success rates observed in older women [1,8].

3.3. Biological Mechanisms of Ovarian Aging

Ovarian aging is driven by multiple, interconnected biological processes that affect both the quantity and, more importantly, the quality of the remaining oocytes. Oxidative stress plays a central role in this decline by generating reactive oxygen species (ROS) that damage cellular components, including proteins, lipids, and nucleic acids. As the oocyte ages, the efficiency of endogenous antioxidant defense mechanisms—such as superoxide dismutase and glutathione peroxidase—decreases significantly. This leads to a state of chronic oxidative stress within the

follicular microenvironment, which contributes to the acceleration of follicular atresia and impairs the developmental competence of the oocyte [17].

Mitochondrial dysfunction is another critical factor in age-related reproductive decline. Mitochondria are the primary source of adenosine triphosphate (ATP), which is essential for the energy-demanding processes of oocyte maturation, spindle assembly, and subsequent embryonic development. Research indicates that aging is associated with decreased mitochondrial membrane potential, reduced ATP production, and the accumulation of mitochondrial DNA (mtDNA) mutations [18,19]. These energy deficits can lead to metabolic exhaustion of the oocyte, resulting in fertilization failure or early embryonic developmental arrest.

Furthermore, aging profoundly affects the structural integrity of the oocyte's genetic apparatus. One of the most critical molecular changes is the age-related degradation of cohesin proteins. These proteins are responsible for holding sister chromatids together from their formation during fetal life until the completion of meiosis years later. The gradual loss of cohesins leads to spindle instability and errors in chromosome segregation during meiotic divisions. This process results in a significantly higher incidence of aneuploidy in embryos—most commonly trisomies—which explains the exponential increase in miscarriage rates and genetic disorders observed in women of advanced reproductive age [3,18]. These mechanisms do not act in isolation; rather, oxidative damage and mitochondrial failure reinforce one another, creating a cumulative decline in follicular function.

To accurately assess a patient's reproductive potential, it is essential to understand the distinctions between biochemical and biophysical markers of ovarian reserve. A detailed comparison of AMH and AFC, including their cyclic stability and clinical limitations, is presented in Table 1.

Table 1. Molecular and Cellular Mechanisms of Ovarian Aging.

Mechanism	Key Biological Changes	Clinical Consequences	Reference
Oxidative Stress	Accumulation of ROS; decreased antioxidant defense (SOD, GPx)	Damage to lipids, proteins, and oocyte DNA; follicular atresia	[17]
Mitochondrial Dysfunction	Decreased ATP production; mtDNA mutations; low membrane potential	Reduced oocyte competence; fertilization failure; embryo arrest	[18, 19]
Chromosomal Instability	Degradation of cohesin proteins; spindle assembly defects	Increased incidence of aneuploidy (trisomies)	[3, 18]
Telomere Shortening	Loss of TTAGGG repeats at chromosome ends	Cellular senescence; impaired proliferative capacity	[14]
Epigenetic Alterations	Changes in DNA methylation and histone acetylation	Altered gene expression during oogenesis and early embryogenesis	[12, 14]

3.4. Diagnostic Assessment of Age-Related Fertility Decline

Assessment of ovarian reserve is a fundamental component of the fertility evaluation, yet it requires careful clinical interpretation to avoid misleading patients. Anti-Müllerian hormone (AMH) has emerged as the most reliable biochemical marker due to its relative stability throughout the menstrual cycle. AMH is produced specifically by the granulosa cells of preantral and small antral follicles (less than 8 mm in diameter). Its serum concentration reflects the size of the remaining primordial follicle pool [15,16, 24]. While AMH is an excellent tool for predicting the ovarian response to gonadotropin stimulation in IVF and identifying patients at risk of ovarian hyperstimulation syndrome (OHSS), it is important to note that it does not accurately predict the chances of spontaneous conception in a given month [20].

Antral follicle count (AFC), performed via transvaginal ultrasound, serves as a direct visual surrogate for the functional ovarian reserve. For clinical accuracy, AFC should be assessed during the early follicular phase (typically days 2–5 of the cycle), counting all follicles measuring 2–10 mm in both ovaries. A low AFC is strongly associated with poor ovarian response in assisted reproduction. In contrast, basal follicle-stimulating hormone (FSH) and estradiol levels, while traditionally used, are subject to significant inter-cycle and intra-cycle variability. A rise in basal FSH (typically >10-12 IU/L) often only occurs when the ovarian reserve is already severely compromised, making it a late marker of reproductive aging [7,22].

The most critical limitation of all current ovarian reserve tests is that they primarily measure the quantity of the remaining follicles and not the quality (competence) of the oocytes. Clinical data consistently show that female age remains a far more potent predictor of oocyte quality and live birth rates than any biochemical marker. For example, a 42-year-old woman with a "normal" AMH level still faces a significantly higher risk of aneuploidy and infertility than a 30-year-old with a low AMH level. Therefore, normal results in ovarian reserve testing should not provide a false sense of security to women of advanced reproductive age, as the biological clock of oocyte quality continues to decline regardless of the follicle count [7, 25]. The main differences and clinical applications of AMH and AFC are summarized in Table 2.

Table 2. Main differences and clinical applications of AMH and AFC.

Feature	Anti-Müllerian Hormone (AMH)	Antral Follicle Count (AFC)
Method of Assessment	Biochemical (Blood Test)	Biophysical (Transvaginal Ultrasound)
Source	Granulosa cells of preantral and small antral follicles	Visualized follicles (2–10 mm in diameter)
Cycle Stability	High (stable throughout the menstrual cycle) [15,16]	High (best assessed in early follicular phase) [7, 22]
Primary Predictio n	Quantitative ovarian reserve and response to stimulation [20, 24]	Current functional ovarian reserve [7, 22]
Main Advantage	Low inter-cycle variability; independent of observer bias [15]	Immediate results; direct visualization of ovaries [7]
Main Limitation	Does not predict oocyte quality or spontaneous conception [20, 25]	Dependent on equipment quality and sonographer experience
Clinical Value in ART	Predicts poor or hyper-response to gonadotropins [20, 24]	Guides dose adjustment for ovarian stimulation [9]

3.5. Therapeutic Strategies

3.5.1. Ovulation induction

Ovulation induction is useful in women with ovulatory disorders. However, in age-related infertility, its effectiveness is limited because the primary issue is reduced oocyte quality rather than ovulatory dysfunction [1,22]. Nevertheless, in selected patients it may still improve cycle regularity and increase the likelihood of conception when ovulatory dysfunction coexists with age-related subfertility.

3.5.2. Assisted reproductive technologies (IVF, ICSI)

Assisted reproductive technologies such as IVF and ICSI are widely used in infertility treatment. These techniques improve fertilization and embryo selection but do not fully overcome age-related decline in oocyte quality [1,9,21]. For this reason, early referral for fertility treatment is often more beneficial than repeated delays in the expectation of spontaneous conception.

3.5.3. Oocyte donation

Oocyte donation is an effective treatment for women with diminished ovarian reserve. By using oocytes from younger donors, it bypasses age-related decline in oocyte quality and significantly improves pregnancy rates [8]. This option is particularly valuable in women with poor ovarian response, repeated ART failure, or markedly advanced reproductive age.

3.5.4. Fertility preservation (oocyte freezing)

Oocyte cryopreservation is an increasingly popular option for women who wish to delay childbearing. Its success depends strongly on the age at which oocytes are frozen, with better outcomes observed at younger ages [8,23]. Its clinical value is greatest when undertaken before the steepest age-related decline in ovarian reserve has already occurred.

The correlation between maternal age and ART outcomes is closely linked to the rising incidence of embryonic aneuploidy. Table 3 summarizes live birth rates across different age groups and suggests clinical strategies based on current ASRM and ESHRE guidelines.

Table 3. Age-Related Outcomes in Assisted Reproductive Technology (ART).

Maternal Age (Years)	Oocyte Aneuploidy Rate (%)	Live Birth Rate (Per Transfer)	Recommended Strategy / Intervention	Reference
< 35	~10–30%	~45–55%	Expectant management (6–12 months); IVF	[1, 3]
35 - 37	~30–45%	~35–40%	Faster transition to ART; Oocyte freezing	[2, 8]
38 - 40	~50–65%	~20–25%	IVF with PGT-A (optional); Close monitoring	[3, 22]
41 - 42	~70–85%	~10–15%	IVF with PGT-A; Discussion of Egg Donation	[1, 3]
> 42	>90%	<5%	Egg Donation (highest success rate); PGT-A	[2, 6]

3.6. Psychosocial Aspects

Age-related infertility is not merely a biological challenge; it carries significant psychological and social implications that profoundly affect the well-being of women and their partners. A primary issue in modern society is the "fertility literacy gap"—many women consistently underestimate the physiological impact of age on natural fertility and simultaneously overestimate the success rates of assisted reproductive technologies (ART) [6]. This lack of

accurate information often leads to a false sense of security, causing further delays in childbearing for professional or personal reasons.

The diagnosis of age-related subfertility or diminished ovarian reserve often triggers a cascade of negative emotional responses. Infertility is clinically recognized as a major life stressor, frequently associated with elevated levels of emotional distress, clinical anxiety, and depression. For many women, the realization that their reproductive window is closing leads to a sense of "biological guilt" and a perceived loss of control over their life trajectory. These psychological burdens can significantly reduce the overall quality of life and, in some cases, negatively interfere with the success of fertility treatments by increasing the dropout rate from ART programs due to emotional exhaustion [1].

Moreover, societal pressures and cultural expectations regarding parenthood can exacerbate this psychological stress. In professional and athletic environments, women often face a "double bind": the pressure to reach peak performance and career stability during their most fertile years, followed by societal scrutiny when they struggle to conceive later in life. The "social clock" often conflicts with the "biological clock," creating a state of chronic tension.

Effective clinical management must, therefore, extend beyond medical intervention. Education and proactive counseling are essential components of care. Providing patients with realistic, evidence based data about age-related chances of success helps align their expectations with biological reality. Addressing these concerns through a multidisciplinary approach—involving psychologists and counselors—can mitigate anxiety, improve coping mechanisms, and help patients make more informed, realistic decisions about their future family planning and the use of donor gametes or other alternative strategies [1,6].

3.7. Physical Activity and the Ovarian Microenvironment

The relationship between physical activity and reproductive aging is complex and mediated by the same biological mechanisms that drive age-related fertility decline. Oxidative stress, which is a central driver of ovarian aging, plays a dual role in the context of exercise. While chronic, moderate physical activity is known to enhance antioxidant defenses, extreme physical exertion without adequate recovery can exacerbate the production of reactive oxygen species (ROS), potentially damaging cellular components, including oocyte DNA and mitochondria [17].

Mitochondrial dysfunction is another critical factor in reduced oocyte competence observed with advancing age. Research suggests that the metabolic demands of high-intensity training may influence mitochondrial efficiency within the ovarian microenvironment. As female

reproductive capacity is determined by a finite pool of oocytes established during fetal life, any external factor that accelerates follicular atresia through cumulative DNA damage or impaired energy production can theoretically shorten the reproductive lifespan [19]. In athletes, the clinical interpretation of biomarkers such as Anti-Müllerian Hormone (AMH) and Antral Follicle Count (AFC) requires caution. While these markers are reliable indicators of the follicular pool size, their correlation with actual reproductive outcomes in highly active populations remains a subject of ongoing investigation.

3.8. Psychosocial Well-being and Quality of Life in Aging Athletes

The trend of delayed childbearing is particularly relevant in the athletic community, where professional peak performance often coincides with the period of peak biological fertility. For many women engaged in competitive sports, the decision to postpone pregnancy is driven by professional goals, leading to a significant discrepancy between social planning and biological reality.

Infertility, especially when diagnosed at an advanced reproductive age, is associated with profound emotional distress, anxiety, and a significant reduction in the quality of life. Athletes may experience additional psychological pressure due to the perceived conflict between their physical identity and reproductive limitations. Education regarding the biological time-limit of fertility is essential to support informed decision-making. Early counseling and the use of diagnostic tools, such as AMH-based assessment, can empower women to make proactive choices, such as elective oocyte cryopreservation [8]. By integrating reproductive health awareness into the general medical management of active women, it is possible to mitigate the psychological burden of age-related subfertility and optimize long-term health outcomes [1].

4. Conclusions

Female age remains the most significant and independent predictor of reproductive potential and obstetric outcomes. The decline in fertility is a multifaceted process driven by both quantitative and qualitative changes in the oocyte pool. These changes are fundamentally mediated by cellular mechanisms such as increased oxidative stress, progressive mitochondrial dysfunction, and the degradation of structural proteins like cohesins, which collectively lead to higher rates of aneuploidy and early pregnancy loss [17,18,23].

Although modern assisted reproductive technologies (ART) have achieved remarkable progress, they cannot fully compensate for the irreversible biological effects of ovarian aging. Diagnostic tools, including AMH and AFC, are invaluable for assessing the follicular pool and

individualizing treatment protocols; however, they must be interpreted with caution. These markers primarily reflect the quantity of the ovarian reserve and should not be used as a definitive measure of oocyte quality, which is more accurately predicted by chronological age [2,7].

From a clinical and public health perspective, increasing social awareness regarding the biological limits of the reproductive window is essential. For women in demanding fields, including professional athletes, proactive reproductive planning and early assessment of ovarian reserve are crucial to mitigate the long-term impact of delayed childbearing. Integrating reproductive health counseling into routine medical care for active women can improve the quality of decision-making and reduce the psychological burden associated with age-related subfertility.

In conclusion, while therapeutic strategies like oocyte donation and cryopreservation offer viable options for many, the most effective approach remains early education and timely intervention. Future research should continue to explore molecular interventions to improve oocyte competence, but at present, female age remains the definitive boundary of human reproductive capacity.

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Supplementary Materials

No supplementary materials are associated with this article.

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