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UNRAVELLING REPRODUCTIVE SENESCENCE: INSIGHTS FROM RAT AND MOUSE MODELS IN AGING RESEARCH

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Abstract: Reproductive aging, characterized by the progressive decline in ovarian function and hormonal regulation, has been extensively investigated using rodent models, particularly rats and mice. These models have provided crucial insights into the biological, hormonal, neuroendocrine, and molecular mechanisms underlying reproductive senescence. Follicular atresia and reduction in ovarian reserve, coupled with disrupted levels of gonadotropins (FSH, LH) and sex steroids (estrogen, progesterone), have been consistently observed in aging rodents, closely resembling human menopausal transitions. Alterations in the hypothalamic-pituitary-gonadal (HPG) axis, including dysregulated GnRH secretion and age-related changes in kisspeptin and neurokinin B signaling, have further clarified the central neuroendocrine control of fertility loss. Genetic studies using knockout and transgenic mice have revealed key molecular players in reproductive aging, including hormone receptors and senescence markers. Environmental factors such as diet, stress, and endocrine disruptors have also been explored using rodent models to assess intervention strategies. Despite species-specific limitations, rodent models remain indispensable for bridging basic science with translational applications. The integration of omics technologies, advanced imaging, and artificial intelligence promises to refine these models further, enhancing their relevance for human reproductive health research and potential therapeutic development.

Keywords: **Reproductive aging, Rodent models, Ovarian reserve, HPG axis, Hormonal regulation, Transgenic mice**

1. Introduction

Reproductive aging is a complex biological process characterized by a gradual decline in fertility and reproductive hormone production, ultimately leading to reproductive senescence. In females, this process encompasses changes in ovarian function, menstrual or estrous cyclicity, and endocrine signalling. Understanding the mechanisms underlying reproductive aging is essential for developing interventions to address age-related fertility decline, menopause-associated health issues, and associated systemic disorders such as osteoporosis and cardiovascular disease (Mayo et al., 2020).

Rodents, particularly rats (*Rattus norvegicus*) and mice (*Mus musculus*), have emerged as indispensable models in reproductive aging research due to their well-characterized genetics, short reproductive cycles, and relative ease of handling. These models closely mimic several aspects of human reproductive aging, including hormonal changes, follicular depletion, and alterations in neuroendocrine regulation (Nelson et al., 1992; Wise et al., 2002). Additionally, the use of genetically modified mice has allowed for targeted investigations into the roles of specific genes and pathways involved in reproductive decline (Lubahn et al., 2014).

The rat model has been extensively used to study the perimenopausal transition, especially the Long-Evans and Sprague-Dawley strains, which exhibit gradual ovarian aging similar to humans (Finch, 2014). Mice, particularly C57BL/6, provide valuable insights into the genetic and molecular aspects of reproductive aging, with studies often focusing on ovarian reserve, hypothalamic-pituitary-gonadal (HPG) axis regulation, and associated metabolic changes (Liu & Tsai, 2021).

The relevance of these rodent models lies not only in their physiological similarities to humans in reproductive decline but also in their utility for longitudinal and interventional studies. Given ethical constraints and logistical limitations of human reproductive research, rodents offer a practical and ethically viable alternative to study age-related reproductive changes, therapeutic targets, and underlying molecular mechanisms (Bellino & Wise, 2003).

This review aims to synthesize current knowledge on the use of rats and mice in reproductive aging studies, highlighting their contributions to the understanding of ovarian senescence, hormonal regulation, and neuroendocrine alterations, while also discussing the limitations and translational relevance of these models.

2. Overview of Reproductive Aging

Reproductive aging has been recognized as a progressive, physiological decline in reproductive function, largely governed by ovarian follicle depletion and endocrine changes. In females, the process has been characterized by a reduction in both the quantity and quality of oocytes, altered hormonal rhythms, and eventual cessation of cyclic reproductive activity (Mayo et al., 2020).

This transition has been marked by irregularity in estrous or menstrual cycles, diminished responsiveness of the hypothalamic-pituitary-gonadal (HPG) axis, and depletion of ovarian follicles (Finch, 2014). The most evident indicator of reproductive aging in females has been menopause in humans and persistent estrus or acyclicity in rodents (Nelson et al., 1992). These stages have been accompanied by increased follicle-stimulating hormone (FSH) levels, reduced estradiol secretion, and disrupted gonadotropin feedback loops (Wise et al., 2002).

In rodent models, reproductive senescence has been observed without a complete cessation of hormonal activity, but with prolonged anovulatory cycles and irregular hormonal patterns (Bellino & Wise, 2003). Ovarian follicular atresia has been identified as a central mechanism contributing to reproductive aging, with accelerated loss of primordial follicles having been observed in aging rodents (Liu & Tsai, 2021).

Additionally, neuroendocrine aging has been implicated in the dysregulation of GnRH pulsatility and altered hypothalamic responsiveness to steroid feedback (Mobbs et al., 2005). The deterioration of central regulation, combined with peripheral ovarian failure, has been considered fundamental in the overall reproductive aging process. Collectively, these physiological changes have been documented as early indicators of systemic aging, influencing broader aspects of health such as metabolism, cognition, and cardiovascular function (Morrison et al., 2006).

2.1. Definition and key physiological markers

Reproductive aging has been defined as the progressive decline in reproductive function that occurs as an organism ages, eventually leading to reproductive senescence and infertility. In females, it has been characterized by a depletion of ovarian follicles, irregularities in estrous or menstrual cycles, and diminished secretion of key reproductive hormones such as estradiol, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) (Mason et al., 2009; Gore et al., 2011).

The onset of reproductive aging has been marked by subtle neuroendocrine changes that impair hypothalamic-pituitary-gonadal (HPG) axis regulation, often observed before the complete cessation of reproductive capacity. In rodent models, this process has typically been identified through irregular or prolonged estrous cycles, decreased fertility, and histological evidence of follicular atresia in the ovaries (Nelson et al., 1981; Wise et al., 2002). Vaginal cytology has frequently been used to monitor estrous cyclicity, with persistent diestrus or estrus phases indicating a disrupted cycle (Huang et al., 2021).

Additional physiological markers that have been associated with reproductive aging included altered levels of anti-Müllerian hormone (AMH), a reliable indicator of ovarian reserve, and reduced responsiveness to gonadotropins (Broer et al., 2014). Furthermore, elevated gonadotropin levels—particularly FSH—alongside decreased estradiol concentrations, have often been recorded as classic endocrine signatures of reproductive aging in both rodents and humans (Hall, 2007; Finch, 2014).

These physiological markers have not only served to define reproductive aging in experimental studies but have also facilitated the evaluation of therapeutic interventions aimed at delaying or mitigating the effects of reproductive senescence.

2.2. Differences between chronological and reproductive aging

Chronological aging has been defined as the passage of time marked by an individual's increasing age in years, whereas reproductive aging has been characterized by the functional decline of the reproductive system, independent of chronological age (Finch, 2014). While chronological aging affects all body systems uniformly, reproductive aging has been observed to occur earlier and more abruptly, particularly in females (Mayo et al., 2020).

Reproductive aging has been associated with the depletion of the ovarian follicle pool, reduced oocyte quality, and irregular hormonal patterns, which have not necessarily aligned with the individual's overall chronological health status (Nelson et al., 1992). In contrast, individuals of the same chronological age have exhibited

considerable variability in reproductive function, indicating that reproductive aging has not been solely dictated by chronological factors (Broekmans et al., 2009).
Moreover, chronological aging has typically been measured by lifespan, whereas reproductive aging has been measured by parameters such as the onset of irregular cycles, diminished ovarian reserve, or menopause in women and comparable senescence markers in rodent models (Wise et al., 2002).

2.3. Relevance to female health and fertility

Reproductive aging has been recognized as a critical determinant of female health and fertility, having been associated with a natural decline in ovarian reserve, hormonal fluctuations, and eventual cessation of menstruation. This process has been linked to increased risks of infertility, miscarriages, and adverse pregnancy outcomes (Broekmans et al., 2009). Furthermore, the onset of menopause has been found to coincide with heightened susceptibility to age-related conditions such as cardiovascular disease, osteoporosis, and metabolic disorders due to estrogen deficiency (Santoro & Randolph, 2011). The biological mechanisms driving reproductive aging have been investigated extensively using animal models, given their contribution to identifying therapeutic targets and strategies for fertility preservation and hormone replacement therapies (Nelson, 2009). Consequently, understanding reproductive aging has been considered vital for addressing both reproductive and non-reproductive health concerns in aging women.

3. Why Rats and Mice? Advantages of Rodent Models

3.1. Short life span and rapid reproductive cycles

Rodents such as rats and mice have been widely preferred in reproductive aging studies due to their short life span and rapid reproductive cycles, which have allowed researchers to observe the full spectrum of reproductive aging within a manageable timeframe. Mice typically have a life expectancy of 1.5 to 3 years, while rats live around 2 to 3.5 years, making them suitable models for longitudinal studies on reproductive decline (Flurkey et al., 2007). Their estrous cycles, lasting only 4–5 days, have enabled detailed and frequent assessments of hormonal and ovarian changes across aging stages (Nelson et al., 1992).
This accelerated life course has facilitated the identification of age-related reproductive changes that would otherwise take decades to manifest in humans. Furthermore, multiple generations have been monitored within a short duration, offering insights into hereditary and environmental influences on reproductive aging (Finch, 2014). These characteristics have significantly reduced the time and cost associated with aging studies and have contributed to the development of standardized protocols for assessing reproductive senescence in laboratory settings.

3.2. Well-characterized estrous cycles

The estrous cycles of rats and mice have been extensively characterized, making them ideal models for studying reproductive aging. Unlike the human menstrual cycle, the rodent estrous cycle is short—typically lasting 4 to 5 days—and has been divided into four distinct stages: proestrus, estrus, metestrus (or diestrus I), and diestrus (or diestrus II) (Becker et al., 2005). These stages have been identified based on cytological changes in vaginal smears and corresponding hormonal fluctuations, allowing for precise monitoring of reproductive status and hormonal regulation over time. The predictability and reproducibility of these cycles have enabled researchers to track age-related disruptions in ovarian and neuroendocrine function. As rodents aged, the cycles were often prolonged, irregular, or ceased entirely—mirroring aspects of human perimenopause (Nelson et al., 1981). Furthermore, the ability to stage the estrous cycle non-invasively through vaginal cytology has provided a practical and cost-effective method for daily assessment, which has been widely adopted in laboratory studies (Goldman et al., 2007). These well-defined cyclic patterns have facilitated the investigation of reproductive hormones, ovarian follicular dynamics, and hypothalamic-pituitary signalling during the aging process, establishing rodents as foundational models in the field of reproductive senescence.

3.3. Availability of inbred strains and transgenic models

The utility of rats and mice in reproductive aging studies has been significantly enhanced by the availability of well-characterized inbred strains and genetically modified models. Inbred strains such as C57BL/6 mice and Fischer 344 rats have been extensively used due to their genetic uniformity, which has minimized variability in experimental outcomes and allowed for reproducible longitudinal studies of reproductive senescence (Nelson et al., 1992; Carey et al., 1995). These models have been selectively bred to ensure homogeneity across generations,

thereby facilitating the identification of age-related reproductive changes without confounding genetic differences.

Transgenic and knockout models have also been widely developed and utilized to explore specific genes implicated in reproductive aging. For instance, mice lacking estrogen receptor α (ERα) or β (ERβ) have been employed to dissect the roles of estrogen signalling in ovarian and neuroendocrine aging (Lubahn et al., 2014). Similarly, transgenic lines expressing fluorescent markers or reporters under hormone-responsive promoters have been designed to trace cellular changes across the aging reproductive axis (Lee et al., 2012). These advancements have allowed for precise mechanistic investigations that were previously unattainable in larger or less genetically tractable organisms. Thus, the availability of genetically defined rodent models has provided a robust foundation for dissecting the multifaceted mechanisms underlying reproductive aging.

3.4. Ethical and logistical considerations

Rodents such as rats and mice have been widely preferred in reproductive aging research due to their compliance with ethical standards and logistical practicality. Compared to non-human primates or human studies, rodent models have been approved under less restrictive ethical frameworks, as their use involved lower perceived sentience and minimized ethical complexities (Festing & Wilkinson, 2007). Institutional Animal Care and Use Committees (IACUCs) have commonly reviewed and regulated these experiments, ensuring that procedures adhered to the principles of the 3Rs—*Replacement, Reduction, and Refinement* (Russell & Burch, 1959).

Logistically, rodents have been favoured for their small size, ease of housing, rapid breeding cycles, and lower maintenance costs. Large cohorts have been easily maintained under controlled laboratory conditions, allowing for long-term, reproducible, and high-throughput studies on aging and reproductive decline (van der Worp et al., 2010). Moreover, their short life spans have enabled the observation of age-related changes within a manageable research timeline, a feature critical for studies on reproductive senescence.

The ethical acceptability, coupled with practical advantages, has positioned rats and mice as indispensable tools in the field of reproductive aging research, enabling both mechanistic understanding and preclinical evaluation of therapeutic strategies.

4. Ovarian Aging in Rodents

Ovarian aging in rodents has been widely utilized as a model to study the decline in reproductive capacity that parallels the human menopausal transition. In rats and mice, reproductive senescence has been characterized by a progressive depletion of the ovarian follicular pool, leading to irregular estrous cycles and eventual acyclicity (Nelson et al., 1992). This depletion has been associated with increased follicular atresia and a reduced number of primordial and antral follicles, which mirrored the pattern observed in aging women (Mason et al., 2009).

Histological evaluations of rodent ovaries have demonstrated degenerative changes including interstitial gland hypertrophy, stromal fibrosis, and luteinized unruptured follicles, particularly in middle-aged females (Hirshfield, 1991). The ovarian reserve has been significantly diminished by midlife, which has been marked by alterations in the responsiveness of ovarian follicles to gonadotropins (Felicio et al., 1983).

Hormonal profiling in aging rodents has revealed elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), coupled with diminished estradiol production—reflecting a dysregulated hypothalamic-pituitary-gonadal (HPG) axis similar to that of perimenopausal women (Wise et al., 2002). These endocrine changes have been linked to the diminished functionality of granulosa cells and impaired steroidogenic activity (Bellino & Wise, 2003).

Furthermore, molecular studies have identified decreased expression of anti-Müllerian hormone (AMH) and other ovarian reserve markers in aged rodent ovaries, which have been proposed as reliable biomarkers for reproductive aging (Kano et al., 2017). The aging ovary has also been shown to accumulate oxidative stress and mitochondrial dysfunction, contributing to compromised oocyte quality and fertility potential (Lim & Luderer, 2011).

Collectively, these findings have confirmed that ovarian aging in rodents shares multiple phenotypic and molecular hallmarks with human reproductive aging, thereby validating the use of rats and mice as effective models in aging studies.

4.1. Follicular atresia and decline in ovarian reserve

Follicular atresia has been recognized as a key biological process responsible for the depletion of the ovarian follicle pool during aging. In rats and mice, this process has been observed to begin early in life, with a continuous and accelerated loss of primordial and growing follicles over time (Tilly, 2001). The initial endowment of follicles, established during foetal or early postnatal life, has been progressively diminished due to apoptosis-driven follicular atresia, particularly in pre-antral and antral follicles (Hsueh et al., 1994). With aging, the rate of follicular loss has been increased, and the ovarian reserve has been significantly reduced, ultimately leading to

reproductive senescence. Histological and hormonal studies conducted in rodents have confirmed that the decline in follicle number has been accompanied by reduced estrogen and inhibin levels, contributing to elevated gonadotropin (FSH and LH) concentrations as compensatory responses (Wang et al., 2021).
These findings in rodent models have mirrored the patterns of ovarian aging observed in women and have provided crucial insights into the timing and mechanisms of reproductive decline.

4.2. Changes in hormone levels

During reproductive aging in rats and mice, significant hormonal alterations have been observed, reflecting declining ovarian function. As ovarian follicles have undergone atresia and the ovarian reserve has diminished, circulating levels of estrogen and progesterone have been markedly reduced (Nelson et al., 1982). This reduction in steroid hormone production has disrupted the normal feedback mechanisms within the hypothalamic-pituitary-gonadal (HPG) axis. In response to reduced estrogen and inhibin secretion, levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) have been elevated, a pattern also documented in aging human females during perimenopause and menopause (Wise et al., 2002). These elevated gonadotropins have been associated with irregular estrous cycles and eventual anovulation in aged rodents (Finch & Felicio, 1984).
The hormonal profile characterized by low estrogen and progesterone and high FSH and LH has been commonly used as an endocrine signature of reproductive senescence in laboratory rodents, making them valuable models for studying menopause-related endocrine transitions.

4.3. Comparison with human ovarian aging

Ovarian aging in rodents and humans has shared several physiological and endocrine features, although distinct differences in cycle type and reproductive lifespan have been observed. In both species, follicular depletion, hormonal dysregulation, and reproductive senescence have marked the transition from fertility to infertility (Woodruff & Walker, 2008). Rodents have exhibited short, polyestrous cycles, whereas human females have undergone monthly menstrual cycles. Despite this difference, both systems have experienced declining estrogen and progesterone production with age and increased gonadotropin (FSH, LH) levels due to reduced negative feedback from the ovary (Felicio et al., 1983; Wise et al., 2002).
Rodent models have been used extensively to simulate perimenopause and menopause-like states, although they do not undergo complete ovarian follicle depletion as humans do. Instead, aged rodents have retained some ovarian follicles and do not experience a true menopause, but rather enter an estropause, a state of acyclicity and hormonal imbalance (Finch, 2014). Still, the parallels in neuroendocrine aging and ovarian hormone dynamics have made rodents suitable models for investigating therapeutic interventions relevant to human reproductive aging.

Table 1. Comparison of Ovarian Aging in Rodents and Humans

Feature	Rodents (Rats/Mice)	Humans
Cycle type	Estrous (4–5 days, polyestrous)	Menstrual (approx. 28 days, monthly)
Menopause equivalent	Estropause (persistent estrus/diestrus)	Menopause (complete follicle depletion)
Hormonal change	↓ Estrogen, ↓ Progesterone, ↑ FSH/LH	↓ Estrogen, ↓ Progesterone, ↑ FSH/LH
Ovarian follicle depletion	Partial, follicles remain in old age	Nearly complete at menopause
Neuroendocrine involvement	Age-related GnRH, kisspeptin disruption	Similar hypothalamic-pituitary changes
Research value	Mechanistic and preclinical modelling	Clinical observation and therapeutic targets

5. Neuroendocrine Regulation of Reproductive Aging

5.1. HPG Axis Dysfunction

Reproductive aging has been increasingly linked to dysfunction within the hypothalamic-pituitary-gonadal (HPG) axis, a central regulatory system that coordinates reproductive hormone production and release. In aging rodents and humans, diminished ovarian steroid feedback has been observed to disrupt the pulsatile nature of gonadotropin-releasing hormone (GnRH) secretion, contributing to irregular estrous or menstrual cycles (Gore et al., 2000). The pituitary responsiveness to GnRH has remained relatively intact with age, suggesting that primary neuroendocrine alterations originate in the hypothalamus (Downs & Wise, 2009).

5.2. Alterations in GnRH Secretion and Feedback Mechanisms

With advancing age, both the frequency and amplitude of GnRH pulses have been altered, particularly due to decreased negative feedback from estradiol and inhibin. This has led to increased secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Rehman et al., 2021). Additionally, increased GnRH mRNA

expression and disrupted feedback sensitivity to estrogen have been reported in aged female rats, highlighting the central role of GnRH neuronal regulation in reproductive senescence (Helena et al., 2006).

5.3. Age-Related Changes in Kisspeptin and Neurokinin B Systems

Kisspeptin and neurokinin B (NKB) neurons in the hypothalamic arcuate nucleus (ARC) have been identified as key modulators of GnRH secretion. Age-associated declines in kisspeptin expression have been documented in both rodents and primates, impairing the excitatory input to GnRH neurons (Rance et al., 2009). Similarly, dysregulation of the neurokinin B/NK3 receptor pathway has been implicated in the attenuation of GnRH/LH surges during aging (Yang et al., 2018). These alterations have disrupted the normal reproductive hormone rhythms and have contributed to the decline in fertility with age.

Table 2. Neuroendocrine Changes During Reproductive Aging

Neuroendocrine Component	Age-Related Change Observed	Model Organism	Reference
HPG Axis	Dysregulated GnRH release and LH/FSH elevation	Rats, Humans	Gore et al., 2000
GnRH Pulsatility and Feedback	Altered pulse frequency and reduced estrogen feedback	Rats	Helena et al., 2006
Kisspeptin Neurons (ARC)	Decreased kisspeptin expression in aging	Rodents, Primates	Rance et al., 2009
Neurokinin B / NK3R Pathway	Impaired LH surge and hypothalamic signaling	Rats	Yang et al., 2018
Pituitary Gonadotropin Response	Preserved response despite hypothalamic decline	Mice	Downs & Wise, 2009

6. Genetic and Molecular Insights from Mouse Models

6.1. Role of Gene Knockouts and Transgenic Mice

Gene knockout and transgenic mouse models have been extensively used to unravel the genetic mechanisms underlying reproductive aging. Deletion of specific genes involved in hormone signalling, folliculogenesis, and oocyte maturation has enabled researchers to simulate age-related infertility and menopause-like states in mice. For instance, knockout of the *Gdf9* (growth differentiation factor 9) gene has resulted in impaired follicular development and premature ovarian failure (Dong et al., 1996). Likewise, *Foxo3a*-deficient mice have displayed accelerated primordial follicle activation, mimicking early depletion of the ovarian reserve (Castrillon et al., 2003).

Transgenic mice overexpressing or lacking components of the hypothalamic-pituitary-gonadal (HPG) axis, including *Kiss1*, *Gnrh*, and *Fshr*, have helped delineate their critical roles in reproductive lifespan regulation (Seminara et al., 2003).

6.2. Studies on Estrogen and Progesterone Receptor Pathways

Estrogen and progesterone signalling pathways have been shown to play crucial roles in regulating the reproductive axis and uterine and ovarian function. Studies using estrogen receptor alpha (ERα) and progesterone receptor (PR) knockout mice have demonstrated infertility, abnormal folliculogenesis, and disrupted luteinization, underscoring their necessity for reproductive competency (Lubahn et al., 1993; Lydon et al., 1995).

Aged ERα-deficient mice have exhibited altered feedback responses to gonadotropins and loss of estrous cyclicity, mirroring neuroendocrine dysregulation seen in human menopausal transition. Similarly, PR-null mice have been shown to lack the ability to ovulate due to disrupted LH-induced follicular rupture (Lydon et al., 1995).

6.3. Molecular Markers of Reproductive Senescence

At the molecular level, several markers of reproductive aging have been identified in mice, including decreased expression of anti-Müllerian hormone (AMH), inhibin B, and GDF9, as well as increased oxidative stress markers such as 8-OHdG and lipid peroxides (Tatone et al., 2008). Declines in mitochondrial function and increased DNA damage markers in oocytes and granulosa cells have also been documented in aged mice, supporting the idea that molecular deterioration contributes to reproductive decline (Tilly & Sinclair, 2013).

7. Environmental and Lifestyle Influences

7.1. Impact of Diet, Stress, and Endocrine Disruptors in Rodents

Environmental and lifestyle factors have been recognized as critical modulators of reproductive aging. In rodent models, dietary composition, chronic stress, and exposure to endocrine-disrupting chemicals (EDCs) have significantly influenced the onset and progression of ovarian senescence.

High-fat and calorie-dense diets have been shown to accelerate reproductive aging in mice by promoting metabolic disturbances, oxidative stress, and inflammation, leading to a reduction in ovarian follicle count and hormonal imbalance (Minge et al., 2008). Caloric restriction, in contrast, has extended reproductive lifespan by preserving follicular reserve and reducing DNA damage in oocytes (Selesniemi et al., 2008).

Psychological and physical stressors have induced disruptions in the hypothalamic–pituitary–gonadal (HPG) axis, resulting in irregular estrous cycles and impaired ovarian function in aged female rats (Kinsey-Jones et al., 2009). Glucocorticoid excess has been associated with decreased gonadotropin secretion and suppressed ovulatory activity.

Exposure to endocrine disruptors such as bisphenol A (BPA) and phthalates has caused premature ovarian insufficiency and altered hormone receptor expression in rodents. Perinatal or chronic exposure to BPA disrupted estrous cyclicity, reduced ovarian follicle numbers, and altered serum estradiol levels (Peretz et al., 2011).

7.2. Use of Rodent Models in Intervention and Prevention Studies

Rodent models have provided a powerful platform for testing interventions aimed at preventing or reversing reproductive aging. Dietary interventions, such as resveratrol supplementation, have improved mitochondrial activity and delayed ovarian aging (Luo et al., 2012). Antioxidant treatments (e.g., melatonin or coenzyme Q10) have been shown to preserve follicular integrity and improve oocyte quality in aged mice (Tamura et al., 2008). Hormonal therapies, including dehydroepiandrosterone (DHEA) and gonadotropin-releasing hormone (GnRH) agonists, have also been evaluated to restore hormonal balance and improve ovarian outcomes (Zhao et al., 2010). These preclinical rodent studies have guided potential therapeutic strategies in humans.

Table 3. Environmental and Lifestyle Factors in Rodent Reproductive Aging

Factor	Observed Effects in Rodents	Key References
High-fat diet	Accelerated follicular depletion, hormonal imbalance	Minge et al., 2008
Caloric restriction	Preserved ovarian reserve, delayed aging	Selesniemi et al., 2008
Chronic stress	Disrupted HPG axis, reduced fertility	Kinsey-Jones et al., 2009
BPA exposure	Irregular cycles, reduced follicle count	Peretz et al., 2011
Resveratrol	Improved mitochondrial function, delayed ovarian aging	Luo et al., 2012
Melatonin	Reduced oxidative damage, improved oocyte quality	Tamura et al., 2008
DHEA supplementation	Restored hormonal profile, enhanced folliculogenesis	Zhao et al., 2010

8. Limitations and Translational Challenges

8.1. Differences Between Rodent and Human Reproductive Physiology

Although rodent models have provided significant insights into reproductive aging, important species-specific physiological differences limit direct translation to human conditions. Mice and rats undergo estrous cycles, which last 4–5 days, unlike the monthly menstrual cycle in women. Moreover, rodents typically experience reproductive senescence without complete follicular depletion, whereas human females undergo menopause due to exhaustion of the ovarian reserve (Kermath et al., 2023).

Rodents exhibit continuous folliculogenesis and ovulation until late life, often entering an anovulatory state due to hypothalamic-pituitary changes, rather than ovarian failure (Nilsson et al., 2018). In contrast, in humans, ovarian aging is driven primarily by the decline in follicle number and quality. Additionally, hormonal profiles during aging differ in magnitude and pattern, particularly with respect to FSH and estrogen dynamics.

8.2. Strain-Specific Variations and Inconsistencies

Rodent strain-specific genetic and phenotypic variations have posed challenges in experimental consistency. For instance, C57BL/6 and BALB/c mice show different rates of ovarian follicular depletion, reproductive lifespan, and hormone levels (Byers et al., 2020). Such differences have led to inconsistent results in reproductive aging studies and complicate the generalization of findings. Furthermore, transgenic and knockout models have sometimes introduced off-target effects or strain-specific phenotypes, making it difficult to discern whether observed reproductive changes were due to aging or genetic manipulation (Flaws et al., 2021). These issues necessitate the careful selection of strains and appropriate controls in experimental design.

8.3. Ethical and Reproducibility Concerns in Animal Research

Ethical concerns regarding the use of animals in reproductive studies have intensified, especially when considering long-term or invasive protocols. The use of aged animals also raises welfare issues due to increased susceptibility to disease and stress (National Academies of Sciences, Engineering, and Medicine, 2022). Many institutions now require refinement, reduction, and replacement (3Rs) in animal research practices, which can limit the scope of longitudinal reproductive studies. Moreover, reproducibility issues have affected the reliability of rodent studies. Variability in housing conditions, diet, handling, and estrous cycle monitoring has contributed to irreproducible outcomes, undermining confidence in data translation (Voelkl et al., 2020). Inadequate reporting standards for experimental protocols further exacerbate this problem.

Table 4. Key Translational Challenges in Rodent Reproductive Aging Studies

Challenge	Implication	Reference
Estrous vs. menstrual cycle	Limits direct hormonal comparisons	Kermath et al., 2023
Incomplete ovarian depletion	Limits modelling of human menopause	Nilsson et al., 2018
Strain-specific differences	Reduces consistency across studies	Byers et al., 2020
Transgenic off-target effects	Confounds results in molecular studies	Flaws et al., 2021
Ethical restrictions on aging studies	Limits duration and invasiveness of experiments	NASEM, 2022
Reproducibility variability	Decreases reliability and data translation	Voelkl et al., 2020

9. Future Directions

9.1. Integration of Omics Technologies in Rodent Studies

The integration of omics technologies, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics, has been increasingly adopted to unravel the complex biological pathways involved in reproductive aging. These approaches have allowed researchers to identify age-associated molecular signatures in ovarian tissue, hypothalamic regions, and serum biomarkers (Zhang et al., 2021). In particular, single-cell RNA sequencing (scRNA-seq) has enabled the identification of heterogeneous cell populations and gene expression changes in aging ovaries (Zhao et al., 2020).

Moreover, epigenomic profiling in rodents has revealed age-related alterations in DNA methylation and histone modification patterns, which may serve as early indicators of reproductive decline. These findings have paved the way for the identification of potential therapeutic targets for delaying or mitigating reproductive senescence.

9.2. Development of More Humanized Rodent Models

Traditional rodent models have often lacked the physiological complexity of human reproductive aging, necessitating the development of humanized models. These include transgenic mice carrying human hormone receptor genes, xenograft models with human ovarian tissue, and CRISPR-based modifications that mimic human-specific mutations linked to menopause and ovarian dysfunction (Brady et al., 2022).

Recent efforts have also involved using immunodeficient mice to support human ovarian tissue engraftment, allowing longitudinal studies of follicular development and hormonal responses in vivo (Geens et al., 2020). Such models have improved the translational value of rodent research and offer new platforms for testing reproductive aging interventions, including hormone replacement therapy and regenerative medicine.

9.3. Role of AI and Imaging in Tracking Reproductive Aging

The application of artificial intelligence (AI), machine learning (ML), and advanced imaging technologies is transforming the way reproductive aging is assessed in rodents. AI-based image analysis can quantify follicle number, size, and vascularization from ovarian histology and ultrasound data with high precision and reproducibility (Dong et al., 2023). Machine learning algorithms have also been trained to predict reproductive age based on multi-parameter datasets, including hormonal levels, gene expression, and behavioural metrics.

In addition, non-invasive imaging techniques such as high-resolution ultrasound and MRI have been utilized to longitudinally monitor ovarian and uterine changes, minimizing the need for euthanasia and repeated sampling (Khan et al., 2019). These tools enhance both the efficiency and ethical compliance of reproductive aging studies in rodents.

Table 5. Emerging Directions in Rodent Reproductive Aging Research

Future Direction	Application	Reference
Omics technologies	Identification of molecular markers and therapeutic targets	Zhang et al., 2021; Zhao et al., 2020
Humanized rodent models	Enhanced translational accuracy	Brady et al., 2022; Geens et al., 2020
AI and advanced imaging	Non-invasive tracking and predictive modelling	Dong et al., 2023; Khan et al., 2019

10. Conclusion

Rodent models, particularly rats and mice, have played a pivotal role in advancing our understanding of reproductive aging. This review highlighted multiple dimensions of how rodent studies have contributed to unravelling the complex biological, hormonal, genetic, and environmental factors that drive age-related reproductive decline.

Key findings from rodent studies have shown that follicular atresia and declining ovarian reserve occurred progressively with age, mirroring human reproductive aging patterns. Hormonal dysregulation—marked by altered levels of FSH, LH, estrogen, and progesterone—had been well-documented and closely paralleled changes observed in menopausal transition. Dysfunctions in the hypothalamic-pituitary-gonadal (HPG) axis, particularly through disrupted GnRH signalling and kisspeptin/neurokinin B pathways, have been critical in understanding central neuroendocrine mechanisms underlying reproductive senescence.

Genetic and molecular insights derived from knockout and transgenic mouse models have elucidated the roles of hormone receptors and senescence markers. Additionally, environmental and lifestyle variables—such as dietary restriction, stress exposure, and endocrine disruptors—have been systematically tested in rodents, supporting their value for both mechanistic discovery and intervention trials.

Despite the translational challenges posed by interspecies differences, rodent models remain indispensable due to their short reproductive lifespan, genetic manipulability, and ethical feasibility. Recent integration of omics technologies, humanized genetic modifications, and AI-enhanced imaging tools has further enhanced the depth and translational relevance of rodent-based reproductive aging research.

In conclusion, rodent models have not only clarified fundamental mechanisms of reproductive aging but also served as vital platforms for testing potential therapeutic approaches. Bridging these insights with clinical applications in women's health will require continued innovation in model refinement, data integration, and cross-species validation, ultimately contributing to improved management of reproductive aging and menopausal health.

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