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Reproductive aging in farm animals: Impacts on fertility and strategies for mitigation: A narrative review

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ABSTRACT

The livestock sector is a vital component of India's agricultural economy, providing essential support to rural communities and ensuring food security. Efficient reproductive performance is critical to sustaining livestock productivity, yet age-related declines in both male and female fertility pose significant challenges. The current review highlights that male reproductive efficiency is closely tied to semen quality, which deteriorates with age due to oxidative stress, leading to reduced fertilizing capacity and embryonic developmental potential. Similarly, female reproductive longevity is predominantly influenced by ovarian health, which declines with age due to diminished oocyte quality and quantity. This decline is exacerbated by oxidative stress and mitochondrial dysfunction, leading to reproductive senescence and reduced offspring viability. Understanding the mechanisms of reproductive aging and developing strategies to mitigate its effects are crucial for enhancing livestock productivity and sustaining the agrarian economy.

KEYWORDS: Sperm; Oocyte; Oxidative stress; Mitochondrial dysfunction; Reactive oxygen species; Anti-oxidants

1. Introduction

The livestock sector is a cornerstone of India's agricultural economy, providing vital livelihood support to rural populations and significantly contributing to food and nutritional security. Efficient reproductive performance is central to successful livestock production, requiring animals to reach sexual maturity, undergo regular estrous cycles, ovulate, and be mated or artificially inseminated at the appropriate time. The availability of frozen semen has increased demand for superior breeding males, particularly buffalo bulls[1].

Reproductive processes in livestock are categorized into distinct

stages: sex differentiation, sexual maturation, germ cell development (spermatogenesis and oogenesis), mating, fertilization, pregnancy, and parturition. Conception rates using frozen semen are directly influenced by semen characteristics, which in turn are affected by environmental factors, age, season, breed, and genetics[2,3].

While male animals consistently produce sperm throughout their lives, female fertility typically declines after five years of age, leading to increased incidences of abortion, reduced conception rates, and accelerated reproductive senescence, often due to gamete abnormalities. The age at mating is critical in determining reproductive performance. Bulls exhibit peak fertility between 2-4 years, with a noticeable decline after 5-6 years. Similarly, goats reach their reproductive prime between 5-7 years of age[4]. For Sahiwal bulls, optimal semen quality is maintained up to 5 years[5]. In rams, older individuals (5-6 years) may have a greater scrotal circumference but show reduced semen quality compared to younger rams (2.5-3 years)[6].

Female reproductive longevity is primarily influenced by ovarian health, with accelerated ovarian aging leading to diminished fertility or potential infertility. In female animal, fertility increases up to the age of 4 years, levels off till 6 years of age, and gradually decreases afterwards[7]. Ovarian aging is marked by a decline in

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oocyte quality and a reduction in the number of follicles and oocytes. Advanced paternal age also impacts reproductive efficiency and offspring health, though this has been less studied. Increased paternal age is associated with reduced fertility, poorer offspring health, and diminished functionality of the reproductive system. In assisted reproductive techniques like *in vitro* fertilization and intrauterine insemination, both implantation and pregnancy rates decrease with increasing paternal age, and there is a higher risk of embryonic death or abortion above 8 years of age in bovines[8–10].

2. Age-related fertility decline and oxidative stress

Age-related fertility decline is closely linked to the deterioration of gamete quality, leading to infertility and adverse effects on offspring[11,12]. Conventional semen quality parameters, such as count, motility, and morphology, deteriorate with age. Detailed analysis using computer-assisted sperm analysis (CASA) reveals significant declines in sperm motility[13,14]. Age also affects sperm ultrastructure and proteome, impacting motility and fertilization potential[15,16].

Oxidative stress plays a crucial role in age-related male fertility decline, consistent with the free radical theory of aging[17]. Aging reduces the body's capacity to prevent, detect, and repair cellular damage from free radicals, leading to oxidative stress and physiological deterioration[18]. The accumulation of oxidative damage in proteins, lipids, and nucleic acids compromises cellular functions, resulting in aging and impaired fertility. In male fertility, oxidative stress due to reduced antioxidant protection and excessive reactive oxygen species (ROS) generation significantly contributes to age-related infertility[19,20].

Oxidative stress leads to the loss of sperm motility, DNA damage, increased ROS generation, and impaired sperm chromatin protamination, as observed in male mice lacking antioxidant enzymes[21]. Age-dependent increases in sperm lipid peroxidation and DNA fragmentation further exacerbate fertility decline[22]. Advanced paternal age contributes to oxidative stress in the germ line, leading to oxidative DNA damage across the genome, exacerbated by decreased DNA repair capacity and reduced antioxidant protection[23–25].

Oxidative stress also affects the functionality of Sertoli and Leydig cells, with mitochondrial oxidative stress being a significant contributor in aging Leydig cells[26]. Supplementation with antioxidants like coenzyme Q10, alpha-lipoic acid, selenium, taurine, or soy isoflavones has shown positive effects on semen quality and reproductive performance in aged animals[27–30]. Cerium dioxide nanoparticles have also been found to mitigate aging effects on reproductive systems, enhancing testosterone levels and spermatogenesis quality[31].

Age-related effects are not limited to bulls; other species also exhibit reduced fertility with aging. For example, in boars, older sperm result in lower fertilization rates, reduced pregnancy rates, and decreased embryo survival[32]. The functionality of female gametes is heavily reliant on mitochondria, which are crucial for adenosine triphosphate (ATP) production, cytoplasmic and nuclear maturation, spindle formation, and polar body extrusion[33,34]. Inefficient mitochondrial bioenergetics can impair oocyte maturation, chromosomal distribution, and embryo development, with oxidative stress being a central factor in reproductive aging[35,36].

In the reproductive system, ROS play a dual role, regulating normal processes like folliculogenesis, meiosis, and ovulation, but causing oxidative stress and reproductive diseases like endometriosis when in excess[37–39].

Mitochondria are the primary source of ROS, and the accumulation of oxidative damage contributes to aging and its associated reproductive decline[40]. Excessive ROS lead to mutations in mtDNA, impairing ATP production and compromising sperm motility[41]. ROS also cause DNA strand breaks and telomere damage, leading to genomic instability[42]. The excessive accumulation of ROS results in oxidative damage to macromolecules, cells, and overall function of organs[43].

Mitochondria are crucial regulators of structure formation, metabolic activity, and oocyte function[44]. The oocyte contains a high number of mitochondria, essential for its quality and subsequent fertilization and embryo development[45]. Mitochondrial dysfunction, often linked to aging, can lead to heightened ROS levels and compromised reproductive outcomes[46,47].

Elevated ROS levels contribute to oocyte impairment, leading to mitochondrial dysfunction, telomere shortening, and abnormal meiotic division, resulting in reduced egg quality and increased chromosomal errors[48–50]. In the absence of antioxidant genes, elevated ROS can disrupt follicular growth and cause embryonic toxicity and teratogenic effects in various mammals[51,52]. The complex interplay between age-related fertility decline and oxidative stress, including its effects on gamete quality, and mitochondrial function, is represented in Figure 1.

3. Epigenetic changes in aged gametes

The epigenome, which consists of DNA methylation, histone modifications, and various RNA species, plays a crucial role in regulating gene expression and influencing phenotype. These epigenetic marks are dynamic and can be inherited by the embryo post-fertilization, thereby affecting the subsequent development and health of the fetus[53]. The formation of the epigenome involves multiple processes, such as DNA methylation, chromatin remodeling, histone modifications, and the regulation of noncoding RNAs, as well as maintaining genome stability[54]. Epigenetic

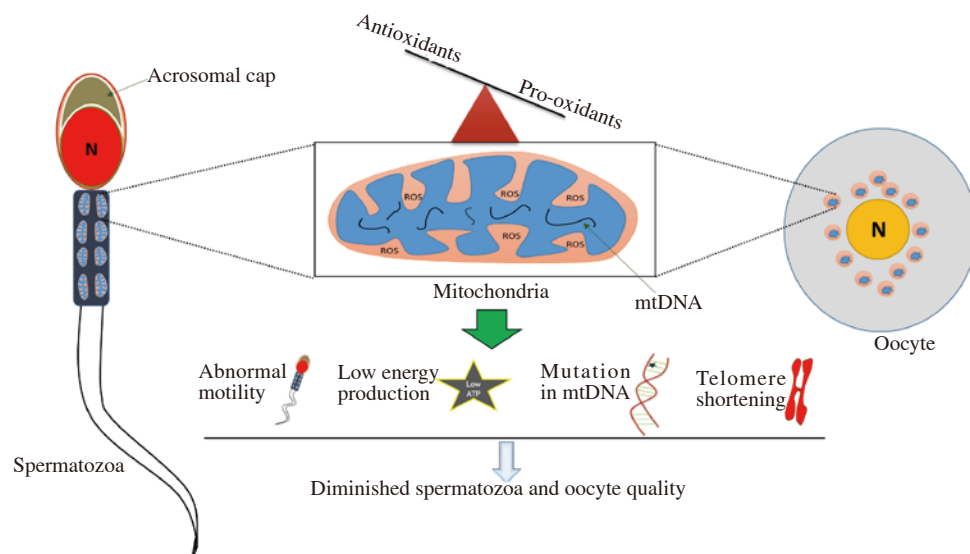


Figure 1. The age-related decline in sperm and oocyte quality, largely attributed to oxidative stress and its impact on gamete functionality. N: nucleus, mtDNA: mitochondrial DNA, ROS: reactive oxygen species, ATP: adenosine triphosphate.

mechanisms, including paramutation, imprinting, and gene silencing, are integral in determining cell fate, phenotypic plasticity, and behavior.

Age-related physiological changes in the male reproductive system affecting the testis, seminal vesicles, prostate, and epididymis, also impact the sperm epigenome. Research indicates that aging alters sperm DNA methylation patterns, small non-coding RNAs, and histone modifications, which in turn influence intergenerational and transgenerational epigenetic inheritance[55,56]. Environmental factors, such as extreme temperatures, can exacerbate these effects by inducing heat stress, thereby compromising sperm quality and overall fertility[57–60].

Understanding the sperm epigenome in bovines is essential for improving reproductive outcomes and genetic selection. Identifying epigenetic biomarkers related to sperm quality can aid in selecting superior bulls, thereby enhancing male fertility and the genetic traits of offspring[61]. Additionally, age-related declines in female fertility, associated with reduced ovarian reserve and oocyte function, further highlight the importance of epigenetic factors in reproductive efficiency[62]. Integrating epigenetic insights into breeding programs can therefore help mitigate the age-related changes on livestock productivity.

4. Mitigation strategies

Oxidative stress, driven by the accumulation of ROS, plays a significant role in age-related reproductive decline. Monitoring ROS levels in follicular fluid can serve as a valuable biochemical marker for assessing follicular metabolic age and male infertility. To counteract these effects, dietary modifications and antioxidant

supplementation are potential interventions that can slow down reproductive aging. Herbs and herbal substances, rich in bioactive constituents, protect semen from ROS-induced quality deterioration caused by various stressors[63]. Oral supplementation with herbal mixtures has been shown to improve semen quality and reduce oxidative stress parameters[64]. For example, curcumin supplementation has been associated with improvements in sperm quality, including increases in total sperm count, concentration, and motility, as well as enhancements in total antioxidant capacity, reductions in malondialdehyde levels, and decreases in inflammatory markers like C-reactive protein and tumor necrosis factor (TNF)[65]. Additionally, supplementation with *Murraya koenigii* (curry) and *Aegle marmelos* (bel) may stimulate gonadotropin hormone release from the anterior pituitary, potentially restoring cyclicity in anestrus animals[66]. Antioxidants in these supplements may enhance folliculogenesis by preventing ROS-induced apoptosis of oocytes[67]. Similarly, betaine supplementation has been shown to significantly enhance antioxidant defense mechanisms and accelerate the regeneration of testicular epithelial cells[68]. Melatonin, an indole derivative secreted by the pineal gland[69], effectively scavenges free radicals, including hydroxyl radicals[70,71], stimulates antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx)[72], maintains plasma and mitochondrial membrane integrity[73], and improves semen characteristics, including progressive motility, viability, and sperm concentration[74]. Improved sperm and oocyte quality has also been observed with the supplementation of vitamins C and E, folic acid, and myo-inositol[75]. In addition to these strategies, regular semen evaluations for both breeding males and females can aid in the early detection of reproductive issues, allowing for timely interventions and better fertility management in aging livestock.

5. Conclusions

Reproductive aging in farm animals presents a significant challenge to both fertility and overall livestock productivity. The complex interplay between aging, oxidative stress, and epigenetic changes highlights the intricate nature of reproductive aging. However, understanding these underlying mechanisms opens potential avenues for intervention, such as the use of antioxidants and other strategies to mitigate the adverse effects of aging. While most studies have focused on specific species, there is a lack of comprehensive data across a broader range of livestock. Additionally, the effectiveness of mitigation strategies, including antioxidant supplementation and hormonal therapies, remains inconclusive, with varying results across different environments and animal breeds. Long-term studies are needed to better understand the cumulative effects of oxidative stress on fertility and refine strategies for mitigating reproductive aging. Furthermore, advancements in reproductive technologies may offer additional approaches to counteract the impact of aging on fertility. Continued research is crucial to develop effective management practices that can enhance reproductive longevity and productivity in farm animals.

Conflict of interest statement

The authors declare no competing interests.

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Authors' contributions

Akhter Rasool was responsible for writing, editing, and reviewing the original draft. Sachin reviewed the study's concept and design. Irtiq Manzoor and Akshata Patil contributed to the literature search, writing, and supervision. All authors have read and approved the final version of the manuscript.

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