

Are antioxidants always beneficial in reproduction? Rethinking evidence from animal models

Antioksidanlar üremede her zaman faydalı mıdır? Hayvan modellerinden elde edilen kanıtların yeniden gözden geçirilmesi

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Oxidative stress is widely recognized as a central contributor to reproductive dysfunction, influencing key processes such as gametogenesis, fertilization, and early embryonic development. Consequently, antioxidant supplementation has become a routine strategy in both experimental animal models and clinical reproductive research. However, emerging evidence suggests that this approach may be overly simplistic, as the biological role of reactive oxygen species (ROS) in reproductive systems is far more complex and context-dependent than previously appreciated (1,2). This evolving understanding raises critical concerns regarding the widespread and often uncritical use of antioxidant interventions.

ROS should not be viewed solely as harmful metabolic byproducts; rather, they act as essential signaling mediators in physiological reproductive processes. Controlled ROS levels are required for sperm capacitation, hyperactivation, acrosome reaction, oocyte maturation, and follicular development (3). These processes are tightly regulated through redox-sensitive pathways involving mitochondrial activity, calcium signaling, and kinase-driven cascades (4). Therefore, excessive suppression of ROS through high-dose or prolonged antioxidant exposure may interfere with these finely tuned signaling mechanisms, potentially compromising reproductive competence.

Animal studies provide important insights into this paradox. Antioxidants such as resveratrol, quercetin, melatonin, and N-acetylcysteine have been shown to mitigate oxidative damage in models of reproductive toxicity, including testicular injury, ovarian dysfunction, and follicular atresia (5,6). These protective effects are commonly associated with reduced lipid peroxidation, modulation of apoptotic regulators (e.g., BAX/BCL-2 balance), and activation of cytoprotective pathways such as Nrf2/HO-1 signaling (7). Nevertheless, accumulating evidence also indicates that antioxidant interventions may yield inconsistent or even adverse outcomes, particularly when applied without appropriate consideration of dose, timing, and physiological context (8,9).

Importantly, excessive antioxidant exposure may induce “reductive stress,” a condition characterized by an

imbalance toward an overly reduced intracellular environment. This state can impair mitochondrial respiration, disrupt redox-sensitive transcriptional regulation, and alter apoptosis dynamics, ultimately compromising cellular homeostasis. In reproductive tissues, where tightly regulated apoptosis is essential for follicular selection and spermatogenic quality control, such disturbances may have unintended detrimental effects (10).

A key limitation in the current literature is the lack of methodological standardization. Variability in antioxidant type, dosage, treatment duration, and experimental design hinders the comparability of findings and may contribute to conflicting results. Furthermore, many studies rely predominantly on indirect oxidative stress markers, such as malondialdehyde (MDA), total antioxidant capacity (TAC), or total oxidant status (TOS), without integrating functional reproductive outcomes (e.g., fertilization rate, embryo quality, or sperm motility) or dynamic redox measurements (e.g., real-time intracellular ROS monitoring or redox-sensitive signaling activity). Such approaches risk oversimplifying the intricate balance between ROS generation, antioxidant defense, and cellular adaptation. These considerations challenge the prevailing assumption that reducing oxidative stress uniformly improves reproductive outcomes. Instead, oxidative stress should be viewed as a continuum, where both excessive ROS and insufficient ROS can be detrimental. Maintaining redox balance, rather than indiscriminately suppressing ROS, should therefore be a central objective in reproductive research.

To address these challenges, future animal studies should focus on defining optimal antioxidant dosing strategies and treatment windows based on physiological redox requirements, incorporating multiple complementary biomarkers that reflect both oxidative damage and redox signaling, evaluating potential adverse effects alongside beneficial outcomes, and considering tissue-specific as well as stage-specific redox dynamics within reproductive systems. Such an integrated approach may improve the reproducibility, mechanistic interpretation, and translational relevance of findings in reproductive research. In addition,

biomarker-guided and individualized antioxidant strategies based on the redox status of reproductive tissues may help optimize therapeutic efficacy while minimizing the risk of excessive antioxidant exposure.

In conclusion, while antioxidants remain valuable tools in reproductive research, their application should be guided by a nuanced understanding of redox biology rather than a generalized assumption of benefit. A paradigm shift toward preserving redox equilibrium may not only refine mechanistic insights but also enhance the translational relevance of experimental findings in reproductive science. Future translational studies should also explore biomarker-guided and individualized antioxidant interventions tailored to the physiological redox status of reproductive tissues.

Ethical Approval

This manuscript is a Letter to the Editor and does not involve any human participants, animals, or clinical data. Therefore, ethical approval and informed consent were not required.

Conflict of Interest

The author reports no conflicts of interest related to this study.

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Authors' Contributions

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the author used AI-assisted technologies to improve the language, readability, and clarity of the text. The author subsequently reviewed and edited the content and take full responsibility for the final version of the manuscript.

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