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Oxidative Stress and Molecular Biomarkers of Male Infertility: From Redox Imbalance to Histological Injury

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Narrative Literature Review

Abstract: Roughly one in six couples worldwide struggle with infertility, and a male factor is involved in about half of these cases. A growing body of work points to oxidative stress (OS) - an imbalance between reactive oxygen species (ROS) and the antioxidant systems meant to keep them in check - as one of the main biochemical threads connecting very different risk factors (infection, varicocele, obesity, smoking, environmental toxins) to a single downstream problem: damaged, poorly functioning sperm. This review brings together the histological and biochemical evidence on how oxidative stress injures the male reproductive tract, what molecular biomarkers are currently used to detect it, and how close (or far) this evidence is from being clinically useful. Low, tightly controlled levels of ROS are actually necessary for normal sperm capacitation, the acrosome reaction and fertilization; the problem starts once ROS output outpaces the antioxidant defenses of seminal plasma and sperm cells themselves. When that happens, membrane lipids peroxidize, sperm DNA fragments, and germ cells within the seminiferous epithelium begin to undergo apoptosis - changes that are visible histologically and measurable biochemically through markers such as malondialdehyde, 8-hydroxy-2'-deoxyguanosine, total antioxidant capacity, oxidation-reduction potential and pro-inflammatory cytokines. None of these markers work perfectly on its own, and none has an agreed clinical cut-off yet, which is exactly why they are usually discussed together rather than as a single diagnostic test. This review pulls that picture together and considers what would need to change for oxidative-stress testing to move from a research tool to routine practice.

Keywords: male infertility; oxidative stress; reactive oxygen species; sperm DNA fragmentation; malondialdehyde; 8-OHdG; seminal biomarkers; spermatogenesis; antioxidant therapy

Introduction

A male factor contributes to roughly half of all infertility cases, whether on its own or together with a female-factor diagnosis. What complicates the picture clinically is that a standard semen analysis - concentration, motility, morphology - often comes back "normal" in men who are still struggling to conceive. A large share of these cases end up labeled idiopathic, essentially meaning that routine testing did not find the cause. That gap is one of the main reasons researchers have turned to oxidative stress: it is a mechanism that operates upstream of the numbers a standard spermogram reports.

In simple terms, oxidative stress happens when reactive oxygen species (ROS) are produced faster than the antioxidant systems in seminal plasma and sperm can neutralize them. Mature spermatozoa are especially exposed to this kind of damage - they carry very little cytoplasm (and therefore few antioxidant enzymes) and their membranes are rich in polyunsaturated fatty acids,

which are chemically an easy target for ROS. It would be a mistake, though, to think of ROS as simply "bad": at low, controlled levels they are required for capacitation, hyperactivated motility and the acrosome reaction. So the question is never whether ROS are present, but whether their level is within a range the cell can handle[1-3].

On tissue sections, prolonged oxidative injury within the seminiferous epithelium and epididymal duct shows up as germ-cell apoptosis, disorganized spermatogenic layers and altered epididymal epithelium. On the biochemical side, the same process leaves behind measurable traces - oxidized lipids, oxidized DNA bases, a depleted antioxidant reserve. Connecting these two levels of description is really the point of this review: to summarize what is known about the histological and biochemical mechanisms of oxidative-stress-related male infertility, look critically at the biomarkers currently proposed for its diagnosis, and be honest about how far this field still is from routine clinical use.

Materials and Methods

Study design

This work was designed as a narrative literature review. Its objective was to integrate histological, cellular and biochemical concepts related to oxidative stress in male infertility and to examine the diagnostic value of the biomarkers used to assess it. No original experiments involving human participants, animals, tissue samples or laboratory assays were performed.

Literature search

A literature search was performed using PubMed/MEDLINE and Google Scholar. Search terms included combinations of "oxidative stress", "male infertility", "reactive oxygen species", "sperm DNA fragmentation", "malondialdehyde", "8-hydroxy-2'-deoxyguanosine", "total antioxidant capacity", "seminal biomarkers", "spermatogenesis" and "antioxidant therapy". Priority was given to peer-reviewed publications from 2021-2026, while selected earlier publications were retained when they provided essential mechanistic or conceptual foundations[4-5].

Selection and synthesis

Publications were selected according to their relevance to the mechanisms of ROS generation, histological consequences of oxidative injury in the male reproductive tract, and the diagnostic performance of proposed molecular biomarkers. The literature was synthesized qualitatively rather than pooled quantitatively, and findings were organized around the relationship between redox biochemistry and its histological and clinical manifestations.

Physiological and Pathological Roles of Reactive Oxygen Species

Reactive oxygen species are generated in the male reproductive tract by several sources, including the mitochondrial electron-transport chain of spermatozoa, NADPH oxidase activity of immature germ cells and leukocytes, and xanthine oxidase activity within seminal plasma. At physiological concentrations, ROS act as signaling molecules that regulate tyrosine phosphorylation cascades required for capacitation, hyperactivation and the acrosome reaction, processes that are indispensable for successful fertilization .

The transition from a physiological to a pathological role occurs when ROS production overwhelms local antioxidant defenses, which include superoxide dismutase, catalase, glutathione peroxidase and low-molecular-weight scavengers such as vitamin C, vitamin E and free thiols. Excessive ROS accumulation, referred to as oxidative stress, damages polyunsaturated fatty acids within the sperm plasma membrane through lipid peroxidation, compromises mitochondrial membrane potential, and induces single- and double-strand DNA breaks. These molecular events collectively reduce motility, impair capacitation and diminish fertilizing capacity[6-7].

Recognized clinical sources of excessive ROS production include varicocele, genital tract infection and leukocytospermia, obesity and metabolic syndrome, exposure to tobacco smoke, alcohol and environmental toxicants such as heavy metals, pesticides and bisphenol A, as well as advanced paternal age Because several of these factors coexist in idiopathic infertility, oxidative stress is

increasingly regarded as a convergent pathway through which heterogeneous risk factors produce a common pattern of sperm dysfunction.

Histological Consequences of Oxidative Injury

Within the seminiferous epithelium, sustained oxidative stress is associated with increased apoptosis of germ cells at various stages of spermatogenesis, disruption of Sertoli-cell junctional complexes, and disorganization of the normally ordered spermatogenic layers. Sharma and colleagues emphasize that oxidative stress can shift the balance between apoptosis and autophagy in germ cells, so that either excessive elimination or abnormal survival of damaged cells may occur, both of which compromise spermatogenic efficiency.

Oxidative and inflammatory pathways are closely interconnected in the testicular microenvironment. Pro-inflammatory infiltration and cytokine release can damage the blood-testis barrier, allowing exposure of previously sequestered germ-cell antigens to the immune system and promoting antisperm-antibody formation, which further amplifies local oxidative and inflammatory injury in a self-reinforcing cycle. In the epididymis, oxidative damage to the epithelial lining can impair the maturation environment required for spermatozoa to acquire full motility and fertilizing competence, even when testicular histology remains relatively preserved.

These histological changes are not independent of the biochemical alterations described above; rather, they represent the morphological expression of cumulative lipid, protein and DNA damage at the cellular level, which is why molecular biomarkers of oxidative stress are of direct relevance to understanding tissue-level pathology[8].

Molecular Biomarkers of Oxidative Stress

Lipid peroxidation markers

Malondialdehyde (MDA) is the most widely used marker of lipid peroxidation and reflects oxidative damage to polyunsaturated fatty acids within the sperm membrane; elevated seminal and, in some studies, systemic MDA levels correlate with reduced sperm motility. F2-isoprostanes, generated through non-enzymatic peroxidation of arachidonic acid, are considered more chemically stable than MDA and are being explored as an alternative or complementary lipid-peroxidation marker.

DNA damage markers

8-hydroxy-2'-deoxyguanosine (8-OHdG) is a well-characterized product of ROS-mediated oxidative DNA damage and is used together with the sperm DNA fragmentation index to assess genomic integrity in spermatozoa . Elevated sperm DNA fragmentation has been associated with reduced fertilization rates, impaired embryo development and adverse outcomes in assisted reproduction, which gives this category of biomarkers particular clinical relevance beyond conventional semen parameters .

Total antioxidant capacity and oxidation-reduction potential

Total antioxidant capacity (TAC) provides an integrated measure of the seminal antioxidant reserve, while oxidation-reduction potential (ORP) directly quantifies the balance between oxidant and antioxidant species in a single assay and has been proposed as a practical point-of-care biomarker. Free thiols, a component of the reactive-species interactome, have also been investigated as accessible indicators of local and systemic redox status.

Inflammatory biomarkers and the oxidative-inflammatory cycle

Pro-inflammatory cytokines, including interleukin-6, interleukin-8 and tumor necrosis factor-alpha, are frequently elevated in the seminal plasma of infertile men with leukocytospermia or genital tract infection and correlate with impaired semen parameters [9]. Because inflammation both results from and amplifies oxidative stress, combined assessment of oxidative and inflammatory biomarkers has been proposed to better capture the underlying pathophysiology, particularly in idiopathic cases where a single marker may be insufficient.

Table 1. Conceptual comparison of physiological reactive-oxygen-species activity and

pathological oxidative stress in the male reproductive tract.

Parameter	Physiological ROS activity	Oxidative stress state
ROS concentration	Low, tightly regulated	Excessive, unregulated
Sperm function	Capacitation, acrosome reaction, motility	Impaired motility, reduced fertilizing capacity
Lipid membrane	Structurally intact	Peroxidative damage (elevated MDA)
DNA integrity	Preserved	Fragmentation, elevated 8-OHdG
Antioxidant balance	TAC sufficient to neutralize ROS	TAC depleted, ORP elevated
Germ-cell fate	Normal proliferation and maturation	Apoptosis, abnormal autophagy
Histological picture	Preserved seminiferous epithelium	Epithelial disorganization, germ-cell loss

Diagnostic Significance and Translational Challenges

Despite consistent associations between oxidative biomarkers and impaired semen parameters, clinical translation remains limited by methodological heterogeneity across laboratories, the absence of internationally validated reference thresholds, and variability introduced by sample handling and assay timing. Consequently, oxidative-stress testing is not yet part of standard infertility work-up in most clinical settings, although several authors argue that it should be regarded as a diagnosable and monitorable entity rather than an optional research measure[10].

The clinical response to these findings has also been inconsistent - though not uniformly disappointing. Several recent randomized trials report measurable improvement after a few months of oral antioxidant treatment: in one placebo-controlled trial of 263 men, three months of combined micronutrients and L-carnitine significantly lowered the sperm DNA fragmentation index and improved motility compared with placebo. A separate randomized study in 48 subfertile men found a similar drop in DNA fragmentation and an improved histone-to-protamine ratio after antioxidant supplementation, even though total antioxidant capacity itself did not change significantly between groups - a reminder that clinical improvement and a chosen laboratory marker do not always move together. At the same time, a Cochrane systematic review of antioxidant trials in subfertile men concluded that, while some evidence suggests a benefit for live-birth and pregnancy rates, the overall evidence base is still of low quality, with small trials, inconsistent antioxidant combinations and doses, and a real risk of publication bias. Taken together, this suggests antioxidant therapy is not the disappointment older narratives sometimes describe, but it is also not yet a therapy that can be prescribed uniformly without first confirming that oxidative stress, specifically, is the problem. Empirical supplementation given without that confirmation risks inconsistent results and, in some cases, may even induce reductive stress by suppressing ROS signaling that the cell actually needs. The more defensible path is biomarker-guided: confirm oxidative stress first, then treat it, rather than treating everyone the same way[11].

Result and discussion

Putting the reviewed literature side by side, a fairly consistent picture emerges. Oxidative stress is not a fixed presence-or-absence state but a quantitative imbalance, and the same ROS that are essential for normal sperm function turn damaging once that balance tips. That imbalance leaves a histological fingerprint - germ-cell apoptosis, disorganized seminiferous epithelium, blood-testis-barrier disruption - that lines up with what is happening biochemically at the same time. Oxidative and inflammatory pathways rarely act separately; they reinforce each other, which is probably why idiopathic infertility so often involves both.

No single biomarker captures this whole picture. MDA and F2-isoprostanes reflect lipid damage, 8-OHdG and the DNA fragmentation index reflect genomic damage, TAC and ORP reflect the overall redox balance, and cytokines such as IL-6, IL-8 and TNF-alpha reflect the inflammatory component - each one tells only part of the story, and using them together is what actually adds diagnostic value . Recent randomized trials also show that these markers are not purely academic: DNA fragmentation, in particular, responds measurably to targeted antioxidant treatment in several independent studies. What still holds the field back is not a lack of promising biomarkers but a lack of standardization - different labs use different assay conditions, and no internationally agreed cut-off values exist yet, which makes it hard to compare studies directly or design trials with a clear, shared endpoint[12].

The findings summarized in this review indicate that oxidative stress functions as a convergent mechanistic pathway linking diverse etiological factors of male infertility - varicocele, infection, obesity, environmental exposure and idiopathic causes - to a common pattern of histological and molecular sperm injury. This perspective helps explain why conventional semen analysis alone is often insufficient: parameters such as concentration and morphology capture the downstream consequences of oxidative damage but do not identify its underlying biochemical cause[13-14].

Integrating molecular biomarkers with histological assessment offers a more mechanism-based diagnostic framework, but the field would benefit from standardized assay protocols, externally validated reference thresholds, and larger prospective studies correlating specific biomarker profiles with fertility outcomes and treatment response. Future work combining redox biomarkers with omics-based approaches may help move male infertility diagnosis from a purely descriptive semen analysis toward a mechanism-based, individualized model of assessment and treatment[15].

Conclusion

Oxidative stress ties together a wide range of otherwise unrelated risk factors for male infertility - infection, varicocele, lifestyle, environmental exposure - into one shared pattern of injury, visible both under the microscope and in seminal biomarkers. There is not yet a single test or cut-off value that can diagnose it reliably on its own, and antioxidant treatment is clearly not a cure-all. But the combination of histological assessment with a panel of complementary biomarkers, paired with biomarker-guided rather than empirical treatment, looks like a realistic and evidence-based direction for managing oxidative male infertility more precisely.

References

1. F. Mottola, I. Palmieri, M. Carannante, A. Barretta, S. Roychoudhury, and L. Rocco, "Oxidative stress biomarkers in male infertility: Established methodologies and future perspectives," Genes, vol. 15, no. 5, p. 539, 2024. https://doi.org/10.3390/genes15050539
2. A. T. Bergsma, H. T. Li, J. Eliveld, M. L. C. Bulthuis, A. Hoek, H. van Goor, A. R. Bourgonje, and A. E. P. Cantineau, "Local and systemic oxidative stress biomarkers for male infertility: The ORION study," Antioxidants, vol. 11, no. 6, p. 1045, 2022. https://doi.org/10.3390/antiox11061045
3. H. Pavuluri, Z. Bakhtiary, M. K. Panner Selvam, and W. J. G. Hellstrom, "Oxidative stress-associated male infertility: Current diagnostic and therapeutic approaches," Medicina, vol. 60, no. 6, p. 1008, 2024. https://doi.org/10.3390/medicina60061008
4. P. Sengupta, G. M. Pinggera, A. E. Calogero, and A. Agarwal, "Oxidative stress affects sperm health and fertility—Time to apply facts learned at the bench to help the patient: Lessons for busy clinicians," Reproductive Medicine and Biology, vol. 23, Art. no. e12598, 2024. https://doi.org/10.1002/rmb2.12598
5. A. Mannucci, F. R. Argento, E. Fini, M. E. Coccia, N. Taddei, M. Becatti, and C. Fiorillo, "The impact of oxidative stress in male infertility," Frontiers in Molecular Biosciences, vol. 8, Art. no. 799294, 2022. https://doi.org/10.3389/fmolb.2021.799294
6. S. Dutta, P. Sengupta, P. Slama, and S. Roychoudhury, "Oxidative stress, testicular inflammatory pathways, and male reproduction," International Journal of Molecular Sciences, vol. 22, no. 18, p. 10043, 2021. https://doi.org/10.3390/ijms221810043
7. J. Hallak, R. J. Aitken, J. S. Hallak, A. F. Q. Lozano, and T. A. Teixeira, "Oxidative stress and male infertility: A critical analysis of current diagnostic and therapeutic methods," Antioxidants, vol. 15, no. 8, p. 937, 2026. https://doi.org/10.3390/antiox15080937
8. D. Pourbagher, R. Bakhtiari Lafmejani, P. Namdar, A. Akhavan, A. Nikfarjam, and A. Soleimanzadeh, "Inflammation and oxidative stress in male infertility: A narrative review," Reproductive Medicine and Biology, 2026. https://doi.org/10.1002/rmb2.70090
9. J. T. Choy and M. L. Eisenberg, "Male infertility as a window to health," Fertility and Sterility, vol. 110, no. 5, pp. 810–814, 2018. https://doi.org/10.1016/j.fertnstert.2018.08.015
10. L. Boeri, H. Kandil, and J. Ramsay, "Idiopathic male infertility—What are we missing?" Arab Journal of Urology, vol. 23, no. 3, pp. 215–229, 2025. https://doi.org/10.1080/20905998.2024.2381972
11. P. Sharma, N. Kaushal, L. R. Saleth, S. Ghavami, S. Dhingra, and P. Kaur, "Oxidative stress-induced apoptosis and autophagy: Balancing the contrary forces in spermatogenesis," Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, vol. 1869, no. 4, Art. no. 166742, 2023. https://doi.org/10.1016/j.bbadis.2023.166742
12. A. Agarwal, R. A. Saleh, and M. A. Bedaiwy, "Role of reactive oxygen species in the pathophysiology of human reproduction," Fertility and Sterility, vol. 79, no. 4, pp. 829–843, 2003. https://doi.org/10.1016/S0015-0282(02)04948-8
13. M. Sengul, N. Hekim, R. Asci, and S. Gunes, "The impact of antioxidants on antioxidant capacity, DNA fragmentation, and chromatin quality in subfertile men: A randomized clinical trial study," Revista da Associação Médica Brasileira, vol. 70, no. 10, 2024. https://doi.org/10.1590/1806-9282.20240211
14. M. Lahimer, O. Gherissi, N. Ben Salem, H. Ben Mustapha, V. Bach, H. Khorsi-Cauet, H. Khairi, H. Ben Ali, M. BenKhalifa, and M. Ajina, "Effect of micronutrients and L-carnitine as antioxidant on sperm parameters, genome integrity, and ICSI outcomes: Randomized, double-blind, and placebo-controlled clinical trial," Antioxidants, vol. 12, no. 11, p. 1937, 2023. https://doi.org/10.3390/antiox12111937
15. R. M. Smits, R. Mackenzie-Proctor, A. Yazdani, M. T. Stankiewicz, V. Jordan, and M. G. Showell, "Antioxidants for male subfertility," Cochrane Database of Systematic Reviews, vol. 2019, no. 3, Art. no. CD007411, 2019. https://doi.org/10.1002/14651858.CD007411.pub4