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Oxidative Stress Biomarkers as Predictors of Male Infertility: A Comprehensive Review

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Abstract: ***Male infertility, a global health challenge affecting millions of couples, is significantly influenced by oxidative stress—an imbalance between excessive reactive oxygen species production and insufficient antioxidant defenses. While physiological levels of these reactive molecules are vital for essential sperm functions like capacitation and fertilization, supraphysiological concentrations are profoundly detrimental. Spermatozoa are uniquely vulnerable to oxidative attack due to their high content of polyunsaturated fatty acids and limited cytoplasmic antioxidant capacity, which predisposes them to severe damage. This oxidative imbalance manifests as lipid peroxidation, compromising sperm membrane integrity and motility; DNA damage and fragmentation, jeopardizing genetic information; protein oxidation, impairing structural and enzymatic functions; mitochondrial dysfunction, depleting energy reserves and promoting cell death; and adverse epigenetic modifications, potentially affecting transgenerational health. Understanding these intricate molecular mechanisms is crucial for advancing diagnostic precision and developing targeted therapeutic interventions. This comprehensive review synthesizes current knowledge on oxidative stress in male infertility, categorizing key biomarkers of lipid peroxidation, DNA damage, antioxidant status, and overall redox balance. It critically evaluates their diagnostic utility, from established assays to innovative tools like the MiOXSYS System, and explores emerging proteomic, genomic, and RNA-based biomarkers. Furthermore, the review analyzes current therapeutic strategies, particularly antioxidant supplementation, discussing its proposed benefits, existing limitations, and future directions towards personalized medicine. Ultimately, this work highlights critical knowledge gaps, advocates for standardized diagnostic approaches, and calls for mechanism-based interventions to improve outcomes for individuals affected by oxidative stress-related male infertility.***

Keywords: Male infertility, Reactive Oxygen Species, Oxidative stress, polyunsaturated fatty acids, DNA damage

1. Introduction

Male infertility constitutes a significant global health concern, impacting millions of couples and contributing to approximately half of all infertility cases worldwide (Agarwal et al., 2020; Huang et al., 2023). Characterized by impaired sperm production, function, or delivery, this multifaceted condition arises from a complex interplay of genetic factors, anatomical anomalies, endocrine dysfunctions, infections, environmental exposures, and lifestyle choices (Agarwal et al., 2020). Despite considerable advancements in reproductive medicine, a substantial proportion of male infertility remains idiopathic, highlighting persistent gaps in our understanding of its underlying pathophysiological mechanisms (Alahmar, 2019).

Male fertility can be affected by oxidative stress, a condition in which a redox imbalance occurs between the production of reactive oxygen species and the cells' antioxidant protection systems (Agarwal et al., 2014; Pavuluri et al., 2024). While physiological levels of ROS are crucial for vital sperm functions, including capacitation and the acrosome reaction, excessive ROS generation proves profoundly detrimental (Atukeren, 2018; Mancini et al., 2023; Plessis et al., 2015). However, an excess of ROS leads to OS, which causes structural and functional damage to sperm cells, including lipid peroxidation, protein oxidation, and DNA damage, resulting in decreased male fertility and the risk of genetic abnormalities in progeny (Agarwal et al., 2014; Bisht et al., 2017; Wang et al., 2025).

Spermatozoa are vulnerable to oxidative attack due to both their limited cytoplasmic volume, which restricts their defensive enzymes, and the susceptibility of their membrane lipids caused by significant amounts of polyunsaturated fatty acids (Aitken et al., 2015; Drevet et al., 2021; Wang et al., 2025). Furthermore, the scarcity of cytoplasm in spermatozoa translates to a restricted pool of antioxidant enzymes and molecules, making them ill-equipped to counteract a surge in oxidative insult (Wang et al., 2025). This vulnerability culminates in a cascade of deleterious effects, including DNA damage and fragmentation, protein oxidation, and mitochondrial dysfunction, ultimately impairing sperm motility, viability, and fertilization capacity (Aitken et al., 2012; Hussain et al., 2023; Wang et al., 2025). When spermatozoa are under stress, they undergo an intrinsic apoptotic cascade that includes the production of mitochondrial ROS, loss of mitochondrial membrane potential, activation of caspases, exposure of phosphatidylserine, and oxidative DNA damage (Ávila et al., 2022; Castellini et al., 2021).

Given the critical role of oxidative stress in male infertility, the identification and quantification of reliable biomarkers have become paramount (Kaltsas, 2023; Pavuluri et al., 2024). Such biomarkers are indispensable for accurate diagnosis, elucidating specific pathophysiological pathways, monitoring disease progression, and guiding the development and assessment of therapeutic interventions (Du et al., 2024). These encompass markers of lipid peroxidation (e.g., malondialdehyde, F2-isoprostanoids), DNA damage (e.g., 8-hydroxy-2-deoxyguanosine), protein damage, and various indicators of antioxidant capacity. An effective sperm-oocyte interaction depends on antioxidant defense. Under normal circumstances, antioxidant enzyme superoxide dismutase transforms ROS into hydrogen peroxide, which is then broken down into water and oxygen by catalase and glutathione peroxidase, reducing intracellular stress. Male infertility is linked to testicular morphological abnormalities caused by an

imbalance in these antioxidant defense mechanisms, which also impairs ejaculate quality.

This comprehensive review aims to synthesize the current understanding of oxidative stress as a critical factor in male infertility. We examine the diverse array of oxidative stress biomarkers, classify them based on specific aspects of OS they reflect, and critically evaluate their diagnostic utility and predictive power. Furthermore, we delve into the advancements in diagnostic methodologies, contrasting traditional assays with novel, more comprehensive tools. The review will also provide an in-depth analysis of current therapeutic strategies targeting oxidative stress, specifically focusing on antioxidant supplementation, its proposed benefits, current challenges, and future directions for clinical management. Ultimately, this work seeks to identify existing knowledge gaps, propose avenues for future research, and advocate for the development of standardized, personalized approaches to diagnose and treat male infertility driven by oxidative stress (Agarwal et al., 2019).

2. Mechanisms of Oxidative Stress in Male Infertility

The intricate balance between the production of reactive oxygen species and the capacity of antioxidant defense systems is fundamental to cellular health, particularly within the male reproductive system (Signorini et al., 2020). When this equilibrium is disrupted, leading to an overwhelming excess of ROS, oxidative stress ensues, profoundly impacting sperm function and male fertility (Signorini et al., 2020).

2.1 Sources and Dual Role of Reactive Oxygen Species

ROS are highly reactive molecules derived from oxygen metabolism, including superoxide anion (O_2^-), hydrogen peroxide H_2O_2 and hydroxyl radicals (OH) (Ansari et al., 2025). At physiological levels, ROS play a critical role in regulating biochemical changes, releasing enzymes vital for egg fusion, and modulating signaling pathways for hormone synthesis. They are indispensable for essential sperm functions such as spermatogenesis, sperm capacitation, hyperactivation, acrosome reaction, and sperm-oocyte fusion (Durairajanayagam, 2018; Kurhaluk et al., 2025; Plessis et al., 2015). However, supraphysiological ROS levels lead to oxidative stress, inducing cellular damage to sperm membranes, proteins, and DNA, thereby impairing sperm function (Aitken et al., 2012; Alahmar, 2019; Traini et al., 2022).

ROS in semen originate from various sources. Endogenous sources include immature and mature spermatozoa, polymorphonuclear leukocytes and macrophages activated during inflammation, mitochondrial electron transport chain activity, and the NADPH oxidase system (Gibb et al., 2020; Sanocka & Kurpisz, 2004; Traini et al., 2022). Exogenous sources contributing to ROS production encompass environmental toxins, radiation, heavy metals, and lifestyle factors such as smoking and alcohol consumption, as well as pathological conditions like reproductive tract infections (Atukeren, 2018; Traini et al., 2022).

2.2 Molecular Targets and Deleterious Effects of Excessive ROS

Spermatozoa are highly susceptible to oxidative stress due to their high polyunsaturated fatty acid content, which renders them extraordinarily vulnerable to lipid peroxidation (Agarwal et al., 2014). LPO directly impairs sperm motility, reduces viability, and hinders essential physiological changes for fertilization. Mature spermatozoa possess minimal cytoplasm, leading to a restricted pool of antioxidant enzymes and non-enzymatic scavengers (Atukeren, 2018). Sperm DNA is a critical target for oxidative attack, significantly contributing to male infertility (Atukeren, 2018). Potent ROS inflict various DNA lesions, including base oxidation and single- or double-strand breaks (Ogawa et al., 2024). Lipid peroxidation compromises membrane integrity and motility, while protein oxidation disrupts structural and enzymatic functions essential for motility and morphology. ROS-induced DNA damage, including strand breaks and base modifications, compromises genetic integrity, reduces fertilization rates, and increases miscarriage risk (Kaltsas, 2023). Mitochondrial dysfunction further impairs ATP production and motility while promoting apoptosis (Kumar et al., 2024; Wang et al., 2025). ROS also drive epigenetic alterations, impacting gene expression and potential transgenerational effects (Ménézo et al., 2016; Sharma et al., 2019; Sudhakaran et al., 2024).

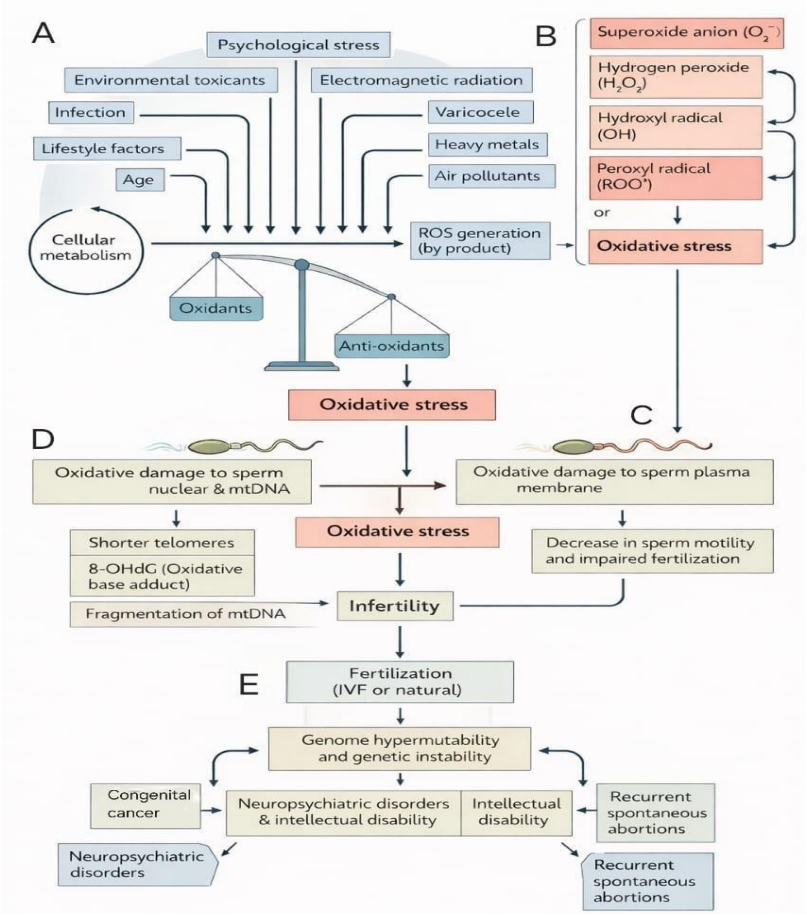

Figure 1: Impact of Oxidative Stress on Male Infertility

3. Key Oxidative Stress Biomarkers

Biomarkers offer diagnostic, prognostic, and therapeutic guidance by reflecting oxidative damage or antioxidant capacity (Baszyński et al., 2025; Mottola et al., 2024). They include lipid peroxidation markers, DNA damage markers, antioxidant status indicators, comprehensive redox balance markers, and emerging proteomic, genomic, and RNA-based biomarkers (Mottola et al., 2024).

3.1 Lipid Peroxidation Markers

Lipid peroxidation is a critical consequence of excessive ROS, particularly in sperm membranes rich in polyunsaturated fatty acids (Mottola et al., 2024). Markers of LPO are direct indicators of this damaging process. Malondialdehyde is an established end-product of lipid peroxidation from polyunsaturated fatty acids, directly reflecting oxidative damage to sperm membranes (Bergsma et al., 2022; Szymański et al., 2024). Seminal plasma MDA levels are elevated in infertile men and negatively correlate with motility, morphology, and viability (Kumar et al., 2024). Therefore, MDA is considered a promising biomarker for predicting male infertility, reflecting the extent of oxidative damage to sperm membranes (Kumar et al., 2024). F2-isoprostanoids, derived from arachidonic acid oxidation, are chemically stable indicators of lipid oxidative damage, significantly elevated in infertile men and associated with sperm immaturity and varicocele (Collodel et al., 2021; Longini et al., 2020; Moretti et al., 2022) (Table 1).

3.2 DNA Damage Markers

Oxidative stress directly attacks sperm DNA, leading to various lesions that compromise genetic integrity (Alahmar, 2019; Ghaleno et al., 2021). As a specific marker of oxidative DNA damage, 8-OHdG is formed when guanine bases in DNA are hydroxylated by ROS (Gholinezhad et al., 2020; Mottola et al., 2024). Elevated levels of 8-OHdG are consistently detected in infertile men and are negatively correlated with sperm volume, total sperm counts, and morphology (Gholinezhad et al., 2020; Mishra, 2014). Given that spermatozoa possess limited DNA repair mechanisms, increased 8-OHdG levels indicate compromised genetic integrity, making it a critical and sensitive biomarker for evaluating oxidative sperm DNA damage and its impact on fertility (Amor et al., 2021; Blumenberg et al., 2023) (Table 1).

3.3 Antioxidant Status Markers

These biomarkers reflect the capacity of the seminal fluid to neutralize ROS and protect spermatozoa from oxidative damage (Mancini et al., 2023; Palani & Alahmar, 2020). Free thiols represent a crucial component of the seminal antioxidant defense system (Bergsma et al., 2022; Krzyściak et al., 2020). They reflect the overall reductive capacity and protective mechanisms against oxidative damage by directly scavenging ROS (Bergsma et al., 2022). Studies have demonstrated a significant positive correlation between seminal plasma-free thiol levels and key sperm parameters such as concentration and progressive motility (Bergsma et

al., 2022). This suggests that free thiols can serve as promising local oxidative stress biomarkers, indicating the adequacy of the seminal antioxidant shield (Bergsma et al., 2022) (Table 1).

3.4 Comprehensive Redox Balance Markers

Oxidation-Reduction Potential measures the overall balance between oxidants and reductants in seminal plasma (García-Segura et al., 2020). Higher ORP is observed in infertile men and demonstrates high sensitivity and specificity for diagnosing oxidative stress-mediated infertility (Tan et al., 2024). ORP measurement using the MiOXSYS System offers standardization, rapid assessment, and improved reproducibility (Douglas et al., 2019; Henkel, 2024; Vassiliou et al., 2020).

Table 1: Key Oxidative Stress Biomarkers and Diagnostic Utility

Biomarker Category	Specific Biomarker	Description & Significance	Diagnostic Utility	References
Lipid Peroxidation	Malondialdehyde	End-product of PUFA oxidation; reflects oxidative damage to sperm membranes	Elevated in infertile men; correlates negatively with motility, viability, and morphology	(Bergsma et al., 2022; Bruno et al., 2022; Kumar et al., 2024)
Lipid Peroxidation	F2-isoprostanoids	Stable prostaglandin-like compounds from arachidonic acid oxidation	Elevated in infertile men; indicates lipid peroxidation events	(Collodel et al., 2021; Longini et al., 2020; Moretti et al., 2022)
DNA Damage	8-OHdG	Oxidative DNA lesion; guanine hydroxylation	Elevated in infertile men; correlates with sperm count, morphology	(Gholinezhad et al., 2020; Mishra, 2014; Mottola et al., 2024)
Antioxidant Status	Free thiols	Reflects total reductive capacity; scavenges ROS	Positively correlates with sperm motility and concentration	(Bergsma et al., 2022; Krzyściak et al., 2020)
Redox Balance	ORP	Net balance between oxidants and reductants	High ORP indicates infertility, as measured by MiOXSYS	(Douglas et al., 2019; Henkel, 2024; Tan et al., 2024)
Emerging Biomarkers	Proteins, Epigenetic & RNA markers	Reflect oxidative protein modifications, DNA/histone changes, and non-coding RNA alterations	Offer diagnostic/prognostic insights into OS-mediated infertility	(Agarwal et al., 2014; Baszyński et al., 2025; Cannarella et al., 2020; Fietz et al., 2024; Hosseini et al., 2024; Hussain et al., 2023; Kaiyal et al., 2024; Larriba et al., 2023; Leggio et al., 2024; Mehta & Rajender, 2024; Rotondo et al., 2021; Sudhakaran et al., 2024)

3.5 Emerging Biomarkers

Proteomic analysis of seminal plasma and spermatozoa identifies specific protein modifications and changes in protein expression that are indicative of oxidative stress (Agarwal et al., 2014; Cannarella et al., 2020; Hussain et al., 2023; Sharma et al., 2013). For instance, certain proteins involved in oxidative stress pathways are found overexpressed in infertile patients (Cannarella et al., 2020). Conversely, fertile men with high ROS levels may exhibit upregulated antioxidant proteins to counteract damage (Krzastek et al., 2020). Examples include DJ-1, PIP, lactotransferrin, peroxiredoxin, and mucin 5B, which are being explored for their potential as diagnostic and prognostic markers (Agarwal et al., 2014) (Table 1).

Oxidative stress can induce significant changes in the sperm epigenome, including alterations in DNA methylation patterns, histone modifications, and non-coding RNA expression (Hosseini et al., 2024; Leggio et al., 2024; Mottola et al., 2024; Rotondo et al., 2021; Sudhakaran et al., 2024). These epigenetic changes can profoundly impact gene expression and cellular function, exacerbating the detrimental effects of OS on male fertility (Sudhakaran et al., 2024). Studies show that sperm from infertile men often exhibit high histone retention and oxidative stress-induced epigenetic alterations, such as DNA hypomethylation (Krzastek et al., 2020). The study of RNA markers, including microRNAs and long non-coding RNAs, in seminal plasma and spermatozoa is gaining traction (Hussain et al., 2023; Larriba et al., 2023; Mehta & Rajender, 2024). These non-invasive biomarkers reflect the oxidative stress status and its impact on male fertility (Baszyński et al., 2025; Mottola et al., 2024). Specific transcripts, such as PRDX6, NOS3, SOD, BAK, and BCL2L11, have been linked to fertility and redox processes (Hussain et al., 2023). Altered expression profiles of lncRNAs and mRNAs are increasingly observed in male infertility, suggesting their potential as diagnostic and prognostic tools (Hussain et al., 2023).

4. Diagnostic Approaches for Oxidative Stress

The accurate and reliable assessment of oxidative stress in semen is paramount for identifying affected individuals, understanding the underlying pathophysiology of their infertility, and guiding personalized treatment decisions (Longini et al., 2020). However, the field has historically faced significant challenges in standardizing diagnostic methodologies, leading to variability and hindering widespread clinical utility (Du et al., 2024). Historically, various assays have been employed to quantify different components of oxidative stress in seminal plasma and spermatozoa (Larriba et al., 2023; Robert et al., 2020). While these methods have provided foundational insights, they often suffer from significant limitations, primarily their focus on

measuring single constituents of the complex oxidative cascade (Larriba et al., 2023).

Reactive Oxygen Species assays, total antioxidant capacity assays, and malondialdehyde assays directly measure specific ROS, such as superoxide anion or hydrogen peroxide, often using methods like chemiluminescence (Larriba et al., 2023; Robert et al., 2020). While offering direct quantification, ROS are highly unstable and short-lived, making their accurate measurement technically challenging and prone to rapid degradation during sample processing (Larriba et al., 2023). TAC assays aim to quantify the cumulative antioxidant potential of seminal plasma, reflecting the combined activity of various enzymatic and non-enzymatic antioxidants (Mancini et al., 2023; Palani & Alahmar, 2020). MDA is a widely used biomarker to quantify the extent of lipid peroxidation, often through colorimetric assays (Szymański et al., 2024) Figure 2. Elevated levels of seminal plasma MDA are consistently observed in infertile men and negatively correlate with vital sperm parameters (Kumar et al., 2024). While MDA is considered a promising biomarker reflecting oxidative damage to sperm membranes, it represents only one end-product of lipid peroxidation and does not provide comprehensive information on other forms of oxidative damage or the primary source of ROS (Larriba et al., 2023).

The MiOXSYS System measuring Oxidation-Reduction Potential represents an advance by providing a holistic, real-time assessment of net oxidative stress, improving standardization, reproducibility, and clinical applicability (Douglas et al., 2019; Henkel, 2024) Figure 2. ORP provides a real-time, comprehensive measure of the overall balance between oxidants and reductants within seminal plasma (Gibb et al., 2020). Unlike traditional assays that target individual components, ORP assesses the net effect of all pro-oxidants and antioxidants present in the sample. This holistic measurement offers a more accurate reflection of the dynamic redox environment, effectively capturing the cumulative burden of oxidative stress that individual biomarker measurements might overlook.

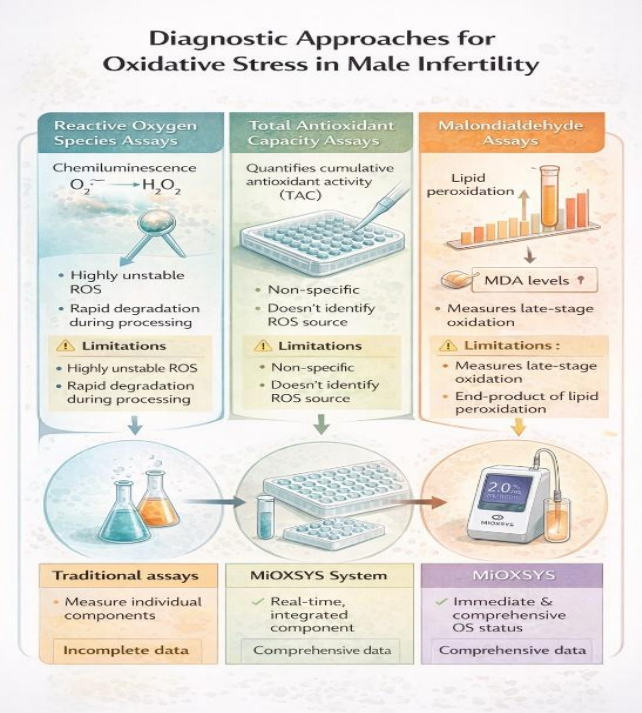

Figure 2: Diagnostic Approaches for Oxidative Stress in Male Infertility

Higher ORP levels are consistently found in infertile men compared to fertile counterparts, demonstrating high sensitivity and specificity for diagnosing male infertility (Tan et al., 2024). ORP is increasingly recognized as a direct and promising diagnostic tool that effectively captures the overall oxidative stress status, significantly complementing traditional semen analyses (Tan et al., 2024). Its ability to provide an immediate and integrated assessment of oxidative balance allows for a more definitive diagnosis of OS-related infertility. The MiOXSYS System offers significant advantages in terms of standardization and reproducibility (Vassiliou et al., 2020). It is described as an automated, easy-to-use platform that quantifies static and dynamic ORP (Gibb et al., 2020). This system provides a quick and reliable diagnostic method (Henkel, 2024), thereby reducing inter-laboratory variability and improving the consistency of results (Vassiliou et al., 2020).

5. Therapeutic Strategies Targeting Oxidative Stress

The rationale for antioxidant supplementation stems directly from the understanding that an imbalance between excessive reactive oxygen species production and insufficient antioxidant defenses leads to sperm damage. By introducing exogenous antioxidants, the goal is to neutralize harmful ROS, reduce oxidative damage to spermatozoa's membranes, DNA, and proteins, and thereby improve sperm parameters, function, and ultimately, fertility outcomes. This approach seeks to bolster the natural antioxidant capacity of the seminal plasma and spermatozoa, creating a more favorable environment for sperm survival and function.

Numerous dietary and pharmaceutical antioxidants have been extensively investigated for their potential to ameliorate oxidative stress and improve male fertility outcomes. These

include a wide array of vitamins, minerals, amino acids, and other compounds (Cannarella et al., 2020).

5.1 Vitamins

A potent lipid-soluble antioxidant, Vitamin E protects sperm membranes from lipid peroxidation, preserving membrane integrity and fluidity. Studies often report improved sperm motility and morphology with supplementation (Cannarella et al., 2020). A water-soluble antioxidant, Vitamin C scavenges ROS directly within the seminal plasma and regenerates Vitamin E (Cannarella et al., 2020; Ghaleno et al., 2021). It is known to reduce sperm DNA damage and improve sperm concentration and motility (Cannarella et al., 2020). Often combined with zinc, folic acid plays a crucial role in DNA synthesis and repair, indirectly mitigating oxidative damage by ensuring genomic integrity.

5.2 Minerals

An essential trace element, selenium is a cofactor for the antioxidant enzyme glutathione peroxidase, which neutralizes hydrogen peroxide. Supplementation has been linked to improved sperm motility and morphology. Zinc plays a role in spermatogenesis, steroidogenesis, and maintaining sperm membrane stability. It also acts as an antioxidant by stabilizing sulfhydryl groups in proteins and reducing susceptibility to oxidative attack. It is a cofactor for superoxide dismutase, A powerful lipid-soluble antioxidant, and a key component of the mitochondrial electron transport chain. CoQ10 protects against mitochondrial ROS production. It enhances ATP synthesis. Supplementation has shown promise in improving sperm motility and concentration (Cannarella et al., 2020).

Table 2: Key Antioxidants for Male Infertility

Category	Antioxidant	Primary Benefit	Key Citations
Vitamins	Vitamin E	Protects sperm membranes from oxidative damage; improves motility.	(Cannarella et al., 2020)
	Vitamin C	Scavenges ROS in seminal plasma; reduces sperm DNA damage.	(Cannarella et al., 2020)
	Folic Acid	Supports DNA integrity and repair; improves sperm count.	
Minerals	Selenium	Essential for antioxidant enzyme function; improves sperm quality.	(Cannarella et al., 2020)
	Zinc	Maintains sperm membrane stability; acts as an antioxidant.	(Cannarella et al., 2020)
Coenzyme	Coenzyme Q10	Protects against mitochondrial ROS; enhances sperm energy.	(Cannarella et al., 2020)
Amino Acids & Derivatives	L-Carnitine	Provides energy for sperm motility; antioxidant properties.	(Mottola et al., 2024)
	N-Acetyl Cysteine	Enhances endogenous antioxidant defense; reduces DNA fragmentation.	(Cannarella et al., 2020)
	L-Arginine	Improves blood flow and sperm quality; prevents lipid peroxidation.	
Other Compounds	Alpha-Lipoic Acid	Regenerates other antioxidants; comprehensive protection.	
	Lycopene	Potent antioxidant; improves sperm concentration, motility, and morphology.	

5.3 Amino Acid Derivatives

L-Carnitine and Acetyl-L-Carnitine compounds are crucial for mitochondrial fatty acid transport and beta-oxidation, providing energy for sperm motility (Mottola et al., 2024). They also possess antioxidant properties and have been associated with improved sperm quality, particularly motility and morphology (Mottola et al., 2024). N-Acetyl Cysteine is a precursor to glutathione. NAC directly scavenges ROS and enhances the body's primary endogenous antioxidant defense system. It has been shown to improve sperm parameters and reduce DNA fragmentation (Cannarella et al., 2020). L-Arginine is a precursor for nitric oxide synthesis, and can improve blood flow and sperm quality, though NO itself has a dual role, being both beneficial and harmful depending on its concentration.

5.4 Other Compounds

Antioxidant supplementation aims to neutralize harmful reactive oxygen species and reduce oxidative damage to spermatozoa, thereby improving sperm parameters and fertility outcomes (Cannarella et al., 2020). This approach strengthens seminal plasma and sperm's natural antioxidant capacity.

Vitamins such as Vitamin E, a lipid-soluble antioxidant, protect sperm membranes from lipid peroxidation, improving motility and morphology (Cannarella et al., 2020; Sabetian et al., 2021). Vitamin C, a water-soluble antioxidant, scavenges ROS, regenerates Vitamin E, reduces sperm DNA damage, and can enhance sperm concentration and motility (Cannarella et al., 2020; Ghaleno et al., 2021; Qamar et al., 2022). Folic Acid, often combined with zinc, is crucial for DNA synthesis and repair, indirectly mitigating oxidative damage (Erdoğan et al., 2023).

Among Minerals**,** Selenium acts as a cofactor for glutathione peroxidase, neutralizing hydrogen peroxide and improving sperm motility and morphology (Amor et al., 2021; Cannarella et al., 2020; Erdoğan et al., 2023). Zinc supports spermatogenesis and sperm membrane stability, acting as an antioxidant and a cofactor for superoxide dismutase (Cannarella et al., 2020; Erdoğan et al., 2023; Veselinović et al., 2025). Coenzyme Q10, a powerful lipid-soluble antioxidant, protects against mitochondrial ROS production, enhances ATP synthesis, and improves sperm motility and concentration, with seminal levels correlating directly with semen quality (Alahmar, 2022; Alahmar et al., 2021; Cannarella et al., 2020).

Amino Acid Derivatives like L-Carnitine are vital for mitochondrial fatty acid transport, providing energy for sperm motility and possessing antioxidant properties that improve sperm quality, especially motility and morphology (Ghorbani et al., 2021; Koohpeyma et al., 2022; Mottola et al., 2024). N-Acetyl Cysteine, a glutathione precursor, directly scavenges ROS and bolsters endogenous antioxidant defenses,

improving sperm parameters and reducing DNA fragmentation (Cannarella et al., 2020). L-Arginine is a precursor for nitric oxide synthesis, potentially enhancing blood flow and sperm quality.

Several other Compounds also demonstrate therapeutic value. Alpha-Lipoic Acid, an amphipathic antioxidant, directly scavenges ROS and uniquely regenerates other key antioxidants, enhancing mitochondrial function and significantly improving sperm concentration, motility, and reducing oxidative damage (Dong et al., 2022; Hodeeb et al., 2022; Zhang et al., 2022). Lycopene, a potent carotenoid, is an exceptional quencher of singlet oxygen, offering robust protection against lipid peroxidation and DNA damage, consistently improving sperm concentration, motility, and morphology (Agarwal et al., 2014; Nouri et al., 2019; Tvrdá et al., 2018). Quercetin, a flavonoid, acts as a strong antioxidant, improving sperm motility and viability, and reducing lipid peroxidation (Winn & Whitaker, 2020). Resveratrol and Curcumin also show promise through their antioxidant and anti-inflammatory properties, with curcumin notably improving sperm parameters and protecting against reproductive toxicity (Silva, 2017; Tarlan et al., 2025; Tsao et al., 2022).

5.5 Challenges and Future Directions

Oxidative stress remains a critical, yet complex, factor deeply intertwined with the etiology and pathophysiology of male infertility. The comprehensive assessment of oxidative stress biomarkers offers invaluable insights into the mechanisms of sperm dysfunction and holds significant promise for developing more precise diagnostic and therapeutic strategies (Du et al., 2024). A paramount need exists for universally accepted, standardized, and reproducible diagnostic assays for oxidative stress (Baszyński et al., 2025; Du et al., 2024). While advanced tools like the MiOXSYS System are promising (Agarwal & Bui, 2018), widespread clinical adoption requires consensus on reference values, methodologies, and quality control. Future research must focus on validating these standardized approaches across diverse populations to ensure consistent and reliable assessment of oxidative stress in clinical settings. While many biomarkers correlate with infertility, their predictive power for concrete clinical outcomes, such as natural pregnancy rates and live birth rates, remains largely unestablished. Future studies need to move beyond surrogate endpoints and conduct large-scale, prospective trials to determine which specific biomarkers, or combinations thereof, are robust predictors of fertility outcomes and treatment success (Du et al., 2024).

The current "one-size-fits-all" approach to antioxidant supplementation has yielded inconsistent results. The future of therapeutic management lies in personalized medicine, wherein treatment strategies are tailored to an individual's specific oxidative stress profile. This requires developing algorithms that integrate various biomarker data to identify the precise nature of the redox imbalance and guide targeted antioxidant or other mechanism-based therapies (Du et al., 2024). Continued exploration and validation of emerging biomarkers, particularly in proteomics, genomics, epigenetics, and RNA analysis, are crucial (Baszyński et al., 2025; Mottola et al., 2024). These advanced molecular tools offer the potential to uncover novel, highly specific, and sensitive indicators of oxidative damage or antioxidant deficiencies that may not be captured by current methods, leading to earlier and more accurate diagnoses (Mottola et al., 2024). Moving beyond broad-spectrum antioxidant supplementation, future therapies should aim for mechanism-based interventions. This could involve developing agents that specifically target particular ROS-generating pathways, bolster specific deficient antioxidant enzymes, or protect vulnerable molecular targets. Such targeted approaches, potentially incorporating advanced drug delivery systems, promise greater efficacy and reduced off-target effects compared to current strategies.

6. Conclusion

Oxidative stress stands unequivocally as a pivotal and modifiable factor in the complex etiology of male infertility, profoundly impacting sperm function and integrity (Agarwal et al., 2014; Pavuluri et al., 2024). While physiological levels of ROS are indispensable for critical sperm processes, an overwhelming imbalance between ROS generation and compromised antioxidant defenses inflicts severe and widespread damage, manifesting as lipid peroxidation, DNA fragmentation, protein damage, and mitochondrial dysfunction (Bisht et al., 2017; Bui et al., 2018; Castellini et al., 2021; Chianese & Pierantoni, 2021; Ghaleno et al., 2021; MB, 2023; Mo et al., 2025; Sanocka & Kurpisz, 2004; Wang et al., 2025). Despite significant advancements in identifying a diverse array of biomarkers—from traditional lipid peroxidation and DNA damage markers to comprehensive redox balance indicators like Oxidation-Reduction Potential and cutting-edge omics-based approaches, the field has been hampered by a lack of diagnostic standardization and inconsistent clinical evidence, particularly concerning the efficacy of broad-spectrum antioxidant supplementation. Moving forward, the imperative is clear: rigorous, large-scale clinical trials focused on live birth rates, coupled with the adoption of biomarker-guided, personalized therapeutic strategies, are essential (Du et al., 2024). By investing in the standardization of advanced diagnostics and fostering mechanism-based interventions, we can transcend current limitations, offering more precise diagnoses and effective, tailored treatments that will ultimately improve reproductive outcomes for the countless individuals affected by male infertility globally.

References

[1] Agarwal, A., Baskaran, S., Parekh, N., Cho, C., Henkel, R., Vij, S. C., Arafa, M., Selvam, M. K. P., & Shah, R. (2020). Male infertility [Review of *Male infertility*]. *The Lancet*, *397*(10271), 319. Elsevier BV. https://doi.org/10.1016/s0140-6736(20)32667-2

[2] Agarwal, A., & Bui, A. (2018). Oxidation-Reduction Potential Methodology Using the MiOXSYS System. In *Elsevier eBooks* (p. 217). Elsevier BV. https://doi.org/10.1016/b978-0-12-812501-4.00020-1

[3] Agarwal, A., Durairajanayagam, D., Halabi, J., Peng, J., & Vazquez-Levin, M. H. (2014). Proteomics, oxidative stress and male infertility [Review of *Proteomics, oxidative stress and male infertility*]. *Reproductive*

BioMedicine Online, *29*(1), 32. Elsevier BV. https://doi.org/10.1016/j.rbmo.2014.02.013

[4] Agarwal, A., Parekh, N., Selvam, M. K. P., Henkel, R., Shah, R., Homa, S. T., Ramasamy, R., Ko, E., Tremellen, K., Esteves, S. C., Majzoub, A., Álvarez, J. G., Gardner, D. K., Jayasena, C., Ramsay, J., Cho, C., Saleh, R., Sakkas, D., Hotaling, J. M., … Harlev, A. (2019). Male Oxidative Stress Infertility (MOSI): Proposed Terminology and Clinical Practice Guidelines for Management of Idiopathic Male Infertility [Review of *Male Oxidative Stress Infertility (MOSI): Proposed Terminology and Clinical Practice Guidelines for Management of Idiopathic Male Infertility*]. *The World Journal of Men s Health*, *37*(3), 296. Korean Society for Sexual Medicine and Andrology. https://doi.org/10.5534/wjmh.190055

[5] Agarwal, A., Virk, G., Ong, C. S. H., & Plessis, S. S. du. (2014). Effect of Oxidative Stress on Male Reproduction [Review of *Effect of Oxidative Stress on Male Reproduction*]. *The World Journal of Men s Health*, *32*(1), 1. Korean Society for Sexual Medicine and Andrology. https://doi.org/10.5534/wjmh.2014.32.1.1

[6] Aitken, R. J., Gibb, Z., Baker, M. A., Drevet, J. R., & Gharagozloo, P. (2015). Causes and consequences of oxidative stress in spermatozoa [Review of *Causes and consequences of oxidative stress in spermatozoa*]. *Reproduction Fertility and Development*, *28*(2), 1. CSIRO Publishing. https://doi.org/10.1071/rd15325

[7] Aitken, R. J., Jones, K. T., & Robertson, S. A. (2012). Reactive Oxygen Species and Sperm Function—In Sickness and In Health [Review of *Reactive Oxygen Species and Sperm Function—In Sickness and In Health*]. *Journal of Andrology*, *33*(6), 1096. https://doi.org/10.2164/jandrol.112.016535

[8] Alahmar, A. T. (2019). Role of oxidative stress in male infertility: An updated review [Review of *Role of oxidative stress in male infertility: An updated review*]. *Journal of Human Reproductive Sciences*, *12*(1), 4. Medknow. https://doi.org/10.4103/jhrs.jhrs_150_18

[9] Amor, H., Shelko, N., Mohammed, M., Jankowski, P. M., & Hammadeh, M. E. (2021). Role of Antioxidants Supplementation in the Treatment of Male Infertility. In *IntechOpen eBooks*. IntechOpen. https://doi.org/10.5772/intechopen.95891

[10] Ansari, W. A., Srivastava, K., Nasibullah, M., & Khan, M. F. (2025). Reactive oxygen species (ROS): sources, generation, disease pathophysiology, and antioxidants. *Discover Chemistry.*, *2*(1). https://doi.org/10.1007/s44371-025-00275-z

[11] Atukeren, P. (2018). Novel Prospects in Oxidative and Nitrosative Stress. In *InTech eBooks*. https://doi.org/10.5772/intechopen.70102

[12] Ávila, C., Vinay, J., Arese, M., Saso, L., & Rodrigo, R. (2022). Antioxidant Intervention against Male Infertility: Time to Design Novel Strategies [Review of *Antioxidant Intervention against Male Infertility: Time to Design Novel Strategies*]. *Biomedicines*, *10*(12), 3058. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/biomedicines10123058

[13] Baszyński, J., Kamiński, P., Szymański, M., Wasilow, K., Stanek, E., Brodzka, S., Grochowalska, R., Stuczyñski, T., Bilski, R., Hromada, M., Kurhaluk, N., & Tkachenko, H. (2025). Non-Enzymatic Antioxidant Defense and Polymorphic Changes in Male Infertility. *Cellular Physiology and Biochemistry*, *59*, 53. https://doi.org/10.33594/000000801

[14] Bergsma, A. T., Li, H. T., Eliveld, J., Bulthuis, M., Hoek, A., Goor, H. van, Bourgonje, A. R., & Cantineau, A. E. (2022). Local and Systemic Oxidative Stress Biomarkers for Male Infertility: The ORION Study. *Antioxidants*, *11*(6), 1045. https://doi.org/10.3390/antiox11061045

[15] Bisht, S., Faiq, M. A., Tolahunase, M., & Dada, R. (2017). Oxidative stress and male infertility [Review of *Oxidative stress and male infertility*]. *Nature Reviews Urology*, *14*(8), 470. Nature Portfolio. https://doi.org/10.1038/nrurol.2017.69

[16] Blumenberg, M., Ahmad, R., María, C., Andres, C., Lastra, J. M. P. de la, Andrés, C., Plou, F. J., Pérez-Lebeña, E., Seychell, B., Vella, M., James, G., Hunter, T., Rodrigues, K. E., De, S., Silva, C. P. D., Prado, A. F. do, Amico, R. D., Cuzzocrea, S., Cordaro, M., … Silva, A. P. da. (2023). Reactive Oxygen Species - Advances and Developments. In *Biochemistry*. IntechOpen. https://doi.org/10.5772/intechopen.107774

[17] Bruno, C., Basile, U., Vergani, E., Napodano, C., Oliva, A., Gulli, F., Meucci, E., Silvestrini, A., Orlando, P., Silvestri, S., Tiano, L., & Mancini, A. (2022). Inflammation and Oxidative Stress in Seminal Plasma: Search for Biomarkers in Diagnostic Approach to Male Infertility. *Journal of Personalized Medicine*, *12*(6), 857. https://doi.org/10.3390/jpm12060857

[18] Bui, A., Sharma, R., Henkel, R., & Agarwal, A. (2018). Reactive oxygen species impact on sperm DNA and its role in male infertility [Review of *Reactive oxygen species impact on sperm DNA and its role in male infertility*]. *Andrologia*, *50*(8). Wiley. https://doi.org/10.1111/and.13012

[19] Cannarella, R., Crafa, A., Barbagallo, F., Mongioì, L. M., Condorelli, R. A., Aversa, A., Calogero, A. E., & Vignera, S. L. (2020). Seminal Plasma Proteomic Biomarkers of Oxidative Stress [Review of *Seminal Plasma Proteomic Biomarkers of Oxidative Stress*]. *International Journal of Molecular Sciences*, *21*(23), 9113. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/ijms21239113

[20] Castellini, C., D'Andrea, S., Cordeschi, G., Totaro, M., Parisi, A., Emidio, G. D., Tatone, C., Francavilla, S., & Barbonetti, A. (2021). Pathophysiology of Mitochondrial Dysfunction in Human Spermatozoa: Focus on Energetic Metabolism, Oxidative Stress and Apoptosis [Review of *Pathophysiology of Mitochondrial Dysfunction in Human Spermatozoa: Focus on Energetic Metabolism, Oxidative Stress and Apoptosis*]. *Antioxidants*, *10*(5), 695. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/antiox10050695

[21] Chianese, R., & Pierantoni, R. (2021). Mitochondrial Reactive Oxygen Species (ROS) Production Alters Sperm Quality [Review of *Mitochondrial Reactive Oxygen Species (ROS) Production Alters Sperm Quality*]. *Antioxidants*, *10*(1), 92. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/antiox10010092

[22] Collodel, G., Noto, D., Signorini, C., Gambera, L., Stendardi, A., Mahmutbegovic, A., Micheli, L., Menchiari, A., & Moretti, E. (2021). Do Seminal Isoprostanes Have a Role in Assisted Reproduction Outcome? *Life*, *11*(7), 675. https://doi.org/10.3390/life11070675

[23] Douglas, C., Parekh, N., Kahn, L. G., Henkel, R., & Agarwal, A. (2019). A Novel Approach to Improving the Reliability of Manual Semen Analysis: A Paradigm Shift in the Workup of Infertile Men [Review of *A Novel Approach to Improving the Reliability of Manual Semen Analysis: A Paradigm Shift in the Workup of Infertile Men*]. *The World Journal of Men s Health*, *39*(2), 172. Korean Society for Sexual Medicine and Andrology. https://doi.org/10.5534/wjmh.190088

[24] Drevet, J. R., Hallak, J., Nasr-Esfahani, M. H., & Aitken, R. J. (2021). Reactive Oxygen Species and Their Consequences on the Structure and Function of Mammalian Spermatozoa [Review of *Reactive Oxygen Species and Their Consequences on the Structure and Function of Mammalian Spermatozoa*]. *Antioxidants and Redox Signaling*, *37*, 481. Mary Ann Liebert, Inc. https://doi.org/10.1089/ars.2021.0235

[25] Du, C., Yu, Y., & Fan, X. (2024). Analysis of research trends (2014-2023) on oxidative stress and male fertility based on bibliometrics and knowledge graphs. *Frontiers in Endocrinology*, *15*. https://doi.org/10.3389/fendo.2024.1326402

[26] Durairajanayagam, D. (2018). Physiological Role of Reactive Oxygen Species in Male Reproduction. In *Elsevier eBooks* (p. 65). Elsevier BV. https://doi.org/10.1016/b978-0-12-812501-4.00008-0

[27] Fietz, D., Sgaier, R., O'Donnell, L., Stanton, P. G., Dagley, L. F., Webb, A. I., Schuppe, H., Diemer, T., & Pilatz, A. (2024). Proteomic biomarkers in seminal plasma as predictors of reproductive potential in azoospermic men. *Frontiers in Endocrinology*, *15*, 1327800. https://doi.org/10.3389/fendo.2024.1327800

[28] García-Segura, S., Ribas-Maynou, J., Lara-Cerrillo, S., García-Peiró, A., Castel, A. B., Benet, J., & Oliver-Bonet, M. (2020). Relationship of Seminal Oxidation-Reduction Potential with Sperm DNA Integrity and pH in Idiopathic Infertile Patients. *Biology*, *9*(9), 262. https://doi.org/10.3390/biology9090262

[29] Ghaleno, L. R., Alizadeh, A., Drevet, J. R., Shahverdi, A., & Valojerdi, M. R. (2021). Oxidation of Sperm DNA and Male Infertility [Review of *Oxidation of Sperm DNA and Male Infertility*]. *Antioxidants*, *10*(1), 97. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/antiox10010097

[30] Gholinezhad, M., Aliarab, A., Abbaszadeh-Goudarzi, G., Pasha, Y. R. Y., Samadaian, N., Rasolpour-Roshan, K., Aghagolzadeh-Haji, H., & Khorasani, M. (2020). Nitric oxide, 8-hydroxydeoxyguanosine, and total antioxidant capacity in human seminal plasma of infertile men and their relationship with sperm parameters. *Daehan Saengsik Uihak Hoeji/Clinical and Experimental Reproductive Medicine*, *47*(1), 54. https://doi.org/10.5653/cerm.2020.00423

[31] Gibb, Z., Griffin, R. A., Aitken, R. J., & Iuliis, G. N. D. (2020). Functions and effects of reactive oxygen species in male fertility [Review of *Functions and effects of reactive oxygen species in male fertility*]. *Animal Reproduction Science*, *220*, 106456. Elsevier BV. https://doi.org/10.1016/j.anireprosci.2020.106456

[32] Henkel, R. (2024). *MiOXSYS* (p. 489). https://doi.org/10.1007/978-3-031-60738-7_18

[33] Hosseini, M., Khalafiyan, A., Zare, M. R., Karimzadeh, H., Bahrami, B., Hammami, B., & Kazemi, M. (2024). Sperm epigenetics and male infertility: unraveling the molecular puzzle [Review of *Sperm epigenetics and male infertility: unraveling the molecular puzzle*]. *Human Genomics*, *18*(1), 57. BioMed Central. https://doi.org/10.1186/s40246-024-00626-4

[34] Huang, B., Wang, Z., Kong, Y., Jin, M., & Ma, L. (2023). Global, regional and national burden of male infertility in 204 countries and territories between 1990 and 2019: an analysis of global burden of disease study. *BMC Public Health*, *23*(1). https://doi.org/10.1186/s12889-023-16793-3

[35] Hussain, T., Kandeel, M., Metwally, E., Murtaza, G., Kalhoro, D. H., Yin, Y., Tan, B., Chughtai, M. I. D., Yaseen, A., Afzal, A., & Kalhoro, M. S. (2023). Unraveling the harmful effect of oxidative stress on male fertility: A mechanistic insight [Review of *Unraveling the harmful effect of oxidative stress on male fertility: A mechanistic insight*]. *Frontiers in Endocrinology*, *14*. Frontiers Media. https://doi.org/10.3389/fendo.2023.1070692

[36] Kaiyal, R. S., Mukherjee, S., Selvam, M. K. P., Miller, A. W., Vij, S. C., & Lundy, S. D. (2024). Mitochondrial dysfunction signatures in idiopathic primary male infertility: a validated proteomics-based diagnostic approach. *Frontiers in Reproductive Health*, *6*, 1479568. https://doi.org/10.3389/frph.2024.1479568

[37] Kaltsas, A. (2023). Oxidative Stress and Male Infertility: The Protective Role of Antioxidants [Review of *Oxidative Stress and Male Infertility: The Protective Role of Antioxidants*]. *Medicina*, *59*(10), 1769. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/medicina59101769

[38] Krzastek, S. C., Smith, R. P., & Kovac, J. R. (2020). Future diagnostics in male infertility: genomics, epigenetics, metabolomics and proteomics [Review of *Future diagnostics in male infertility: genomics, epigenetics, metabolomics and proteomics*]. *Translational Andrology and Urology*, *9*. AME Publishing Company. https://doi.org/10.21037/tau.2019.10.20

[39] Krzyściak, W., Papież, M., Bąk, E., Morava, É., Krzyściak, P., Ligezka, A. N., Gniadek, A., Vyhouskaya, P., & Janeczko, J. (2020). Sperm Antioxidant Biomarkers and Their Correlation with Clinical Condition and Lifestyle with Regard to Male Reproductive Potential. *Journal of Clinical Medicine*, *9*(6), 1785. https://doi.org/10.3390/jcm9061785

[40] Kumar, N., Deepthi, K., Padugupati, S., & Ghose, S. (2024). Assessing Seminal Plasma Malondialdehyde Acid as a Diagnostic Tool for Male Infertility: A Case-Control Study. *Reviews on Recent Clinical Trials*, *20*(1), 36. https://doi.org/10.2174/0115748871306544240826095508

[41] Kurhaluk, N., Kamiński, P., & Tkaczenko, H. (2025). Oxidative Stress, Antioxidants, Gut Microbiota and Male Fertility [Review of *Oxidative Stress,*

Antioxidants, Gut Microbiota and Male Fertility]. *Cellular Physiology and Biochemistry*, *59*, 82. Karger Publishers. https://doi.org/10.33594/000000802

[42] Larriba, S., Vigués, F., & Bassas, L. (2023). Using Small Non-Coding RNAs in Extracellular Vesicles of Semen as Biomarkers of Male Reproductive System Health: Opportunities and Challenges [Review of *Using Small Non-Coding RNAs in Extracellular Vesicles of Semen as Biomarkers of Male Reproductive System Health: Opportunities and Challenges*]. *International Journal of Molecular Sciences*, *24*(6), 5447. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/ijms24065447

[43] Leggio, L., Paternò, G., Cavallaro, F., Falcone, M., Vivarelli, S., Manna, C., Calogero, A. E., Cannarella, R., & Iraci, N. (2024). Sperm epigenetics and sperm RNAs as drivers of male infertility: truth or myth? [Review of *Sperm epigenetics and sperm RNAs as drivers of male infertility: truth or myth?*]. *Molecular and Cellular Biochemistry*, *480*(2), 659. Springer Science+Business Media. https://doi.org/10.1007/s11010-024-04962-w

[44] Longini, M., Moretti, E., Signorini, C., Noto, D., Iacoponi, F., & Collodel, G. (2020). Relevance of seminal F2-dihomo-IsoPs, F2-IsoPs and F4-NeuroPs in idiopathic infertility and varicocele. *Prostaglandins & Other Lipid Mediators*, *149*, 106448. https://doi.org/10.1016/j.prostaglandins.2020.106448

[45] Mancini, A., Oliva, A., Vergani, E., Festa, R., & Silvestrini, A. (2023). The Dual Role of Oxidants in Male (In)fertility: Every ROSe Has a Thorn [Review of *The Dual Role of Oxidants in Male (In)fertility: Every ROSe Has a Thorn*]. *International Journal of Molecular Sciences*, *24*(5), 4994. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/ijms24054994

[46] MB, T. (2023). Lipid Peroxidation in Sperm Cells and the Creation of Reactive Oxygen Species: A Review [Review of *Lipid Peroxidation in Sperm Cells and the Creation of Reactive Oxygen Species: A Review*]. *Journal of Ethology & Animal Science*, *5*(1). https://doi.org/10.23880/jeasc-16000134

[47] Mehta, P., & Rajender, S. (2024). Small RNAs: an ideal choice as sperm quality biomarkers. *Frontiers in Reproductive Health*, *6*. https://doi.org/10.3389/frph.2024.1329760

[48] Ménézo, Y., Silvestris, E., Dale, B., & Elder, K. (2016). Oxidative stress and alterations in DNA methylation: two sides of the same coin in reproduction [Review of *Oxidative stress and alterations in DNA methylation: two sides of the same coin in reproduction*]. *Reproductive BioMedicine Online*, *33*(6), 668. Elsevier BV. https://doi.org/10.1016/j.rbmo.2016.09.006

[49] Mishra, S. (2014). Oxidative Damage to Sperm DNA: Clinical Implications. *Andrology-Open Access*, *3*(1). https://doi.org/10.4172/2167-0250.1000116

[50] Mo, L., Wu, H., Zhang, M., Zhang, P., Peng, W., He, Y., & Gao, F. (2025). The mechanism of oxidative stress in asthenozoospermia and antioxidant strategies: a review [Review of *The mechanism of oxidative stress in asthenozoospermia and antioxidant strategies: a review*]. *Frontiers in Endocrinology*, *16*. Frontiers Media. https://doi.org/10.3389/fendo.2025.1670762

[51] Moretti, E., Signorini, C., Ferretti, F., Noto, D., & Collodel, G. (2022). A Study to Validate the Relevance of Semen F2-Isoprostanes on Human Male Infertility. *International Journal of Environmental Research and Public Health*, *19*(3), 1642. https://doi.org/10.3390/ijerph19031642

[52] Mottola, F., Palmieri, I., Carannante, M., Barretta, A., Roychoudhury, S., & Rocco, L. (2024). Oxidative Stress Biomarkers in Male Infertility: Established Methodologies and Future Perspectives. *Genes*, *15*(5), 539. https://doi.org/10.3390/genes15050539

[53] Ogawa, S., Ota, K., Nishizawa, K., Shinagawa, M., Katagiri, M., Kikuchi, H., Kobayashi, H., Takahashi, T., & Yoshida, H. (2024). Micronutrient Antioxidants for Men (Menevit®) Improve Sperm Function by Reducing Oxidative Stress, Resulting in Improved Assisted Reproductive Technology Outcomes. *Antioxidants*, *13*(6), 635. https://doi.org/10.3390/antiox13060635

[54] Palani, A., & Alahmar, A. T. (2020). Impact of oxidative stress on semen parameters in normozoospermic infertile men: a case–control study. *African Journal of Urology*, *26*(1). https://doi.org/10.1186/s12301-020-00061-6

[55] Pavuluri, H., Bakhtiary, Z., Selvam, M. K. P., & Hellstrom, W. J. G. (2024). Oxidative Stress-Associated Male Infertility: Current Diagnostic and Therapeutic Approaches. *Medicina*, *60*(6), 1008. https://doi.org/10.3390/medicina60061008

[56] Plessis, S. S. du, Agarwal, A., Halabi, J., & Tvrdá, E. (2015). Contemporary evidence on the physiological role of reactive oxygen species in human sperm function [Review of *Contemporary evidence on the physiological role of reactive oxygen species in human sperm function*]. *Journal of Assisted Reproduction and Genetics*, *32*(4), 509. Springer Science+Business Media. https://doi.org/10.1007/s10815-014-0425-7

[57] Robert, K. A., Sharma, R., Henkel, R., & Agarwal, A. (2020). An update on the techniques used to measure oxidative stress in seminal plasma [Review of *An update on the techniques used to measure oxidative stress in seminal plasma*]. *Andrologia*, *53*(2). Wiley. https://doi.org/10.1111/and.13726

[58] Rotondo, J. C., Lanzillotti, C., Mazziotta, C., Tognon, M., & Martini, F. (2021). Epigenetics of Male Infertility: The Role of DNA Methylation [Review of *Epigenetics of Male Infertility: The Role of DNA Methylation*]. *Frontiers in Cell and Developmental Biology*, *9*, 689624. Frontiers Media. https://doi.org/10.3389/fcell.2021.689624

[59] Sanocka, D., & Kurpisz, M. (2004). Reactive oxygen species and sperm cells. [Review of *Reactive oxygen species and sperm cells.*]. *Reproductive Biology and Endocrinology*, *2*(1). BioMed Central. https://doi.org/10.1186/1477-7827-2-12

[60] Sharma, P., Ghanghas, P., Kaushal, N., Kaur, J., & Kaur, P. (2019). Epigenetics and oxidative stress: A twin-edged sword in spermatogenesis [Review of *Epigenetics and oxidative stress: A twin-edged sword in spermatogenesis*]. *Andrologia*, *51*(11). Wiley. https://doi.org/10.1111/and.13432

[61] Sharma, R., Agarwal, A., Mohanty, G., Hamada, A., Gopalan, B., Willard, B., Yadav, S. P., & Plessis, S. S. du. (2013). Proteomic analysis of human spermatozoa

proteins with oxidative stress. *Reproductive Biology and Endocrinology*, *11*(1), 48. https://doi.org/10.1186/1477-7827-11-48

[62] Signorini, C., Moretti, E., & Collodel, G. (2020). Role of isoprostanes in human male infertility [Review of *Role of isoprostanes in human male infertility*]. *Systems Biology in Reproductive Medicine*, *66*(5), 291. Taylor & Francis. https://doi.org/10.1080/19396368.2020.1793032

[63] Sudhakaran, G., Kesavan, D., Kandaswamy, K., Guru, A., & Arockiaraj, J. (2024). Unravelling the epigenetic impact: Oxidative stress and its role in male infertility-associated sperm dysfunction [Review of *Unravelling the epigenetic impact: Oxidative stress and its role in male infertility-associated sperm dysfunction*]. *Reproductive Toxicology*, *124*, 108531. Elsevier BV. https://doi.org/10.1016/j.reprotox.2023.108531

[64] Szymański, M., Janicki, R., Kamiński, P., Wasilow, K., Soltysiak, J., Szyca, R., Szymanska, A., & Arabik, M. (2024). Clinical use of redox biomarkers for diagnosis of male infertility. *Ginekologia Polska*. https://doi.org/10.5603/gpl.98046

[65] Tan, Y., Yuan, Y., Yang, X., Wang, Y., & Liu, L. (2024). Diagnostic value of oxidation-reduction potential for male infertility: a systematic review and meta-analysis [Review of *Diagnostic value of oxidation-reduction potential for male infertility: a systematic review and meta-analysis*]. *Translational Andrology and Urology*, *13*(7), 1228. AME Publishing Company. https://doi.org/10.21037/tau-24-32

[66] Traini, G., Tamburrino, L., Vignozzi, L., Baldi, E., & Marchiani, S. (2022). Is oxidative stress evaluated in viable human spermatozoa a marker of good semen quality? *Frontiers in Endocrinology*, *13*. https://doi.org/10.3389/fendo.2022.1012416

[67] Vassiliou, A. M., Martin, C., Homa, S. T., Stone, J., Dawkins, A., Genkova, M. N., Roca, H. S. D., Parikh, S., Patel, J., Yap, T., & Killeen, A. P. (2020). Redox potential in human semen: Validation and qualification of the MiOX sys assay. *Andrologia*, *53*(2). https://doi.org/10.1111/and.13938

[68] Wang, Y., Fu, X., & Li, H. (2025). Mechanisms of oxidative stress-induced sperm dysfunction [Review of *Mechanisms of oxidative stress-induced sperm dysfunction*]. *Frontiers in Endocrinology*, *16*, 1520835. Frontiers Media. https://doi.org/10.3389/fendo.2025.1520835