Iranian Journal of Basic Medical Sciences
ijbms.mums.ac.ir

The role of oxidative stress in sleep deprivation-induced reproductive dysfunction: A rationale for anti-oxidant intervention

Keke Chen [1, 2], Kaixing Huang [1], Xiaoyu Liu [1], Fengyou Luo [1, 2], Qiping Hu [1]*, Changlong Xu [3]*

[1] Department of Cell Biology and Genetics, School of Basic Medicine, Guangxi Medical University, Nanning, Guangxi, 530021, China
[2] Department of Biochemistry and Molecular Biology, School of Basic Medicine, Guangxi Medical University, Nanning, Guangxi, 530021, China
[3] The Reproductive Medical Center of Nanning Second People's Hospital, the Third Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, 530031, China

ARTICLE INFO

Article type:
Review

Article history:
Received: Aug 18, 2025
Accepted: Oct 19, 2025

Keywords:
Anti-oxidants
Infertility
Oxidative stress
Reproductive health
Sleep deprivation

ABSTRACT

Sleep deprivation (SD) is a significant risk factor for reproductive dysfunction. This review aims to synthesize evidence establishing that oxidative stress (OS) is the key pathological mediator of SD-induced reproductive impairments in both sexes and to provide a comprehensive rationale for anti-oxidant intervention. We conducted a narrative review of peer-reviewed studies (2000-2025) from PubMed, ScienceDirect, Scopus, and Google Scholar. We examined the evidence linking SD, OS, and reproductive health, with a specific focus on recent preclinical and clinical studies that directly investigate the mechanistic role of OS and the efficacy of anti-oxidant therapies. The evidence demonstrates that SD induces systemic OS, which in turn drives reproductive pathology. In males, SD leads to increased testicular OS, resulting in impaired sperm quality and hormonal disruption. In females, SD is associated with diminished ovarian reserve and reduced oocyte quality, mediated by ovarian OS. Crucially, preclinical studies show that various anti-oxidants, including bromelain, vitamin C, and zinc, can successfully ameliorate SD-induced testicular damage. In women, clinical evidence links sleep disorders to lower melatonin levels in follicular fluid and decreased ovarian reserve, supporting a similar OS-mediated mechanism. The synthesized evidence strongly suggests that OS is a key pathological mechanism through which SD impairs reproductive function. This provides a strong scientific foundation for anti-oxidant therapies as a promising strategy to mitigate these harms. Future clinical trials are warranted to develop effective anti-oxidant regimens for individuals whose fertility is compromised by SD.

▶ Please cite this article as:
Chen K, Huang K, Liu X, Luo F, Hu Q, Xu CH. The role of oxidative stress in sleep deprivation-induced reproductive dysfunction: A rationale for anti-oxidant intervention. Iran J Basic Med Sci 2026; 29:191-201. doi: https://dx.doi.org/10.22038/ijbms.2025.90559.19517

Introduction

The World Health Organization (WHO) recommends that adults obtain at least 7 hours of sleep each night. However, in modern society, insufficient sleep has become a prevalent issue, with one-third of adults sleeping less than 7 hours per night (1, 2). Sleep deprivation (SD) is a recognized public health concern, with human studies showing that 9%-24% of the population experiences excessive daytime sleepiness due to nighttime SD, making it one of the primary reasons for visits to sleep clinics (3).

SD poses significant health risks, impacting various bodily systems and contributing to numerous health issues (Figure 1). Central to these issues is the role of chronic sleep deprivation (CSD) in inducing systemic oxidative stress (OS), hormonal imbalances, and inflammation. These pathological changes are known to undermine immune function, weaken anti-oxidant defenses, and increase the risk of cardiovascular and mental health disorders (4-7). For instance, populations with high levels of sleep debt, such as healthcare professionals and other shift workers, exhibit increased DNA damage and impaired repair mechanisms, underscoring the critical importance of adequate sleep (8, 9).

Similar to SD, infertility represents a significant global health concern, affecting 10% to 15% of couples worldwide (10, 11). While a growing body of research links SD to reproductive dysfunction (12-14) and separately establishes SD as a potent inducer of systemic OS (15), the precise role of OS as the intermediary in SD-induced reproductive damage has primarily been a matter of inference, a gap this review aims to address by synthesizing recent direct investigational evidence. The literature is divided into two main streams: one examining the effects of SD on health, and another exploring the role of OS in infertility from various other causes (16-18). Few studies have explicitly bridged these two fields.

This narrative review addresses this gap by synthesizing these two distinct but mechanistically related bodies of

***Corresponding authors:** Qiping Hu. Department of Cell Biology and Genetics, School of Basic Medicine, Guangxi Medical University, Nanning, Guangxi, 530021, China. Email: huqiping@gxmu.edu.cn; Changlong Xu. The Reproductive Medical Center of Nanning Second People's Hospital, the Third Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, 530031, China. Email: xuchanglong2011@hotmail.com

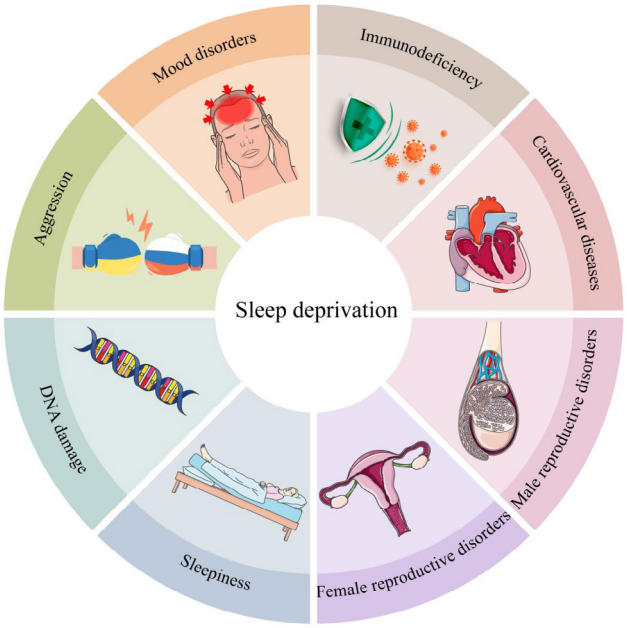

Figure 1. Harms caused by sleep deprivation

literature. First, it reviews the evidence establishing the link between SD and reproductive impairment. Second, it presents the extensive evidence implicating OS as a primary culprit in reproductive disorders. By connecting these two lines of evidence, this review aims to substantiate the hypothesis that OS is a primary pathway through which SD damages reproductive health. Based on this proposed mechanism, we then critically assess the efficacy of anti-oxidants in other OS-driven models to build a robust scientific rationale for their potential therapeutic use in mitigating SD-induced reproductive impairments. This work, therefore, does not merely summarize existing knowledge but actively constructs a conceptual framework to guide future research at the intersection of sleep science, reproductive medicine, and redox biology.

Sleep deprivation as a systemic inducer of oxidative stress

SD is increasingly recognized as a potent physiological stressor that triggers systemic OS, leading to widespread tissue damage and organ dysfunction. The consequences for reproductive health are a central focus of this review, but the impact of SD is far from isolated. Evidence from diverse fields converges to paint a picture of SD as a multi-system threat. For instance, even environmentally-triggered sleep disturbances, such as exposure to aircraft noise, have been shown to exacerbate cardiovascular and brain damage through an OS-mediated mechanism (19), highlighting the sensitivity of these systems to poor sleep quality.

The profound, multi-organ impact of sleep-loss-induced OS is further substantiated across various experimental models. Studies on paradoxical sleep deprivation (PSD) reveal significant oxidative damage in metabolic organs like the liver and pancreas, with a heightened vulnerability observed in older animals (20). This systemic vulnerability extends to the submandibular glands, the thyroid, and, critically, the brain (21, 22). In the central nervous system, SD-induced OS is directly linked to functional impairments, including memory deficits, anxiety, and other neurobehavioral issues, primarily by elevating reactive oxygen species (ROS) and depleting anti-oxidant defenses in crucial areas such as the hippocampus and prefrontal cortex (23-25). These findings, consistent across species and age groups, are supported by human studies showing that SD not only increases pain sensitivity but also leaves a lasting oxidative footprint that is only partially mitigated by recovery sleep (26, 27). Collectively, this body of evidence establishes a critical premise: SD is not a localized issue but a systemic condition that disrupts redox homeostasis throughout the body. Understanding this universal mechanism is fundamental to appreciating its specific and severe consequences for the highly sensitive reproductive system, and it logically points toward systemic interventions, such as anti-oxidant therapies, as a potential therapeutic strategy.

Stress: The critical mechanistic link between sleep deprivation and reproductive dysfunction

While historical research has separately established the negative impacts of SD on reproductive health and the detrimental role of OS in fertility, a growing body of direct evidence now bridges this gap. Indeed, as noted previously, studies have already demonstrated that chronic SD induces erectile dysfunction in male models and that total maternal sleep deprivation (TSD) elevates oocyte OS and impairs embryonic viability (28, 29). Recent preclinical and clinical studies have moved beyond inference to provide compelling validation that OS is a primary pathological mediator through which SD impairs both male and female reproductive function, thereby establishing a clear mechanistic rationale for anti-oxidant-based interventions.

In male models, the pathway from SD to reproductive injury via OS has been robustly demonstrated. A cornerstone study by Hosseinpour *et al.* subjected rats to REM SD and observed not only a significant decline in sperm quality but also a concurrent surge in testicular OS, inflammation, and apoptosis. Critically, concomitant administration of the anti-oxidant bromelain successfully reversed these pathological changes (30). This conclusion is strongly supported by Rizk *et al.*, who found that vitamin C administration significantly counteracted SD-induced reproductive deficits by suppressing OS and up-regulating the Nrf-2 anti-oxidant pathway (31). This therapeutic principle holds for a range of natural substances; for instance, honey (32), *Hibiscus sabdariffa* extract (33), and zinc supplementation (34) have consistently shown the ability to ameliorate testicular OS in sleep-deprived rats. Moreover, the link extends to the neuroendocrine stress axis, as mifepristone, a glucocorticoid receptor antagonist, was also shown to mitigate testicular OS, suggesting that the stress response itself is a major source of OS in SD (35).

However, the intervention outcomes can be nuanced, highlighting the complexity of the recovery process. For example, studies using cannabidiol (36) and olive oil (37) reported improvements in testicular histoarchitecture, such as the restoration of Sertoli and Leydig cells, without a corresponding immediate improvement in sperm function. This suggests that while anti-oxidant support can initiate cellular repair, a longer duration or optimized dosage may be necessary to translate these structural gains into functional recovery.

The mediating role of OS is not confined to males; a multi-layered body of evidence now firmly establishes a

parallel mechanism in female reproductive dysfunction. At the clinical level, human studies have directly linked sleep disorders to tangible impairments in ovarian health. A recent study by Yildiz *et al.* found that women with obstructive sleep apnea, a severe form of sleep disruption, exhibited significantly lower levels of anti-Müllerian hormone (AMH), a key biomarker of ovarian reserve. The authors postulated that this decline in ovarian function was likely attributable to the chronic hypoxia and OS characteristic of the disorder (38).

Mechanistically, this clinical observation is strongly supported by research on the ovarian microenvironment. A primary pathway involves the hormone melatonin, a potent anti-oxidant. Li *et al.* discovered that women with polycystic ovary syndrome, a condition often accompanied by sleep disturbances, had significantly lower melatonin concentrations directly in their follicular fluid, which correlated with poorer-quality embryos (39). These findings are substantiated by preclinical evidence; a pivotal study by Yi *et al.* demonstrated that maternal sleep deprivation in mice directly causes OS and mitochondrial dysfunction in the oocytes themselves, leading to a decline in fertility (28).

Collectively, these studies create a cohesive narrative: sleep disruption suppresses protective anti-oxidant mechanisms, inducing OS and resulting in measurable damage to both male and female reproductive systems. While direct preclinical testing of broader anti-oxidant therapies in female SD models remains urgently needed, the powerful rationale established by these findings warrants further investigation into such interventions.

In summary, OS emerges not as a plausible consequence of SD but as a key mechanism driving reproductive dysfunction in both sexes. The compelling evidence for this mechanistic link provides a robust scientific foundation for the clinical translation of anti-oxidant therapies as a rational and promising strategy for mitigating the reproductive harms of SD.

Sleep deprivation-induced male reproductive dysfunction and the role of anti-oxidants

Sleep deprivation leads to male reproductive dysfunction

SD compromises male reproductive health by initiating a cascade of pathological changes, centered on OS and a profound disruption of hormonal and structural homeostasis (Figure 2). The maintenance of stable circadian rhythms is fundamental for optimal reproductive physiology, and their disruption through sleep loss can lead to significant fertility impairments (12, 40). The duration and type of sleep loss critically modulate the severity and nature of the damage.

The initial and most sensitive indicators of SD-induced damage appear in sperm parameters, particularly motility. In a comprehensive mouse model of CSD (18 hr/day), a significant decline in sperm motility was observed after just 2 weeks, whereas a reduction in sperm concentration only became significant after 3 weeks (41). This finding of motility as an earlier marker is corroborated by rat studies, in which 7 days of total SD significantly reduced sperm motility without yet affecting sperm count (42). These findings suggest a sequential pattern of injury, in which the functional capacity of mature sperm is compromised before a significant impact on overall spermatogenic output becomes evident.

The endocrine system is a primary target of SD. Both acute

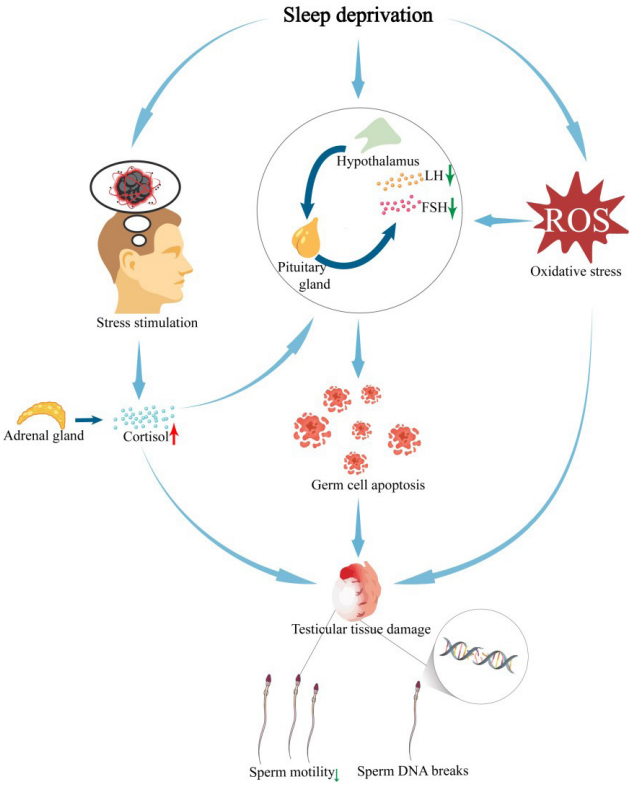

Figure 2. Schematic representation of potential mechanisms by which sleep deprivation leads to male reproductive disorders, with sleep deprivation-induced oxidative stress being a major pathway
LH: luteinizing hormone; FSH: follicle-stimulating hormone; ROS: reactive oxygen species

and chronic sleep loss models consistently demonstrate a suppression of the hypothalamic-pituitary-gonadal (HPG) axis. Acute (PSD) for 96 hr in rats, a model of severe sleep loss, leads to a significant decrease in serum testosterone and impaired sexual behavior. In contrast, a milder, chronic sleep restriction (SR) for 21 days did not affect sexual behavior but still caused a significant drop in sperm viability, indicating that different facets of reproductive function have varying sensitivities to SD duration and type (43). Shorter-term total SD (4 and 7 days) also significantly decreases testosterone while increasing the stress hormone corticosterone, implicating a stress-mediated inhibition of the HPG axis and highlighting the complex interplay between psychological stress, sleep, and fertility (42, 44).

Beyond hormonal shifts, SD also causes direct structural damage to the reproductive tract. A landmark study revealed that just 10 days of CSD (20 h/day) in rats caused a significant increase in the permeability of the blood-testis and blood-epididymis barriers. This breakdown was associated with a marked down-regulation of the expression of key tight junction proteins (occludin, claudin-11) and the androgen receptor, providing a direct structural basis for fertility impairment (45). The clinical relevance of these mechanisms is highlighted in human populations experiencing chronic sleep disruption. For instance, shift workers often exhibit higher rates of oligozoospermia (44), and a multi-arm randomized trial found that men with obstructive sleep apnea (OSA) had significantly lower levels of total and free testosterone and a lower proportion of healthy sperm cells than healthy volunteers (46). This demonstrates how chronic sleep disruption in humans mirrors the pathologies observed

in experimental models (47).

Collectively, these interconnected pathways—OS, HPG axis suppression, and physical barrier breakdown—illustrate that adequate sleep is indispensable for male reproductive health. It maintains a stable hormonal milieu and a protected microenvironment, both of which are essential for the successful production and maturation of sperm (12, 40, 42, 43, 48).

Effects of oxidative stress on male reproductive health

The profound impact of SD on male fertility is best understood through its role as a potent inducer of OS, a central pathogenic mechanism in male reproductive dysfunction. This principle is not confined to sleep loss; a substantial body of evidence demonstrates that diverse factors converge on this common pathway. These include exposure to environmental pollutants, such as industrial chemicals, microplastics, and mobile phone radiation (49-51), as well as lifestyle choices, such as high-fat diets and cannabis use (52, 53). Furthermore, medical contexts, including the use of certain medications and viral infections such as SARS-CoV-2, also significantly contribute to the testicular oxidative burden (54-57). Collectively, these insults elevate ROS, which disrupts reproductive hormones and causes sperm DNA damage, ultimately leading to sperm dysfunction (58).

Regardless of the trigger, the downstream consequences of elevated OS on the male reproductive system are consistent, creating a hostile environment for spermatogenesis, as illustrated in the context of SD in (Figure 2). The core pathologies include: (i) Lipid Peroxidation: The high content of polyunsaturated fatty acids in sperm membranes makes them exceptionally vulnerable to ROS-induced damage, which impairs membrane fluidity and integrity, leading to reduced sperm motility and viability (59). (ii) DNA Damage: ROS can directly cause breaks in sperm DNA, increasing the DNA fragmentation index (DFI), a key marker of infertility that correlates with poor embryo development (49). (iii) Cellular Apoptosis: In the testis, OS can trigger apoptotic pathways in both spermatogenic germ cells and testosterone-producing Leydig cells, leading to a reduction in sperm count and endocrine disruption (54, 60). This established framework of OS-driven pathology provides a compelling rationale for why a systemic stressor like SD has such a profound impact on male reproductive health.

Anti-oxidants as protectors against male reproductive injury

The strong proof-of-concept for the therapeutic application of anti-oxidants in SD is rooted in the central mediating role of OS. This approach is logical, as the body's endogenous anti-oxidant systems can be overwhelmed by chronic stressors like SD, necessitating exogenous support (61). Preclinical successes in SD models—ranging from vitamins and minerals to natural extracts—not only confirm this mechanistic link but also highlight a promising therapeutic avenue (30-35). Furthermore, emerging evidence suggests that OS from SD may also disrupt epigenetic regulation in spermatogenesis, potentially leading to transgenerational effects that anti-oxidants could theoretically mitigate (62).

The protective efficacy of anti-oxidants is further demonstrated across a wide range of analogous OS-driven male infertility models, providing a strong theoretical framework for this approach (Table 1). For instance, in men with high OS undergoing assisted reproductive technology (ART), supplementation with anti-oxidants like selenium and zinc has been shown to improve sperm parameters and pregnancy rates (17, 63). This benefit extends to mitigating reproductive toxicity from various sources, including medications, environmental pollutants, and metabolic conditions such as high-fat diets and diabetes (64-68). In these diverse contexts, a vast array of anti-oxidants has been shown to protect testicular tissue, preserve sperm DNA integrity, and restore hormonal balance (69-71).

However, the application of anti-oxidant therapy requires careful consideration. While a diet rich in natural anti-oxidants is often beneficial (72), therapeutic supplementation must be approached with caution. The goal is to restore redox homeostasis, not to eliminate reactive oxygen species entirely, as a certain level of ROS is necessary for normal sperm function. Irrational or excessive supplementation can lead to "reductive stress," which paradoxically impairs fertility by disrupting essential redox signaling (73, 74). Therefore, the promise of anti-oxidants, including a broad array of micronutrients, lies in their personalized and balanced application, particularly for conditions such as idiopathic oligoasthenospermia (OAT) (75-78). The established success of these therapies in other OS-related infertility scenarios, combined with the direct evidence from SD models, strongly suggests their potential relevance for clinical translation.

Sleep deprivation-induced female reproductive dysfunction and the role of anti-oxidants

Sleep deprivation leads to female reproductive dysfunction

SD profoundly disrupts female reproductive health through a complex interplay of hormonal dysregulation, OS, inflammation, and circadian misalignment, which collectively impair fertility, ovarian function, and pregnancy outcomes (Figure 3). A central mechanism in this process is the suppression of melatonin, an anti-oxidant hormone crucial for protecting ovarian tissue. Human studies indicate that SD-induced reductions in melatonin not only increase the ovaries' vulnerability to oxidative damage but also disrupt the HPG axis, leading to irregular levels of LH and FSH, which are essential for ovulation and menstrual regularity, a finding supported by both clinical and animal research (12, 79, 80).

The clinical consequences of this disruption are particularly evident in populations with chronic sleep disturbances. Female shift workers, for example, who frequently experience CSD, exhibit higher rates of infertility, menstrual dysfunction, and pregnancy complications, with epidemiological data pointing to OS as a pivotal mediator (12, 81, 82). Similarly, women with recurrent pregnancy loss (RPL) have been found to sleep less than fertile controls, suggesting SD is a significant risk factor (83). These human studies confirm that CSD, through the combined effects of reduced melatonin and elevated cortisol, compromises reproductive health via both oxidative and hormonal imbalance (12, 81). The direct impact on ovarian health has been further elucidated in animal models, which demonstrate that prolonged SD inflicts oxidative damage on ovarian tissue, depletes ovarian reserve, reduces oocyte quality, and can even accelerate ovarian aging, leading to conditions like premature ovarian insufficiency (POI). This is often accompanied by systemic changes, such as gut dysbiosis and increased inflammatory markers, which

Table 1. Selected evidence for anti-oxidant therapies in oxidative stress (OS) driven models of male reproductive impairment

Study population/animal model	Anti-oxidant agent(s)	Dosage & administration	Study design	Key outcomes measured	Main findings (vs respective control/toxin group)	References
Male partners (n=84) undergoing ART	Menevit® contains lycopene (6 mg), vitamin E (30 mg), vitamin B6 (1.3 mg), vitamin B12 (2.4 µg), vitamin C (180 mg), zinc (12 mg), selenium (60 µg), folic acid (400 µg), and L-carnitine (50 mg) per serving.	3 tablets daily, orally	6-month prospective cohort study	Sperm concentration; Seminal OS (sORP); Implantation & clinical pregnancy rates	In the high OS subgroup, sperm concentration increased (8.4→14.3 x10^6/ml, P<0.05); implantation (47.1%→76.2%) and pregnancy rate (38.2%→71.4%) improved (P<0.05).	(63)
Mouse germ cells exposed to bisphenol A (BPA)	Glutathione (GSH) & Vitamin E (Vit E)	5 mM & 2 mM, *in vitro*	*In vitro* co-incubation	Motility, ATP levels, acrosome reaction, fertilization & embryo development	GSH & Vit E significantly restored sperm function and fertility potential (P<0.05).	(65)
Mouse sperm exposed to electromagnetic field (EMF)	Aloe arborescens juice	1% (v/v) concentration in culture medium	*In vitro* co-incubation	Intracellular ROS, DNA damage (Comet assay), cell viability & morphology	Significantly reduced EMF-induced ROS levels (P<0.01 vs EMF group) and prevented DNA damage, thereby preserving cell viability.	(66)
Rats fed a high-fat diet (HFD)	Vitamin E, Vitamin C, & Astaxanthin	0.2% Vit E, 0.2% Vit C, 0.6% astaxanthin in diet for 12 weeks	12-week animal study	Sperm count, motility, morphology, viability; Testicular anti-oxidant enzyme levels	Significantly improved sperm motility compared to the HFD group (58.7±8.4 vs 56.3±6.07, P<0.05) and restored testicular Anti-oxidant enzyme levels.	(67)
Streptozotocin-induced diabetic rats	Edaravone or Taurine	10 mg/kg/day or 500 mg/kg/day, intraperitoneally for 4 weeks	4-week animal study	Seminal vesicle weight and structure; Serum & tissue MDA (oxidative stress marker)	Both Anti-oxidants significantly decreased serum MDA levels (e.g., Edaravone vs DM group, p=0.0005) and improved seminal vesicle histology.	(68)
Quinalphos (pesticide)-induced reproductive disorders in mice	*Commelina benghalensis* (CBE) or *Cissus quadrangularis* (CQE) extract	400 mg/kg (CBE) or 350 mg/kg (CQE), orally for 7 days	7-day animal study	Serum testosterone, sperm count & viability, testicular OS markers	Both extracts significantly restored testosterone levels, sperm count, and viability compared to the pesticide-only group (P<0.05).	(71)
Asthenospermic infertile men (n=60)	Zinc sulfate	Two 220 mg capsules daily (total 440 mg), orally for 3 months	3-month clinical intervention	Seminal plasma peroxynitrite, arginase, and NOS activity; Sperm parameters	Restored peroxynitrite and enzyme activities to normal ranges; significantly increased progressive sperm motility (21±9% vs 39±14%, P<0.05).	(78)

further exacerbate the decline in reproductive function (84, 85).

The detrimental effects of SD are not confined to the pre-conception period but extend throughout pregnancy, severely affecting placental function and fetal development. Research in humans has linked maternal SD to elevated markers of OS and inflammation, resulting in increased lipid peroxidation and diminished anti-oxidant capacity in the placenta. This compromises the vital supply of nutrients and oxygen to the fetus, increasing the risk of intrauterine growth restriction, miscarriage, and other placental abnormalities (79, 85). It is noteworthy that such OS-mediated placental dysfunction, particularly in the context of RPL, may be multifactorial, with paternal factors such as sperm DNA fragmentation also implicated as potential contributors (86). The repercussions of maternal SD can even be intergenerational; preclinical models show that maternal SD during pregnancy is associated with altered hormone levels, reduced sexual motivation, and decreased fertility in the offspring, though human data on this topic remain limited (87). This body of evidence paints a clear picture: from impairing the foundational aspects of ovarian fertility to disrupting the life-sustaining environment of the placenta, SD poses a continuous and enduring threat to female reproductive success across the lifespan.

Effects of oxidative stress on female reproductive health

Similar to its impact on males, SD compromises female fertility primarily by inducing systemic OS, a crucial mechanism that adversely affects the entire reproductive timeline. The universal role of OS in female reproductive disorders is well-documented, with evidence linking it to conditions like miscarriage, pre-eclampsia, and infertility (88). This vulnerability is consistently demonstrated across various contexts. Factors such as environmental toxins (e.g., silica, BPA, lead, and phthalates)(89-93) and unhealthy lifestyle choices (e.g., smoking)(94). Various pathological states, including endometriosis and diabetes (95-98), and even unique environmental conditions like microgravity (99), are all known to induce OS and negatively impact

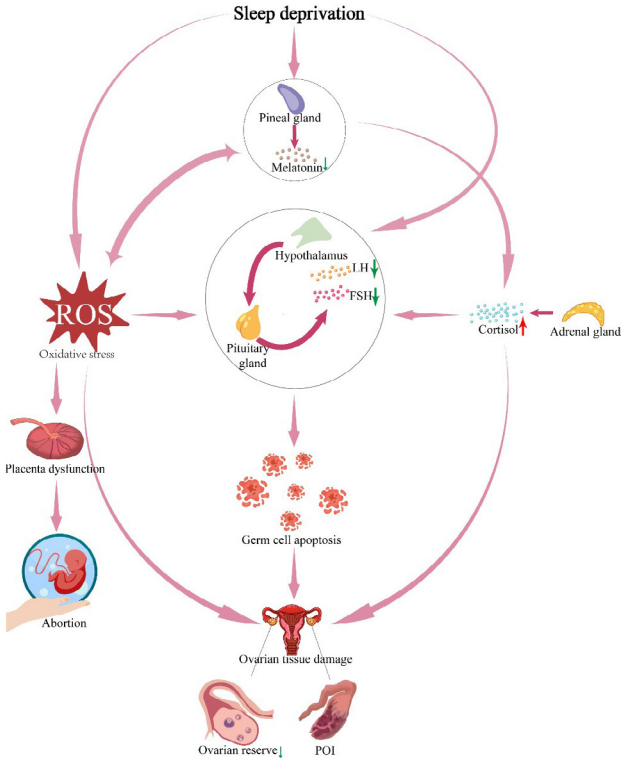

Figure 3. Schematic representation of the potential mechanisms by which sleep deprivation leads to female reproductive disorders, with sleep deprivation-induced oxidative stress being a major pathway
LH: luteinizing hormone; FSH: follicle-stimulating hormone; ROS: reactive oxygen species; POI: premature ovarian insufficiency

female reproductive function.

The mechanisms through which OS impairs female fertility are comprehensive, as summarized in the context of SD in (Figure 3). At the ovarian level, excess ROS induces mitochondrial dysfunction and apoptosis in oocytes and surrounding granulosa cells (90, 93). OS-mediated hormonal disturbances can further disrupt hormone secretion, leading to apoptosis and autophagy of ovarian cells, which ultimately contribute to reproductive disorders (100, 101). This cascade of events diminishes oocyte quality, hinders maturation, and can accelerate the depletion of the ovarian reserve, contributing to premature ovarian insufficiency. For a successful pregnancy, OS must also be tightly regulated. Elevated ROS has been shown to hinder implantation. It is implicated in the pathophysiology of major pregnancy complications like miscarriage and pre-eclampsia, in part through OS-mediated damage to the developing embryo and the placenta (88). The growing understanding of OS-regulating pathways, such as SIRT1 and TLR4/NOX2, further clarifies these damage mechanisms and highlights promising therapeutic targets (102). Given this profound sensitivity of the female reproductive axis to redox balance, it becomes clear why SD, as a potent source of systemic OS, poses such a significant and multifaceted threat to female reproductive success.

Anti-oxidants as protectors of female reproductive injury

Given the shared OS mechanism, the rationale for anti-oxidant therapy extends to female reproductive health as well. This approach stands as a promising, though yet unproven, strategy for addressing the reproductive consequences of SD in women. By examining the established efficacy of anti-oxidants in other female reproductive disorders driven by OS, we can build a strong rationale for their potential application in the context of SD (Table 2).

Anti-oxidants have demonstrated significant benefits across various conditions affecting female fertility. In disorders such as endometriosis-associated infertility and polycystic ovarian syndrome (PCOS), compounds such as vitamins C and E, melatonin, and N-acetylcysteine have been shown to reduce inflammation and oxidative damage (103-105). This protective effect also extends to counteracting environmental toxicity (106) and improving outcomes in assisted reproductive technology (ART) (107). The therapeutic potential of anti-oxidants also includes mitigating age-related reproductive decline, with various compounds enhancing oocyte quality in animal models (108-110). The landscape of potential treatments is broad, encompassing not only essential vitamins but also traditional remedies like Bushen Culuan Decoction (BCD), which show promise in preclinical models (111, 112).

However, a critical caveat applies to all anti-oxidant use in fertility: the principle of balance. Excessive supplementation can disrupt the delicate redox equilibrium essential for processes such as ovulation and implantation, potentially impeding fertility (73, 113). Therefore, while targeting OS is a valid therapeutic concept, the strategy must be tailored. The findings from recent clinical studies suggest that interventions aimed at restoring melatonin levels or protecting against hypoxia-induced OS could be particularly effective (38, 39). Given the compelling mechanistic evidence, future investigations should prioritize promising candidates such as melatonin, Coenzyme Q10, and N-acetylcysteine for preclinical testing and eventual clinical trials in women whose reproductive health is compromised by SD.

Discussion

This narrative review synthesizes a broad spectrum of evidence establishing SD as a significant risk factor for reproductive disorders in both men and women. By systematically linking SD to OS and subsequent cellular damage, a key pathological mechanism has been elucidated. A key strength is the integration of sleep science, reproductive medicine, and redox biology to build a compelling rationale for a mechanistically plausible solution: Anti-oxidant therapy.

However, in interpreting the findings, several limitations inherent to the current body of literature must be acknowledged. A primary methodological consideration in the reviewed preclinical studies is the control over confounding factors. A significant challenge is distinguishing the effects of sleep loss from the inherent stress of deprivation procedures, which can independently elevate OS. Many cited studies commendably addressed this by including robust sham or vehicle-treated control groups, such as placing control animals on grid floors within the same apparatus (37) or administering a vehicle solution to the sleep-deprived control group (31). Nevertheless, the widely used platform-based deprivation techniques inevitably introduce a stress component alongside sleep loss, a point highlighted in recent systematic reviews on the topic (15). Therefore, the observed increase in OS likely represents a composite effect. Future research would benefit from using less stressful deprivation methods and from meticulously

Table 2. Selected evidence for anti-oxidant therapies in oxidative stress (OS) driven models of female reproductive impairment

Study population/animal model	Antioxidant agent(s)	Dosage & administration	Study design	Key Outcomes Measured	Main findings (vs respective control/toxin group)	Reference
Aged rats	(R)-α-Lipoic acid	40 mg/kg/day, intraperitoneally	Animal study	Endothelial-dependent vascular function	Markedly improved age-related decline in vasomotor function, which is relevant to fertility.	(109)
Periconceptional mice	Selenium (from yeast)	0.5 mg/kg in diet/day	Animal study	Blastocyst quality and implantation success	Pregestation supplementation significantly increased the proportion of good-quality blastocysts (73.3% vs 33.3% in the control group) and reduced pre-implantation loss (9.8% vs 38.8%, $P<0.05$).	(110)
Premature ovarian failure (POF) mice (chemo-induced)	Puerarin (PUE)	100 and 200 mg/kg/day, orally for 28 days	28-day animal study	Follicle count, atresia ratio, ovarian OS markers (SOD2, Nrf2)	PUE increased follicle numbers, reduced atresia ($P<0.01$), and significantly elevated levels of antioxidant factors SOD2 and Nrf2 ($P<0.01$).	(111)
Premature ovarian insufficiency (POI) mice (TWP-induced)	Bushen Culuan Decoction (BCD) (herbal formula)	2.67 g/kg/day, orally for 30 days	30-day animal study	Follicle numbers, estrous cycle, hormone levels (AMH, E2), OS markers (MDA, SOD)	BCD restored estrous cycles, increased AMH and E2, and significantly reduced ovarian MDA while increasing SOD and CAT levels ($P<0.01$).	(112)
Reproductive-aged women with endometriosis (n=60)	Vitamin C & Vitamin E	Vit C: 1000 mg/day; Vit E: 800 IU/day, orally	8-week randomized controlled trial	Serum OS markers (MDA, ROS); Pelvic pain scores (VAS)	Significantly reduced serum MDA (p=0.002) and ROS ($P<0.001$); significantly decreased pain scores for dysmenorrhea and dyspareunia ($P<0.001$).	(101)
Polycystic ovarian syndrome (PCOS) rat model	Green tea extract	50, 100, 200 mg/kg/day, intraperitoneally for 10 days	10-day animal study	Serum hormones (LH, testosterone), insulin resistance, ovarian morphology	Dose-dependently reduced LH and testosterone ($P<0.001$), lowered insulin resistance ($P<0.05$), and improved ovarian morphology (fewer cysts, more corpora lutea).	(104)
Chemotherapy-induced accelerated ovarian aging in mice	Resveratrol (Res)	30 and 100 mg/kg/day, orally for 2 weeks	2-week animal study	Follicle count, ovarian OS markers (SOD2)	Low-dose Res (30 mg/kg) significantly increased follicle numbers ($P<0.005$) and raised ovarian SOD2 levels ($P<0.05$), alleviating ovarian aging.	(99)

reporting variables such as dietary composition, which can modulate redox status (114).

Beyond these methodological considerations, the evidence supporting anti-oxidant use is mainly indirect, particularly in the context of SD, particularly for females. There is an apparent lack of studies testing their efficacy directly in sleep-deprived human populations. Furthermore, the included studies exhibit significant heterogeneity in SD protocols, anti-oxidant types, and dosages, making it challenging to formulate specific clinical recommendations.

These limitations clearly define the path for future research and pave the way for translational research from bench to bedside. There is an urgent need for preclinical studies that directly test a broader range of anti-oxidant compounds in standardized female SD animal models. Subsequently, well-designed randomized controlled trials (RCTs) in human populations, such as shift workers or individuals with chronic insomnia, are essential to validate these preclinical findings and confirm the clinical efficacy of anti-oxidant therapies. Future work should also aim to identify reliable biomarkers of OS to pinpoint which individuals are most likely to benefit from such interventions, a significant challenge given the complexities of accurately measuring and interpreting OS in a clinical setting (115). Ultimately, the goal is to develop evidence-based, personalized anti-oxidant regimens that can be integrated into reproductive healthcare as a low-cost, high-impact strategy to counteract the growing challenge of SD in modern society.

Conclusion

A compelling body of evidence, synthesized in this review, suggests that CSD, acting primarily through the induction of OS, is a critical and potentially reversible contributor to reproductive dysfunction. Addressing sleep quality should be considered a fundamental component of reproductive healthcare. The body of evidence reviewed herein strongly supports the view that anti-oxidant therapies represent a promising, mechanistically sound approach to mitigate these harms. While their clinical utility for sleep-deprived individuals remains a compelling hypothesis awaiting

rigorous scientific validation, the potential for these interventions to provide a tangible therapeutic strategy is a significant message of this review.

Acknowledgment

We thank Freepik (www.freepik.com) and Smart (smart.servier.com) for their help in creating the figures. This work was supported by the Nanning Jiangnan District Programme Project (grant number 20230715-07) and the Key Research and Development Programme for Scientific Research and Technology in Liangqing District, Nanning City (grant numbers 202213, 202216, and 202311). The results described in this paper were part of a student's thesis.

Funding

Sources for this project include the Nanning Jiangnan District Programme Project (20230715-07) and the Key Research and Development Programme for Scientific Research and Technology in Liangqing District, Nanning City (grant numbers 202213, 202216, and 202311).

Authors' Contributions

K C conceptualized the study, conducted the literature review, drafted the manuscript, and created the tables and figures. C X provided critical feedback on the manuscript, refined the structure, and contributed to the interpretation of findings. Q H ensured the scientific accuracy of the work, reviewed the tables and figures for clarity, and provided oversight throughout the manuscript development. X L contributed to the initial organization of references and background materials. K H assisted in formatting and proofreading the manuscript. F L supported the preparation and revision of tables and figures. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration

We have not used any AI tools or technologies to prepare this manuscript.

References

1. Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB. Prevalence of healthy sleep duration among adults--United States, 2014. MMWR Morb Mortal Wkly Rep 2016; 65: 137-141.
2. Chan CMH, Siau CS, Wong JE, Wee LH, Jamil NA, Hoe VCW. Prevalence of insufficient sleep and its associated factors among working adults in Malaysia. Nat Sci Sleep 2021; 13: 1109-1116.
3. Kolla BP, He JP, Mansukhani MP, Frye MA, Merikangas K. Excessive sleepiness and associated symptoms in the U.S. adult population: Prevalence, correlates, and comorbidity. Sleep Health 2020; 6: 79-87.
4. Cheng TO. Effect of sleep deprivation on cardiovascular health. Int J Cardiol 2009; 134: 293-294.
5. Cabeza de Baca T, Chayama KL, Redline S, Slopen N, Matsushita F, Prather AA, *et al.* Sleep debt: The impact of weekday sleep deprivation on cardiovascular health in older women. Sleep 2019; 42: 149-157.
6. Uccella S, Cordani R, Salfi F, Gorgoni M, Scarpelli S, Gemignani A, *et al.* Sleep deprivation and insomnia in adolescence: Implications for mental health. Brain Sci 2023; 13: 569-591.
7. Meldrum RC, Restivo E. The behavioral and health consequences of sleep deprivation among U.S. high school students: Relative deprivation matters. Prev Med 2014; 63: 24-28.
8. Cheung V, Yuen VM, Wong GTC, Choi SW. The effect of sleep deprivation and disruption on DNA damage and health of doctors. Anaesthesia 2019; 74: 434-440.
9. Sandoval Y, Lobo AS, Somers VK, Rosenfield K, Bradley SM, Sorajja P, *et al.* Sleep deprivation in interventional cardiology: Implications for patient care and physician-health. Catheter Cardiovasc Interv 2018; 91: 905-910.
10. Ben Khelifa M, Coutton C, Zouari R, Karaouzene T, Rendu J, Bidart M, *et al.* Mutations in DNAH1, which encodes an inner arm heavy chain dynein, lead to male infertility from multiple morphological abnormalities of the sperm flagella. Am J Hum Genet 2014; 94: 95-104.
11. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: A systematic analysis of 277 health surveys. PLoS Med 2012; 9: e1001356-1001368.
12. Lateef OM, Akintubosun MO. Sleep and reproductive health. J Circadian Rhythms 2020; 18:1-12.
13. Zhao F, Hong X, Wang W, Wu J, Wang B. Effects of physical activity and sleep duration on fertility: A systematic review and meta-analysis based on prospective cohort studies. Front Public Health 2022; 10: 1029469-1029483.
14. Caetano G, Bozinovic I, Dupont C, Leger D, Levy R, Sermondade N. Impact of sleep on female and male reproductive functions: A systematic review. Fertil Steril 2021; 115: 715-731.
15. Neculicioiu VS, Colosi IA, Costache C, Toc DA, Sevastre-Berghian A, Colosi HA, *et al.* Sleep deprivation-induced oxidative stress in rat models: A scoping systematic review. Antioxidants (Basel) 2023; 12: 1600-1622.
16. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, *et al.* Reactive oxygen species, toxicity, oxidative stress, and antioxidants: Chronic diseases and aging. Arch Toxicol 2023; 97: 2499-2574.
17. de Ligny W, Smits RM, Mackenzie-Proctor R, Jordan V, Fleischer K, de Bruin JP, *et al.* Antioxidants for male subfertility. Cochrane Database Syst Rev 2022; 5: CD007411-7723.
18. Showell MG, Mackenzie-Proctor R, Jordan V, Hart RJ. Antioxidants for female subfertility. Cochrane Database Syst Rev 2020; 8: CD007807-8011.
19. Kroller-Schon S, Daiber A, Steven S, Oelze M, Frenis K, Kalinovic S, *et al.* Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. Eur Heart J 2018; 39: 3528-3539.
20. Hernandez Santiago K, Lopez-Lopez AL, Sanchez-Munoz F, Cortes Altamirano JL, Alfaro-Rodriguez A, Bonilla-Jaime H. Sleep deprivation induces oxidative stress in the liver and pancreas in young and aging rats. Heliyon 2021; 7: e06466-6473.
21. Lasisi TJ, Shittu ST, Abeje JI, Ogunremi KJ, Shittu SA. Paradoxical sleep deprivation induces oxidative stress in the submandibular glands of Wistar rats. J Basic Clin Physiol Pharmacol 2021; 33: 399-408.
22. Li Y, Zhang W, Liu M, Zhang Q, Lin Z, Jia M, *et al.* Imbalance of autophagy and apoptosis induced by oxidative stress may be involved in thyroid damage caused by sleep deprivation in rats. Oxid Med Cell Longev 2021; 2021: 5645090-5645100.
23. Belali R, Mard SA, Khoshnam SE, Bavarsad K, Sarkaki A, Farbood Y. Anandamide attenuates neurobehavioral deficits and eEG irregularities in the chronic sleep deprivation rats: The role of oxidative stress and neuroinflammation. Neurochem Res 2024; 49: 1541-1555.
24. Lima AM, de Bruin VM, Rios ER, de Bruin PF. Differential effects of paradoxical sleep deprivation on memory and oxidative stress. Naunyn Schmiedebergs Arch Pharmacol 2014; 387: 399-406.
25. Villafuerte G, Miguel-Puga A, Rodriguez EM, Machado S, Manjarrez E, Arias-Carrion O. Sleep deprivation and oxidative stress in animal models: A systematic review. Oxid Med Cell

Longev 2015; 2015: 234952-234967.
26. Khadrawy YA, Nour NA, Aboul Ezz HS. Effect of oxidative stress induced by paradoxical sleep deprivation on the activities of Na+, K+-ATPase and acetylcholinesterase in the cortex and hippocampus of rat. Transl Res 2011; 157: 100-107.
27. Chen S, Xie Y, Li Y, Fan X, Xing F, Mao Y, *et al.* Sleep deprivation and recovery sleep affect healthy male resident's pain sensitivity and oxidative stress markers: The medial prefrontal cortex may play a role in sleep deprivation model. Front Mol Neurosci 2022; 15: 937468-937483.
28. Yi ZY, Liang QX, Zhou Q, Yang L, Meng QR, Li J, *et al.* Maternal total sleep deprivation causes oxidative stress and mitochondrial dysfunction in oocytes associated with fertility decline in mice. PLoS One 2024; 19: e0306152-306173.
29. Zhang Y, Su M, Liu G, Wu X, Feng X, Tang D, *et al.* Chronic sleep deprivation induces erectile dysfunction through increased oxidative stress, apoptosis, endothelial dysfunction, and corporal fibrosis in a rat model. J Sex Med 2024; 21: 1098-1110.
30. Hosseinpour M, Dalband AM, Lajevardi Z, Soltanattar A, Tafazolimoghadam A, Karamian A, *et al.* The protective effect of bromelain on testicular dysfunction and oxidative stress induced by REM sleep deprivation in adult male rats. Tissue Cell 2025; 95: 102927-102937.
31. Rizk NI, Rizk MS, Mohamed AS, Naguib YM. Attenuation of sleep deprivation dependent deterioration in male fertility parameters by vitamin C. Reprod Biol Endocrinol 2020; 18: 2-15.
32. Fabunmi OA, Ajibare AJ, Akintoye OO, Olofinbiyi BA, Olayaki LAJNS. Honey ameliorates imbalance between reactive oxygen species and antioxidant enzymes in the testis of sleep deprived rats. 2021; 3: 40-48.
33. Musah I, Emmanuel N, Adebisi RA, Ali H, Umar B, Malgwi FD, *et al.* Antioxidant effect of hibiscus sabdariffa calyces aqueous extract against sleep deprivation-induced pituitary, testicular and epididymal oxidative damage in wistar Rats. Sahel J Life Sci 2025; 3: 154-164.
34. Muhammad S, Salisu A, Tankon Y, Mohammed A. Insufficient sleep model and male reproductive function; the role of concomitant zinc supplementation. BJMLS 2022; 7: 68-81.
35. Ajibare A, Ayodele O, Olayaki LA. Mifepristone ameliorates sleep deprivation-induced oxidative stress in the testis of rats. Afr J Biomed Res 2020; 23: 239-245.
36. Ema E, Mohammad A, Ekpo U, Oderinde G, Usman A. Evaluation of the effects of cannabidiol and sleep recovery on oxidative stress biomarkers and testicular histoarchitecture in chronic sleep-deprived male Wistar rats. DUJOPAS 2025; 11: 328-338.
37. Karimi F, Noorafshan A, Karbalay-Doust S, Naseh M. Sleep deprivation induces structural changes in the adult rat testis: The protective effects of olive oil. Clin Exp Reprod Med 2023; 50: 19-25.
38. Yildiz H, Alp HH, Ucler R, Bilgin MH. Implications of obstructive sleep apnea on reproductive health: a study on anti-Müllerian hormone levels. Sleep Breath 2024; 28: 1217-1222.
39. Li H, Liu M, Zhang C. Women with polycystic ovary syndrome (PCOS) have reduced melatonin concentrations in their follicles and have mild sleep disturbances. BMC Womens Health 2022; 22: 79-88.
40. Jiang Y, Shi H, Liu Y, Zhao S, Zhao H. Applications of melatonin in female reproduction in the context of oxidative stress. Oxid Med Cell Longev 2021; 2021: 6668365-6668376.
41. Zheng Z, Wang H, Chen Z, Gao H, Gao P, Gao J, *et al.* Impact of chronic sleep deprivation on male reproductive health: Insights from testicular and epididymal responses in mice. Andrology 2024; 13: 968-977.
42. Choi JH, Lee SH, Bae JH, Shim JS, Park HS, Kim YS, *et al.* Effect of sleep deprivation on the male reproductive system in rats. J Korean Med Sci 2016; 31: 1624-1630.
43. Adami LNG, Fernandes GL, Carvalho RC, Okada FK, Tufik S, Andersen ML, *et al.* Effect of chronic sleep deprivation on acrosomal integrity and functional parameters of murine sperm. F S Sci 2023; 4: 11-20.
44. Boeri L, Passarelli F, Basadonna LM, Sorba E, Graps G, Ciamarra F, *et al.* Oxidative stress and semen quality among night- and day-shift workers: A cross-sectional study. Antioxidants (Basel) 2025; 14: 802-814.
45. Dominguez-Salazar E, Hurtado-Alvarado G, Medina-Flores F, Dorantes J, Gonzalez-Flores O, Contis-Montes de Oca A, *et al.* Chronic sleep loss disrupts blood-testis and blood-epididymis barriers, and reduces male fertility. J Sleep Res 2020; 29: e12907-12921.
46. Jhuang YH, Chung CH, Wang ID, Peng CK, Meng E, Chien WC, *et al.* Association of obstructive sleep apnea with the risk of male infertility in Taiwan. JAMA Netw Open 2021; 4: e2031846-2031858.
47. Andersen ML, Gozal D, Pires GN, Tufik S. Exploring the potential relationships among obstructive sleep apnea, erectile dysfunction, and gut microbiota: A narrative review. Sex Med Rev 2023; 12: 76-86.
48. Smits RM, Mackenzie-Proctor R, Fleischer K, Showell MG. Antioxidants in fertility: Impact on male and female reproductive outcomes. Fertil Steril 2018; 110: 578-580.
49. Liu JB, Li ZF, Lu L, Wang ZY, Wang L. Glyphosate damages blood-testis barrier via NOX1-triggered oxidative stress in rats: Long-term exposure as a potential risk for male reproductive health. Environ Int 2022; 159: 107038-107052.
50. Fang Q, Wang C, Xiong Y. Polystyrene microplastics induce male reproductive toxicity in mice by activating spermatogonium mitochondrial oxidative stress and apoptosis. Chem Biol Interact 2024; 396: 111043-111071.
51. Panga MJ, Zhao Y. Male reproductive toxicity of antifouling chemicals: insights into oxidative stress-induced infertility and molecular mechanisms of zinc pyrithione (ZPT). Antioxidants (Basel) 2024; 13: 173-188.
52. Sun J, Li M, Xiong Y, Zhai L, Zhao J. Oxidative stress mediated by N6-methyladenosine methylation contributes to high-fat diet induced male reproductive dysfunction. Mol Nutr Food Res 2023; 67: e2101052-2101080.
53. Xu ZJ, Liu M, Niu QJ, Huang YX, Zhao L, Lei XG, *et al.* Both selenium deficiency and excess impair male reproductive system via inducing oxidative stress-activated PI3K/AKT-mediated apoptosis and cell proliferation signaling in testis of mice. Free Radic Biol Med 2023; 197: 15-22.
54. Yuan W, Ji G, Shi X, Sun Z, Liu C, Yu Y, *et al.* The male reproductive toxicity after 5-Fluorouracil exposure: DNA damage, oxidative stress, and mitochondrial dysfunction *in vitro* and *in vivo*. Ecotoxicol Environ Saf 2024; 278: 116465-116479.
55. Cherif B, Triki H, Sahnoun S, Hamden K, Sallemi A, Charfi S, *et al.* Imipenem toxicity in male reproductive organs as a result of inflammatory microenvironment and oxidative stress in germinal cells. Toxicology 2019; 416: 44-53.
56. Sengupta P, Dutta S, Slama P, Roychoudhury S. COVID-19, oxidative stress, and male reproductive dysfunctions: Is vitamin C a potential remedy? Physiol Res 2022; 71: 47-54.
57. Zhang X, Zhang T, Ren X, Chen X, Wang S, Qin C. Pyrethroids toxicity to male reproductive system and offspring as a function of oxidative stress induction: Rodent studies. Front Endocrinol (Lausanne) 2021; 12: 656106-656118.
58. Kurhaluk N, Kaminski P, Tkaczenko H. Oxidative stress, antioxidants, gut microbiota and male fertility. Cell Physiol Biochem 2025; 59: 82-123.
59. Minamiyama Y, Takemura S, Ichikawa H. Food additive-induced oxidative stress in rat male reproductive organs and hippocampus. Arch Biochem Biophys 2021; 701: 108810-108821.
60. Koohsari M, Ahangar N, Mohammadi E, Talebpour Amiri F, Shaki F. Effects of tramadol administration on male reproductive toxicity in Wistar rats The role of oxidative stress, mitochondrial dysfunction, apoptosis-related gene expression, and nuclear factor kappa B signalling. Bratisl Lek Listy 2020; 121: 400-410.
61. Gibb Z, Blanco-Prieto O, Bucci D. The role of endogenous antioxidants in male animal fertility. Res Vet Sci 2021; 136: 495-

502.
62. Kaltsas A, Markou E, Kyrgiafini MA, Zikopoulos A, Symeonidis EN, Dimitriadis F, *et al.* Oxidative-stress-mediated epigenetic dysregulation in spermatogenesis: Implications for male infertility and offspring health. Genes (Basel) 2025; 16: 93-117.
63. Ogawa S, Ota K, Nishizawa K, Shinagawa M, Katagiri M, Kikuchi H, *et al.* Micronutrient antioxidants for men (Menevit ®) improve sperm function by reducing oxidative stress, resulting in improved assisted reproductive technology outcomes. Antioxidants (Basel) 2024; 13: 635-652.
64. Santiago J, Silva JV, Santos MAS, Fardilha M. Fighting bisphenol A-induced male infertility: The power of antioxidants. Antioxidants (Basel) 2021; 10-289-310.
65. Rahman MS, Kang KH, Arifuzzaman S, Pang WK, Ryu DY, Song WH, *et al.* Effect of antioxidants on BPA-induced stress on sperm function in a mouse model. Sci Rep 2019; 9: 10584-10594.
66. Solek P, Majchrowicz L, Koziorowski M. Aloe arborescens juice prevents EMF-induced oxidative stress and thus protects from pathophysiology in the male reproductive system *in vitro*. Environ Res 2018; 166: 141-149.
67. Mohammadi Roushandeh A, Salehi I, Mortazavi M. Protective effects of restricted diet and antioxidants on testis tissue in rats fed with high-fat diet. Iran Biomed J 2015; 19: 96-101.
68. Tsounapi P, Honda M, Dimitriadis F, Kawamoto B, Hikita K, Muraoka K, *et al.* Impact of antioxidants on seminal vesicles function and fertilizing potential in diabetic rats. Asian J Androl 2017; 19: 639-646.
69. Sheweita SA, El-Dafrawi YA, El-Ghalid OA, Ghoneim AA, Wahid A. Antioxidants (selenium and garlic) alleviated the adverse effects of tramadol on the reproductive system and oxidative stress markers in male rabbits. Sci Rep 2022; 12: 13958-13970.
70. Dehdari Ebrahimi N, Sadeghi A, Shojaei-Zarghani S, Shahlaee MA, Taherifard E, Rahimian Z, *et al.* Protective effects of exogenous melatonin therapy against oxidative stress to male reproductive tissue caused by anti-cancer chemical and radiation therapy: A systematic review and meta-analysis of animal studies. Front Endocrinol (Lausanne) 2023; 14: 1184745-1184761.
71. Kokilavani P, Suriyakalaa U, Elumalai P, Abirami B, Ramachandran R, Sankarganesh A, *et al.* Antioxidant mediated ameliorative steroidogenesis by *Commelina benghalensis* L. and *Cissus quadrangularis* L. against quinalphos induced male reproductive toxicity. Pestic Biochem Physiol 2014; 109: 18-33.
72. Torres-Arce E, Vizmanos B, Babio N, Marquez-Sandoval F, Salas-Huetos A. Dietary antioxidants in the treatment of male infertility: Counteracting oxidative stress. Biology (Basel) 2021; 10: 241-280.
73. Dimitriadis F, Symeonidis EN, Tsounapi P, Kaltsas A, Hatzichristodoulou G, Sokolakis I, *et al.* Administration of antioxidants in infertile male: When it may have a detrimental effect? Curr Pharm Des 2021; 27: 2796-2801.
74. Agarwal A, Majzoub A. Role of antioxidants in assisted reproductive techniques. World J Mens Health 2017; 35: 77-93.
75. Mondal S, Bandyopadhyay A. Antioxidants in mitigating phthalate-induced male reproductive toxicity: A comprehensive review. Chemosphere 2024; 364: 143297-143314.
76. Kaltsas A. Oxidative stress and male infertility: The protective role of antioxidants. Medicina (Kaunas) 2023; 59: 1769-1798.
77. Agarwal A, Leisegang K, Majzoub A, Henkel R, Finelli R, Panner Selvam MK, *et al.* Utility of antioxidants in the treatment of male infertility: Clinical guidelines based on a systematic review and analysis of evidence. World J Mens Health 2021; 39: 233-290.
78. Hadwan MH, Almashhedy LA, Alsalman AR. Study of the effects of oral zinc supplementation on peroxynitrite levels, arginase activity and NO synthase activity in seminal plasma of Iraqi asthenospermic patients. Reprod Biol Endocrinol 2014; 12: 1-9.
79. Li J, Peng X, Zhong H, Liu S, Shi J, Zhou X, *et al.* Sleep deprivation during pregnancy leads to poor fetal outcomes in Sprague-Dawley rats. J Reprod Immunol 2023; 160: 104166-104174.
80. Beroukhim G, Esencan E, Seifer DB. Impact of sleep patterns upon female neuroendocrinology and reproductive outcomes: A comprehensive review. Reprod Biol Endocrinol 2022; 20: 16-33.
81. Caruso CC. Reducing risks to women linked to shift work, long work hours, and related workplace sleep and fatigue issues. J Womens Health (Larchmt) 2015; 24: 789-794.
82. Mahoney MM. Shift work, jet lag, and female reproduction. Int J Endocrinol 2010; 2010: 813764-813773.
83. Caetano G, Rouen A, Dupont C, Levy R, Leger D, Sermondade N, *et al.* Sleep and idiopathic infertility: A case-control study of 360 participants. Reprod Biomed Online 2025; 51: 105040-105049.
84. Yan J, Zhang X, Zhu K, Yu M, Liu Q, De Felici M, *et al.* Sleep deprivation causes gut dysbiosis impacting on systemic metabolomics leading to premature ovarian insufficiency in adolescent mice. Theranostics 2024; 14: 3760-3776.
85. Calegare BFA, Azzolini A, da Silva Vallim JR, Turco EGL, Tempaku PF, da Silva VC, *et al.* Sleep deprivation decreases the reproductive capacity by affecting the arrival of morulas in the uterus. Genesis 2020; 58: e23350-23362.
86. Gkeka K, Symeonidis EN, Tsampoukas G, Moussa M, Issa H, Kontogianni E, *et al.* Recurrent miscarriage and male factor infertility: Diagnostic and therapeutic implications. A narrative review. Cent European J Urol 2023; 76: 336-346.
87. Alvarenga TA, Aguiar MF, Mazaro-Costa R, Tufik S, Andersen ML. Effects of sleep deprivation during pregnancy on the reproductive capability of the offspring. Fertil Steril 2013; 100: 1752-1757.
88. Al-Gubory KH, Fowler PA, Garrel C. The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. Int J Biochem Cell Biol 2010; 42: 1634-1650.
89. Wang C, He C, Xu S, Gao Y, Wang K, Liang M, *et al.* Bisphenol A triggers apoptosis in mouse pre-antral follicle granulosa cells via oxidative stress. J Ovarian Res 2024; 17: 20-31.
90. Huang M, Liu S, Fu L, Jiang X, Yang M. Bisphenol A and its analogues bisphenol S, bisphenol F and bisphenol AF induce oxidative stress and biomacromolecular damage in human granulosa KGN cells. Chemosphere 2020; 253: 126707-126714.
91. Jiang X, Xing X, Zhang Y, Zhang C, Wu Y, Chen Y, *et al.* Lead exposure activates the Nrf2/Keap1 pathway, aggravates oxidative stress, and induces reproductive damage in female mice. Ecotoxicol Environ Saf 2021; 207: 111231-111240.
92. Chen J, Yang S, Ma B, Wang J, Chen J. Di-isononyl phthalate induces apoptosis and autophagy of mouse ovarian granulosa cells via oxidative stress. Ecotoxicol Environ Saf 2022; 242: 113898-113907.
93. Liu T, Di QN, Sun JH, Zhao M, Xu Q, Shen Y. Effects of nonylphenol induced oxidative stress on apoptosis and autophagy in rat ovarian granulosa cells. Chemosphere 2020; 261: 127693-127702.
94. Konstantinidou F, Budani MC, Sarra A, Stuppia L, Tiboni GM, Gatta V. Impact of cigarette smoking on the expression of oxidative stress-related genes in cumulus cells retrieved from healthy women undergoing IVF. Int J Mol Sci 2021; 22: 13147-13166.
95. Didziokaite G, Biliute G, Gudaite J, Kvedariene V. Oxidative stress as a potential underlying cause of minimal and mild endometriosis-related infertility. Int J Mol Sci 2023; 24: 3809-3818.
96. Gupta HP, Pandey R, Ravi Ram K. Altered sperm fate in the reproductive tract milieu due to oxidative stress leads to sub-fertility in type 1 diabetes females: A Drosophila-based study. Life Sci 2023; 313: 121306-121315.
97. Miyashita-Ishiwata M, El Sabeh M, Reschke LD, Afrin S, Borahay MA. Hypoxia induces proliferation via NOX4-Mediated oxidative stress and TGF-beta3 signaling in uterine leiomyoma cells. Free Radic Res 2022; 56: 163-172.
98. Wuri L, Burghardt RC, Arosh JA, Long CR, Banu SK. Hexavalent chromium disrupts oocyte development in rats by elevating oxidative stress, DNA double-strand breaks, microtubule disruption, and aberrant segregation of chromosomes. Int J Mol Sci 2023; 24: 10003-10022.
99. Wu M, Ma L, Xue L, Ye W, Lu Z, Li X, *et al.* Resveratrol alleviates chemotherapy-induced oogonial stem cell apoptosis and ovarian

aging in mice. Aging (Albany NY) 2019; 11: 1030-1044.
100. Cui J, Li Y, Zhang W, Qian H, Zhang Z, Xu K. Alginic acid induces oxidative stress-mediated hormone secretion disorder, apoptosis and autophagy in mouse granulosa cells and ovaries. Toxicology 2022; 467: 153099.
101. Amini L, Chekini R, Nateghi MR, Haghani H, Jamialahmadi T, Sathyapalan T, *et al.* The effect of combined vitamin C and vitamin E supplementation on oxidative stress markers in women with endometriosis: a randomized, triple-blind placebo-controlled clinical trial. Pain Res Manag 2021; 2021: 5529741-5529747.
102. Alam F, Syed H, Amjad S, Baig M, Khan TA, Rehman R. Interplay between oxidative stress, SIRT1, reproductive and metabolic functions. Curr Res Physiol 2021; 4: 119-124.
103. Dymanowska-Dyjak I, Frankowska K, Abramiuk M, Polak G. Oxidative imbalance in endometriosis-related infertility-the therapeutic role of antioxidants. Int J Mol Sci 2024; 25: 6298-6314.
104. Ghafurniyan H, Azarnia M, Nabiuni M, Karimzadeh L. The effect of green tea extract on reproductive improvement in estradiol valerate-induced polycystic ovarian syndrome in rat. Iran J Pharm Res 2015; 14: 1215-1233.
105. Vaskova J, Klepcova Z, Spakova I, Urdzik P, Stofilova J, Bertkova I, *et al.* The importance of natural antioxidants in female reproduction. Antioxidants (Basel) 2023; 12: 907-926.
106. Fan Y, Jiang X, Xiao Y, Li H, Chen J, Bai W. Natural antioxidants mitigate heavy metal induced reproductive toxicity: Prospective mechanisms and biomarkers. Crit Rev Food Sci Nutr 2024; 64: 11530-11542.
107. Oyawoye O, Abdel Gadir A, Garner A, Constantinovici N, Perrett C, Hardiman P. Antioxidants and reactive oxygen species in follicular fluid of women undergoing IVF: Relationship to outcome. Hum Reprod 2003; 18: 2270-2274.
108. Tarin JJ, Perez-Albala S, Cano A. Oral antioxidants counteract the negative effects of female aging on oocyte quantity and quality in the mouse. Mol Reprod Dev 2002; 61: 385-397.
109. Visioli F, Hagen TM. Antioxidants to enhance fertility: Role of eNOS and potential benefits. Pharmacol Res 2011; 64: 431-437.
110. Mamon MAC, Ramos GB. Maternal selenium-supplementation at various stages of periconception period: Influence on murine blastocyst morphology and implantation status. J Anim Sci Technol 2017; 59: 7-20.
111. Chen C, Li S, Hu C, Cao W, Fu Q, Li J, *et al.* Protective effects of puerarin on premature ovarian failure via regulation of Wnt/beta-catenin signaling pathway and oxidative stress. Reprod Sci 2021; 28: 982-990.
112. Chen Y, Fan X, Ma K, Wang K, Tian C, Li M, *et al.* Bushen culuan decoction ameliorates premature ovarian insufficiency by acting on the Nrf2/ARE signaling pathway to alleviate oxidative stress. Front Pharmacol 2022; 13: 857932-857948.
113. Dimitriadis F, Tsounapi P, Zachariou A, Kaltsas A, Sokolakis I, Hatzichristodoulou G, *et al.* Therapeutic effects of micronutrient supplements on sperm parameters: Fact or fiction? Curr Pharm Des 2021; 27: 2757-2769.
114. Ionita-Mindrican CB, Ziani K, Mititelu M, Oprea E, Neacsu SM, Morosan E, *et al.* Therapeutic benefits and dietary restrictions of fiber intake: A state of the art review. Nutrients 2022; 14: 2641-2667.
115. Sies H. Oxidative stress: A concept in redox biology and medicine. Redox Biol 2015; 4: 180-183.