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Psychological Stress and Male Fertility: Pathophysiological Mechanisms, Experimental Models, and Therapeutic Approaches—A Narrative Review

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ABSTRACT

Objective: This narrative review aimed to synthesize current evidence regarding the biological mechanisms linking psychological stress with male reproductive dysfunction and to evaluate potential therapeutic strategies targeting stress-related fertility impairment.

Methods and Materials: A structured narrative review was conducted using PubMed, Scopus, and ScienceDirect databases. Studies published between 1997 and 2024 were identified using keywords related to psychological stress, male fertility, cortisol, hypothalamic–pituitary–adrenal (HPA) axis, hypothalamic–pituitary–gonadal (HPG) axis, oxidative stress, inflammation, spermatogenesis, and semen quality. Human studies, animal models, and experimental investigations examining stress-related reproductive alterations were included. Findings were synthesized narratively according to neuroendocrine mechanisms, oxidative and inflammatory pathways, experimental models, and therapeutic approaches.

Findings: Current evidence suggests that chronic psychological stress may influence male reproductive function through interacting pathways involving HPA axis activation, cortisol elevation, HPG axis suppression, oxidative stress, inflammation, and behavioral factors. Experimental studies demonstrate that increased reactive oxygen species, inflammatory cytokines, and altered hormonal regulation may contribute to impaired spermatogenesis, sperm DNA damage, and reduced semen quality. Animal models provide important mechanistic insights; however, their translation to humans remains limited. Therapeutic approaches, including cognitive-behavioral interventions, lifestyle modification, antioxidant strategies, and selected phytotherapeutic agents, show potential benefits, although clinical evidence remains heterogeneous.

Conclusion: Psychological stress may contribute to male reproductive dysfunction through complex neuroendocrine, oxidative, inflammatory, and behavioral mechanisms. However, current human evidence is insufficient to establish definitive causality. Longitudinal studies and controlled clinical trials are required to clarify mechanisms and evaluate targeted interventions.

Keywords: Psychological Stress, Male Fertility, Cortisol, Oxidative Stress, Spermatogenesis.

Introduction

Psychological stress refers to a state in which environmental, social, emotional, or cognitive demands are perceived as exceeding an individual's adaptive capacity. Unlike physical stressors, which directly affect physiological systems through injury, illness, pain, extreme temperatures, or environmental exposure, psychological stress originates from perceived threats, emotional challenges, occupational demands, interpersonal conflicts, or other psychosocial factors. Psychological stress may be acute or chronic depending on its duration (Nargund, 2015). Chronic stress represents prolonged or repeated exposure to stressors, resulting in sustained activation of stress-response pathways. Psychosocial stress constitutes a specific subtype of psychological stress arising from social and environmental circumstances such as social isolation, financial difficulties, workplace pressure, or adverse life events (Iwasa et al., 2017). In experimental settings, stress can be induced under controlled laboratory conditions using behavioral, social, or environmental paradigms, particularly in animal models, to investigate the biological mechanisms underlying stress-related disorders. Despite differences in their origin and duration, these forms of stress commonly activate the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, thereby influencing multiple physiological processes, including reproductive function (Mbiydzenyuy & Qulu, 2024). This activation stimulates the release of glucocorticoids, primarily cortisol. Cortisol plays a major role in regulating the body's response to stress (Godoy et al., 2018). Acute stress can be advantageous; however, extended exposure leads to persistent dysregulation of the endocrine and immune systems. One of the principal consequences of chronic stress is disruption of the hypothalamic–pituitary–gonadal (HPG) axis, leading to impaired testosterone production and altered spermatogenesis (Nargund, 2015).

Chronic stress also amplifies oxidative and inflammatory responses, as evidenced by elevated levels of pro-inflammatory cytokines and reactive oxygen species (ROS). These factors create a poor environment for sperm to grow, which can lead to problems such as azoospermia and oligospermia (Elyadini et al., 2024; Wingfield & Sapolsky, 2003). Even though we've learned a lot about how stress affects the body, we still don't know enough about its effects on male fertility in humans because it's hard to disentangle how different psychological, environmental, and biological factors interact.

At the cellular level, chronic stress significantly affects testicular function by altering the redox balance. Leydig and Sertoli cells produce excessive reactive oxygen species (ROS) in their mitochondria as glucocorticoid levels rise throughout the body. This oxidative stress causes the membranes of sperm, which are high in polyunsaturated fatty acids, to break down lipids. This makes it harder for sperm to move and hurts the acrosome. An increase in p53 protein levels and the Bax/Bcl-2 ratio activates both intrinsic and extrinsic apoptotic pathways, which rapidly kill germ cells. This molecular cascade explains why traditional sperm parameters decline and the sperm DNA fragmentation index increases. This is an important biomarker that is often linked to problems with conception and early fetal losses. It is important to stress that these mechanisms. At the same time, well-established in experimental models, show considerable variation in humans, particularly due to factors such as lifestyle, other health conditions, and environmental exposures.

The interaction between the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis constitutes the primary mechanism of stress-induced hypogonadism. Glucocorticoids directly inhibit GnRH-producing neurons in the hypothalamus and gonadotropic cells in the adenohypophysis, thereby suppressing the pulsatile release of LH and FSH (Mbiydzenyuy & Qulu, 2024).

There is growing interest in inhibitory neuropeptides, especially gonadotropin-inhibitory hormone (GnIH), which is increased by stress and directly opposes the effects of kisspeptin. This multidimensional inhibition decreases testosterone biosynthesis by Leydig cells, creating an intratesticular microenvironment that is harmful to the differentiation and maturation of spermatozoa (Iwasa et al., 2017).

Even though we know more about how stress affects the body, treating stress-related male infertility is still very difficult. Contemporary therapeutic strategies employ a dual approach: first, pharmacological reduction of the stress response via adaptogenic agents and specific antioxidants (notably coenzyme Q10 or

melatonin) to diminish testicular reactive oxygen species; second, behavioral interventions aimed at altering the neurobiology of stress. Nevertheless, the variability of individual responses and the complexity of neuro-immuno-endocrine interactions require a careful integration of data from both animal models and clinical studies. In vivo experimental models, particularly those utilizing rodents, have been extensively utilized to elucidate the pathophysiological mechanisms linking stress to male infertility. These models simulate various types of psychosocial or physical stress (e.g., restraint, noise, social isolation) and enable the assessment of biological impacts on the neuroendocrine system and reproductive function; they are crucial for identifying biomarkers of stress-induced testicular dysfunction and evaluating potential therapeutic strategies to preserve or restore male fertility (Mbiydzenyuy & Qulu, 2024). Accordingly, this review aimed to address the following questions: (i) What are the principal neuroendocrine, oxidative, inflammatory, and behavioral mechanisms linking psychological stress to male reproductive dysfunction? (ii) What evidence is available from human and animal studies regarding the effects of psychological stress on fertility-related outcomes? (iii) What experimental models are currently used to investigate stress-induced reproductive alterations? and (iv) What therapeutic and preventive strategies have been proposed to mitigate the adverse reproductive consequences of psychological stress?

Methods and Materials

Study Design

This narrative review aimed to comprehensively examine the pathophysiological mechanisms through which chronic psychological stress affects male fertility, with particular emphasis on neuroendocrine, cellular, and behavioral alterations. The review integrates evidence from both human and animal studies. It summarizes current therapeutic approaches, including pharmacological, psychological, and phytotherapeutic interventions, to provide a comprehensive overview of stress-induced male reproductive dysfunction.

Literature Search Strategy

A structured literature search was conducted using the PubMed, Scopus, and ScienceDirect databases. Search terms included combinations of keywords related to stress and male reproductive health, including "psychological stress," "chronic stress," "male fertility," "male infertility," "spermatogenesis," "semen quality," "cortisol," "hypothalamic–pituitary–adrenal (HPA) axis," "hypothalamic–pituitary–gonadal (HPG) axis," "oxidative stress," "sperm DNA fragmentation," and "testosterone." Boolean operators (AND, OR) were used to refine and combine search terms. Reference lists of relevant publications were also manually screened to identify additional studies.

The primary database search covered studies published between 1997 and December 2024. During manuscript preparation and revision, additional relevant publications published in 2025 and 2026 were identified through citation tracking and updated literature surveillance. These more recent publications were incorporated to provide an up-to-date perspective on emerging findings and therapeutic developments but were not included in the original study selection process.

Eligibility Criteria and Study Selection

Articles were selected based on their scientific relevance to the relationship between psychological stress and male fertility. Eligible studies included: (i) original research articles and systematic reviews investigating the effects of psychological stress on male reproductive function; (ii) experimental animal studies exploring underlying pathophysiological mechanisms; and (iii) publications written in English or French.

Studies were excluded if they: (i) focused exclusively on female fertility; (ii) were not peer-reviewed; (iii) lacked sufficient methodological detail or relevant outcome data; or (iv) were duplicate publications.

Study selection was performed in two stages. First, titles and abstracts were screened for relevance. Subsequently, full-text articles were assessed for eligibility. A total of 36 studies meeting the predefined eligibility criteria were included in the primary evidence synthesis.

Data Extraction and Narrative Synthesis

Studies were selected through a two-stage screening process consisting of an initial review of titles and abstracts followed by full-text assessment of potentially relevant articles. A total of 36 articles meeting the predefined eligibility criteria were included in the primary evidence synthesis.

Data extracted from eligible studies included study design, population characteristics, type of stress

exposure, fertility-related outcomes, proposed biological mechanisms, and therapeutic interventions. Human and animal studies were considered separately whenever appropriate to facilitate interpretation of translational relevance.

The findings were synthesized narratively according to major thematic domains, including neuroendocrine dysregulation, oxidative stress, inflammation, experimental animal models, and therapeutic strategies. As the objective of this work was to provide an integrative overview of the available evidence regarding stress-induced male infertility, no formal risk-of-bias assessment, study quality scoring, or quantitative meta-analysis was performed. Therefore, this work should be considered a narrative review rather than a systematic review.

Findings and Results

A total of 36 studies meeting the predefined eligibility criteria were included in the primary evidence synthesis. The included evidence comprised human observational studies, experimental animal studies, and mechanistic investigations examining the relationship between psychological or chronic stress and male reproductive function. The findings were organized into major domains, including neuroendocrine responses to stress, cortisol-related alterations, pathophysiological mechanisms affecting male fertility, semen quality, and sexual function, experimental animal models, stress-related brain alterations, and therapeutic approaches.

Neuroendocrine Responses to Psychological Stress

Stress induces a coordinated systemic response involving neuroendocrine, autonomic, metabolic, and immune pathways. Two major systems are activated during the stress response: the sympathetic nervous system (SNS)–adrenal medullary system and the hypothalamic–pituitary–adrenal (HPA) axis. Activation of the sympathetic nervous system and adrenal medulla results in the rapid release of catecholamines, particularly adrenaline and noradrenaline. During acute stress, these mediators increase heart rate, arterial blood pressure, and circulating glucose concentrations, thereby facilitating the physiological "fight-or-flight" response (Moisan & Le Moal, 2012).

In parallel, activation of the HPA axis initiates a hormonal cascade beginning with the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH subsequently stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which acts on the adrenal cortex to promote cortisol secretion, the principal glucocorticoid involved in the stress response (Verney et al., 2021). Cortisol subsequently participates in regulating metabolic, immunological, cardiovascular, and neuronal processes and contributes to physiological adaptation to stressful conditions.

Cortisol-Related Physiological Alterations

Cortisol plays a central role in maintaining physiological homeostasis during stress exposure. At the metabolic level, cortisol increases the availability of glucose by stimulating hepatic glucose production and reducing peripheral glucose uptake, thereby increasing the amount of circulating glucose available to the brain and skeletal muscles.

At the immune level, cortisol exerts anti-inflammatory effects by inhibiting the production and release of pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). Cortisol also reduces lymphocyte proliferation and activity (Dhabhar & McEwen, 1997). Prolonged elevation of cortisol, however, has been associated with suppression of both innate and adaptive immune responses.

Cortisol also contributes to cardiovascular regulation by enhancing vascular responsiveness to catecholamines, thereby supporting vascular tone and hemodynamic stability (Whitworth et al., 2005). Within the central nervous system, cortisol modulates neural circuits involving the hippocampus and amygdala, which are important for memory processing and emotional regulation (Lupien et al., 2009). Sustained hypercortisolemia has been associated with anxiety disorders, major depressive disorder, and cognitive impairment.

Pathophysiological Mechanisms Linking Chronic Stress to Male Reproductive Dysfunction

The reviewed evidence identified several interconnected biological mechanisms through which chronic stress affects male reproductive function. These mechanisms primarily involve disruption of the hypothalamic–pituitary–gonadal (HPG) axis, oxidative

stress, inflammation, alterations in sperm characteristics, and changes in sexual function.

HPG-Axis Dysregulation and Reproductive Hormones

Chronic stress disrupts the hypothalamic–pituitary–gonadal axis by inhibiting gonadotropin-releasing hormone (GnRH) secretion. Reduced GnRH signaling is accompanied by decreases in luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in impaired testosterone production and alterations in spermatogenesis (Odetayo et al., 2024).

The hormonal sequence identified in the reviewed evidence can therefore be summarized as activation of the HPA axis, increased cortisol secretion, suppression of gonadotropic signaling, reduced reproductive hormone levels, and subsequent impairment of spermatogenesis. Prolonged elevations in cortisol were associated with decreased LH, FSH, and testosterone levels, indicating interactions between stress-related endocrine activity and male reproductive endocrine regulation.

Oxidative Stress and Sperm Damage

Chronic stress was also associated with increased production of reactive oxygen species (ROS). Excessive ROS production contributes to oxidative stress within reproductive tissues and has been associated with sperm DNA damage, disruption of sperm membrane fluidity, lipid peroxidation, and reduced sperm motility (Agarwal et al., 2014).

These effects are particularly relevant to spermatozoa because their membranes contain high concentrations of polyunsaturated fatty acids and are therefore susceptible to oxidative damage. Oxidative injury to sperm membranes can interfere with sperm movement and acrosomal function, while oxidative damage to DNA can increase sperm DNA fragmentation.

Stress-related oxidative alterations have also been associated with activation of apoptotic mechanisms. Increased p53 expression and alterations in the Bax/Bcl-2 ratio have been linked to the activation of apoptotic pathways and germ-cell death. These cellular alterations are accompanied by decreases in conventional sperm parameters and increases in sperm DNA fragmentation.

Inflammatory Mechanisms and the Blood-Testis Barrier

Chronic stress was associated with elevated levels of pro-inflammatory cytokines, particularly TNF-α and IL-6. Increased inflammatory activity can compromise the integrity of the blood-testis barrier and interfere with normal spermatogenesis. Such alterations have been associated with reduced sperm production and reproductive abnormalities, including oligospermia and azoospermia (Hedger, 1997).

Inflammatory processes may therefore act alongside neuroendocrine and oxidative mechanisms in stress-related testicular dysfunction.

Effects on Semen Quality and Sexual Function

The reviewed human evidence identified associations between psychological stress and several indicators of semen quality. Chronic or prolonged stress was associated with reduced sperm concentration and deterioration in seminal parameters, particularly sperm motility and morphology.

Men reporting higher levels of perceived stress were reported to have poorer sperm-quality parameters. In the study reported by Janevic et al. (2014), high perceived stress was also associated with factors including cigarette smoking, lower socioeconomic status, and frequent exposure to stressful life events. The same study reported variation in sperm-quality characteristics by ethnic background, including differences in the proportions of motile and morphologically normal sperm.

In addition to semen-quality alterations, chronic stress was associated with erectile dysfunction. Reported mechanisms included reduced testosterone concentrations, endothelial dysfunction affecting penile vasodilation, and increased adrenaline activity, which interferes with smooth muscle relaxation and erectile function (Kalaitzidou et al., 2014).

Overall, the identified reproductive alterations included reductions in testosterone and gonadotropins, impaired spermatogenesis, decreased sperm concentration and motility, abnormalities in sperm morphology and DNA integrity, and changes in erectile and sexual function. Thus, this allowed us to draw a summary figure of the impact of chronic stress on the hypothalamic-pituitary-adrenal (HPA) axis and its repercussions on male fertility (Figure 1).

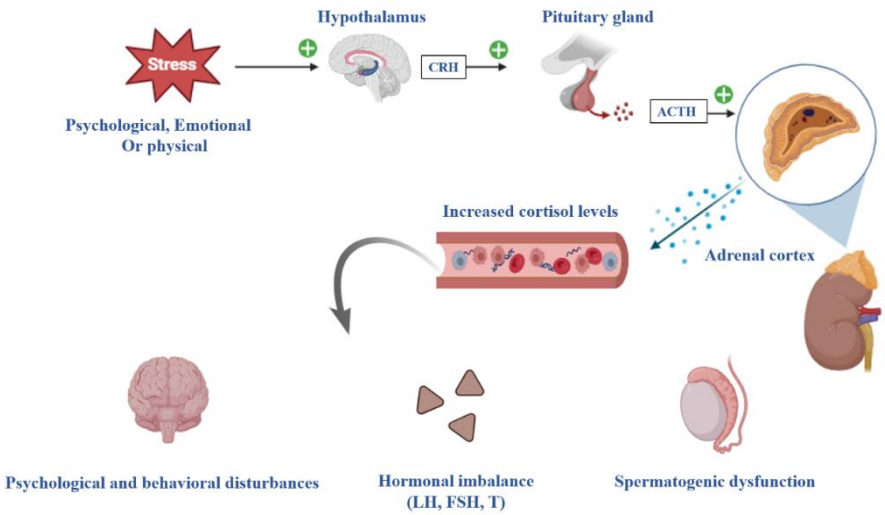

Figure 1

Impact of Chronic Stress on the HPA Axis and Male Fertility

The synthesized pathway illustrated in Figure 1 begins with exposure to psychological, emotional, or physical stress. Stress activates the hypothalamus, stimulating CRH secretion, followed by pituitary ACTH release and adrenal cortex activation. Increased cortisol production is subsequently associated with hormonal imbalance involving LH, FSH, and testosterone, spermatogenic dysfunction, and psychological and behavioral disturbances. A summary of pathophysiological mechanisms is presented in Table 1.

Table 1

Summary of the Main Pathophysiological Mechanisms

Mechanism	Involved pathways	Biological effects	Consequences on fertility	Reference
Activation HHS	CRH → ACTH → cortisol	Hypercortisolism	Inhibition of GnRH, ↓ testosterone	(Herman et al., 2016; McCosh et al., 2022; Rubinow et al., 2005) 08/09/2026 13:33:00
Disequilibria HHG	↓ GnRH, LH, FSH	Hypogonadism	Alteration of spermatogenesis	(Desai et al., 2022; Pitteloud & Dwyer, 2014)
Oxidative stress	ROS ↑	Lipid peroxidation, damaged DNA	↓ mobility, DNA fragmentation	(Gualtieri et al., 2021; Len et al., 2019)
Inflammation	IL-6, TNF-α ↑	BHT Alteration	Oligospermia, azoospermia	(Attia et al., 2021; Hagan et al., 2015; Koumba et al., 2026)
Apoptosis	p53, Bax/Bcl-2	Death of germ cells	↓ sperm production	(Fan et al., 2017; F. Yang et al., 2025)

Experimental Animal Models

Experimental animal models, particularly rodent models, have been extensively used to characterize the biological and reproductive consequences of chronic stress under controlled conditions. These models permit the evaluation of neuroendocrine, biochemical, cellular, behavioral, and reproductive alterations following exposure to defined stress paradigms.

Commonly used stress-induction paradigms include restraint stress, social isolation or crowding, chronic unpredictable stress, and exposure to other aversive stimuli. Activation of the HPA axis in rodents is commonly assessed by measuring circulating or urinary corticosterone concentrations.

Studies using rodent models have demonstrated that chronic stress exposure can alter reproductive-organ characteristics, reduce circulating testosterone levels, and impair sexual function (Arun et al., 2018). Reductions in male sexual behavior and libido have also been observed. By combining behavioral measurements with biochemical and reproductive assessments, these models have enabled simultaneous evaluation of stress responses and reproductive outcomes (Arun et al., 2018; Arun et al., 2021; T. Yang et al., 2025).

Physical and Psychological Stress-Induction Models

Different experimental paradigms have been used to reproduce different components of stress-related reproductive dysfunction.

Restraint Stress

Restraint stress is commonly used as a physical stress paradigm. Immobilization produces marked neuroendocrine alterations and has been associated with a pronounced decrease in testosterone. The decline in testosterone has been linked to inhibition of Leydig-cell steroidogenesis (Kherrab et al., 2024; Mansour et al., 2026; Nassiri et al., 2023). Germ-cell apoptosis has also been reported following restraint stress.

Chronic Unpredictable Mild Stress

Chronic unpredictable mild stress (CUMS) involves repeated exposure to a range of mild, unpredictable stressors. These may include inversion of the light-dark cycle, cage tilting, and brief periods of water deprivation. This model is used to reproduce psychological stress-related alterations and has been associated with decreased libido, sperm DNA fragmentation, and alterations in the kisspeptin/GnRH pathway. These alterations are particularly relevant to the study of stress-associated oligospermia.

Social Stress

Social stress paradigms include conditions such as crowding, overpopulation, and social isolation. These conditions have been associated with alterations in HPA-axis activity and behavioral erectile dysfunction.

Scrotal Thermal Stress

Scrotal thermal stress involves local exposure of the testes to temperatures of approximately 40–42°C. This model produces pronounced testicular effects, including cessation of spermatogenesis and extensive oxidative stress.

Assessment of Sperm Quality and Blood-Testis Barrier Integrity in Animal Models

Assessment of fertility in experimental models extends beyond conventional sperm counts. Recent investigations have also examined blood-testis barrier integrity and molecular markers related to tight junctions.

Stress-induced systemic inflammation has been associated with reduced expression of tight-junction proteins, including claudin-11 and occludin, and consequent impairment of blood-testis barrier integrity (Zhang et al., 2024).

Computer-Assisted Sperm Analysis (CASA) has also been used in rodent studies to quantify sperm-motion characteristics. This approach allows measurement of hyperactivated motility parameters relevant to fertilization capacity that may not be fully captured by conventional manual sperm analysis.

Duration of Stress Exposure

The duration of exposure to a stressor was associated with differences in the reproductive outcomes detected in experimental models. Exposure for approximately 15 days primarily affected erectile function and libido.

Longer exposure periods of approximately 35–52 days, corresponding to a complete spermatogenic cycle in rats, were used to assess more extensive reproductive alterations, including structural damage to seminiferous tubules and epigenetic modifications in spermatozoa (Andreu-Noguera et al., 2023).

Experimental models also permitted assessment of reproductive changes after removal of the stressor, allowing evaluation of the reversibility of stress-induced alterations and changes occurring during therapeutic interventions. Characteristics of in vivo stress models used in the study of testicular dysfunction and infertility in rodents are presented in Table 2.

Table 2

Characteristics of In Vivo Stress Models

Model of Stress	Type of stress	Principal	Impact on fertility	Exposure duration	Limitations	Reference
Restraint stress	Physical	Immobilization (2-6h/jour)	Drastic drop in testosterone, apoptosis of germ cells.	Acute/chronic	Acute stress model poorly representative of chronic human psychosocial stress; artificial experimental conditions; absence of cognitive and emotional components.	(Liu et al., 2017)
CUMS	Psychological	Various and unpredictable stressors	Decreased libido, sperm DNA fragmentation.	Chronic	Significant heterogeneity of protocols; limited reproducibility between studies; strong dependence on the experimenter.	(Sahoo & Das, 2026)

Social stress (Crowding)	Psychosocial	Overpopulation or isolation	Alteration of the HPA axis and behavioral erectile dysfunction.	Long time	Simplification of human social interactions; high interindividual variability; limited control over confounding behavioral factors.	(Wang et al., 2024)
Thermic Stress scrotal	Physical	Local exposure to 40-42°C	Cessation of spermatogenesis and massive oxidative stress.	Acute	Non-specific model of psychological stress; direct induction of testicular lesions; low relevance for the study of psychosocial stress.	(Zhang et al., 2024)

CUMS; Chronic Unpredictable Mild Stress

Effects of Stress on the Brain

Beyond endocrine and reproductive alterations, chronic stress also exerts significant effects on the brain, particularly in regions involved in emotional regulation, hormonal control, and sexual behavior.

Chronic stress profoundly affects both brain structure and neurochemistry. It disrupts neuronal homeostasis and initiates a cascade of biological alterations that accelerate neurodegenerative processes. Prolonged stress exposure leads to notable morphological alterations, including hippocampal atrophy (a region critical for learning and memory), primarily attributed to sustained glucocorticoid exposure, which impairs synaptic plasticity and neuronal survival (Zhu et al., 2014). Concurrently, amygdala hypertrophy has been observed, enhancing emotional reactivity and potentially contributing to anxiety and depressive disorders; these structural modifications reflect a functional reorganization of the brain in response to persistent threats (Moisan & Le Moal, 2012; Terburg et al., 2018). Neurochemically, stress dysregulates neurotransmission across key systems such as dopamine, serotonin, GABA, and glutamate, disruptions that underlie mood, anxiety, and cognitive disorders (Godoy et al., 2018). Elevated cortisol can exert neurotoxic effects on hippocampal neurons by disrupting energy metabolism and promoting apoptosis. (Bremner, 2006). Furthermore, stress acts as a potent inducer of neuroinflammation, with microglial activation driving the release of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), thereby impairing neuronal communication and synaptic plasticity (Liu et al., 2017). Simultaneously, excessive generation of reactive oxygen species (ROS) overwhelms cerebral antioxidant defenses, resulting in oxidative damage to lipids, proteins, and neuronal DNA, all of which are critically implicated in neurodegenerative vulnerability (Salim, 2017). Lastly, chronic stress impairs neurogenesis, particularly in the hippocampus, by reducing proliferation and survival of neural stem cells, a process largely mediated by decreased brain-derived neurotrophic factor (BDNF), a key molecule for neuronal growth, differentiation, and survival; diminished BDNF levels strongly correlate with depression and impaired cognitive adaptability (Bahls et al., 2017; Leschik et al., 2021).

These brain alterations can indirectly impair male reproductive function by disrupting the neural regulation of the hypothalamic-pituitary-gonadal (HPG) axis and reducing sexual behavior.

Therapeutic Approaches for Stress-Related Male Infertility

The therapeutic management of male infertility related to stress remains a challenge due to the multifactorial nature of this condition and the lack of a clearly established clinical consensus. Addressing psychological stress through targeted interventions is a key strategy in improving male fertility outcomes. Cognitive-behavioral therapies (CBT) have been shown to significantly reduce anxiety and psychological distress, leading to improvements in seminal parameters (Ilacqua et al., 2018). Complementary practices such as relaxation techniques, yoga, and meditation effectively lower cortisol levels while enhancing sperm concentration and motility. Psychological support, including participation in support groups, further aids in mitigating the emotional burden associated with infertility (Jadhav et al., 2024). Lifestyle modifications also play a crucial role: moderate physical activity, improved sleep hygiene, and reduced alcohol and tobacco consumption have all demonstrated beneficial effects on spermatogenesis and semen quality (Jóźków & Rossato, 2017). Pharmacological treatments targeting the hypothalamic-pituitary-gonadal (HPG) axis and erectile function include phosphodiesterase type 5 inhibitors (PDE5i), clomiphene citrate, and human chorionic gonadotropin (hCG). PDE5 inhibitors primarily enhance erectile function by increasing cGMP levels in penile tissues and may indirectly support testosterone production. Also, Clomiphene citrate, a selective estrogen receptor modulator, stimulates gonadotropin

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release (LH and FSH) by blocking estrogen negative feedback, thereby enhancing testicular testosterone synthesis. The hCG mimics LH action by directly activating Leydig cells to increase testosterone production, collectively contributing to improved fertility via hormonal rebalancing (Sofikitis et al., 2021).

Antioxidant therapies have garnered substantial interest for their capacity to counteract oxidative stress, which is a key factor in male infertility. Agents such as vitamins C and E, zinc, coenzyme Q10, omega-3 fatty acids, and L-carnitine all neutralize reactive oxygen species, protecting spermatozoa from lipid peroxidation and improving motility and overall semen quality. Vitamin C is particularly important for cellular membrane integrity, whereas vitamin E and coenzyme Q10 support cellular energy metabolism, thereby optimizing sperm function (Kallinikas et al., 2024). However, the available clinical data on antioxidants remain heterogeneous, with sometimes contradictory results, due to variations in doses, therapeutic combinations, and studied populations.

Phytotherapeutic agents also present promising adjunctive benefits. Ashwagandha, an adaptogenic herb, has been extensively studied for its anxiolytic properties and ability to elevate testosterone levels, thereby enhancing sperm quality and concentration through hormonal modulation and stress reduction (Ambiye et al., 2013). Ginseng exerts adaptogenic and circulatory-enhancing effects, improving testicular blood flow and sperm motility (Leung & Wong, 2013). Rhodiola rosea reduces fatigue and bolsters stress resilience, helping to normalize cortisol levels that otherwise impair testicular function (Jówko et al., 2018). Ginger's anti-inflammatory and antioxidant properties, alongside its aphrodisiac effects, promote reproductive tissue circulation and reduce oxidative stress, potentially improving sperm motility and quality (Banihani, 2019; El-Naggar et al., 2020). Although promising, these phytotherapeutic agents require rigorous clinical trials to confirm their long-term efficacy and safety.

Evidence regarding cannabidiol (CBD) and male reproductive health remains limited and inconclusive. Although preclinical studies have suggested potential anti-inflammatory and antioxidant properties, clinical evidence supporting its use for stress-related male infertility is currently insufficient. Moreover, some studies evaluating cannabis-derived products have reported potential adverse reproductive effects. Therefore, CBD should be considered an area of experimental research requiring further investigation before clinical recommendations can be made (Hsiao & Clavijo, 2018). However, the data regarding cannabidiol remains limited and primarily derived from preclinical studies, which does not allow, at this stage, for the formulation of solid clinical recommendations.

Therapeutic approaches are presented in Table 3.

Table 3

Therapeutic approaches

Intervention	Mechanism	Level of evidence	Limits	Reference
CBT	↓ cortisol	Moderate (human)	Depends on membership	(Ilacqua et al., 2018)
Antioxidants	↓ ROS	Variable	Heterogeneous results	-
Clomiphene	↑ LH/FSH	Good	Secondary effects	-
hCG	↑ Testosterone	Good	cost	-
Phytotherapy	adaptogen	low-moderate	Missing RCT	-

CBT: Cognitive-behavioral therapy; ROS: reactive oxygen species; LH: luteinizing hormone; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; RCT: randomized controlled trial.

Discussion and Conclusion

The findings of this narrative review indicate that psychological stress may contribute to male reproductive dysfunction through interconnected neuroendocrine, oxidative, inflammatory, cellular, vascular, and behavioral mechanisms. The available evidence suggests that chronic activation of stress-response pathways, particularly the hypothalamic–pituitary–adrenal (HPA) axis, may interfere with reproductive endocrine regulation and testicular function. At the same time, oxidative stress and inflammatory processes may directly affect spermatogenesis, sperm integrity, and sexual function. However, the strength and consistency of these associations differ considerably between experimental and human studies.

One of the major mechanisms linking psychological stress to male reproductive dysfunction involves interaction between the HPA and hypothalamic–pituitary–gonadal (HPG) axes. During stress, corticotropin-releasing hormone (CRH) stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which subsequently promotes cortisol secretion from the adrenal cortex (Verney et al., 2021). Cortisol plays an important role in physiological adaptation to stress and regulates several metabolic, immune, and neuronal processes (Moisan & Le Moal, 2012). However, prolonged activation of this neuroendocrine pathway may interfere with reproductive hormonal regulation.

Chronic stress has been shown to inhibit GnRH secretion, resulting in reductions in LH and FSH and subsequent impairment of testosterone production and spermatogenesis (Odetayo et al., 2024). Evidence summarized in this review similarly identifies HPA-axis hyperactivation and HPG-axis suppression as important components of stress-related reproductive dysfunction (Herman et al., 2016; McCosh et al., 2022; Rubinow et al., 2005; Desai et al., 2022; Pitteloud & Dwyer, 2014). These findings indicate that neuroendocrine dysregulation represents an important biological pathway through which persistent psychological stress may influence male reproductive function.

Oxidative stress constitutes another major mechanism identified in the reviewed literature. Chronic stress increases the production of reactive oxygen species (ROS), which can cause lipid peroxidation, sperm membrane damage, decreased sperm motility, and sperm DNA fragmentation (Agarwal et al., 2014). Similar evidence indicates that excessive ROS production is associated with oxidative damage to sperm DNA and impaired sperm function (Gualtieri et al., 2021; Len et al., 2019). Because spermatozoa are particularly susceptible to oxidative injury, persistent increases in ROS may substantially contribute to deterioration of semen quality.

Oxidative injury may also be accompanied by activation of apoptotic pathways. Alterations in p53 expression and the Bax/Bcl-2 balance have been associated with germ-cell apoptosis and reductions in sperm production (Fan et al., 2017; F. Yang et al., 2025). These processes provide an additional cellular mechanism linking chronic stress to impaired spermatogenesis.

Inflammatory mechanisms may further contribute to stress-related reproductive dysfunction. Increased concentrations of pro-inflammatory cytokines, particularly IL-6 and TNF-α, can compromise the integrity of the blood-testis barrier and interfere with spermatogenesis (Hedger, 1997). Pro-inflammatory cytokines have also been implicated in male infertility and alterations of the testicular microenvironment (Attia et al., 2021; Hagan et al., 2015; Koumba et al., 2026). Therefore, neuroendocrine dysregulation, oxidative stress, inflammation, and apoptosis should not be regarded as completely independent processes; rather, their interaction may contribute to the overall reproductive effects associated with chronic psychological stress.

Effects on Semen Quality and Sexual Function

The reviewed human evidence suggests that psychological stress may also be associated with deterioration in conventional semen parameters. Men reporting higher perceived stress levels have demonstrated lower sperm concentration and poorer semen quality, including alterations in sperm motility and morphology (Janevic et al., 2014). However, perceived stress in human populations is frequently associated with additional lifestyle and socioeconomic variables, including smoking, adverse life events, and lower socioeconomic status, which complicate interpretation of these associations (Janevic et al., 2014).

Chronic stress may also influence sexual function. Erectile dysfunction has been associated with stress-related reductions in testosterone, endothelial dysfunction that impairs penile vasodilation, and increased adrenergic activity that inhibits smooth muscle relaxation (Kalaitzidou et al., 2014). Therefore, the reproductive consequences of psychological stress may involve not only sperm production and quality but also hormonal and sexual-function alterations.

Human Evidence Versus Experimental Evidence

Despite considerable experimental evidence supporting biological mechanisms linking psychological stress to reproductive dysfunction, establishing a definitive causal relationship in humans remains difficult. Most clinical investigations examining this association are observational and are therefore susceptible to confounding by lifestyle, socioeconomic

status, environmental exposures, and comorbid conditions. Differences in the methods used to assess psychological stress also limit comparability between studies. Some studies rely primarily on subjective questionnaires, whereas others use biological indicators such as salivary or plasma cortisol.

In contrast, animal models provide controlled environments in which the biological consequences of specific stressors can be examined with fewer confounding influences. Rodent models have been widely used to assess the effects of stress on HPA-axis activation, testosterone concentrations, reproductive-organ characteristics, sperm quality, and sexual function (Arun et al., 2018; Arun et al., 2021). Behavioral and biochemical analyses in these models have provided important information regarding the physiological and reproductive consequences of chronic stress (T. Yang et al., 2025).

Nevertheless, the mechanistic strength of experimental studies should not be interpreted as direct evidence of equivalent effects in humans. Animal and human reproductive systems differ in hormonal regulation, spermatogenic-cycle duration, behavioral responses, and the complexity of psychosocial stress exposure. Consequently, experimental findings provide biological plausibility but cannot alone establish the magnitude or causality of stress-related infertility in human populations.

Translational Relevance of Experimental Stress Models

Different animal stress paradigms reproduce different dimensions of stress exposure. Restraint stress is frequently used as a physical stress model and has been associated with marked reductions in testosterone through inhibition of Leydig-cell steroidogenesis (Kherrab et al., 2024; Mansour et al., 2026; Nassiri et al., 2023). In contrast, chronic unpredictable mild stress (CUMS), which involves repeated exposure to varying mild stressors, is intended to model certain aspects of chronic psychological stress and has been associated with alterations in libido, sperm DNA integrity, and the kisspeptin/GnRH pathway.

The duration of experimental stress exposure is another important consideration. Shorter stress exposures may predominantly affect sexual behavior and erectile function. In contrast, longer periods, corresponding to a complete spermatogenic cycle, are required to evaluate structural alterations in the testis and epigenetic modifications in spermatozoa (Andreu-Noguera et al., 2023).

Recent experimental studies have also expanded assessment beyond conventional sperm counts. Alterations in the blood-testis barrier, including reductions in tight-junction proteins such as claudin-11 and occludin, have been associated with stress-induced inflammatory responses (Zhang et al., 2024). Computer-Assisted Sperm Analysis has further enabled detailed assessment of motility characteristics relevant to fertilization capacity.

Although such models are valuable for identifying mechanisms, experimental stressors do not fully reproduce the cognitive, emotional, occupational, interpersonal, and social dimensions of psychological stress experienced by humans. For example, thermal scrotal stress directly induces testicular injury and oxidative stress (Zhang et al., 2024). Still, it should be distinguished from psychological stress, as its primary action is physical rather than psychosocial. Thus, interpretation of animal findings should take into account the specific nature of each experimental paradigm.

Integration of Neuroendocrine, Oxidative, and Inflammatory Mechanisms

Taken together, the reviewed evidence suggests that stress-related reproductive dysfunction is unlikely to result from a single isolated biological abnormality. HPA-axis activation and prolonged cortisol secretion may suppress HPG-axis signaling and reproductive-hormone production, whereas excessive ROS production may simultaneously damage sperm membranes and DNA. Inflammatory cytokines may additionally disrupt the blood-testis barrier and testicular environment, while apoptotic pathways may contribute to germ-cell loss.

These mechanisms may operate simultaneously and may reinforce one another. Such interaction provides a plausible explanation for the range of reproductive alterations reported across the literature, including decreased testosterone, impaired spermatogenesis, reduced sperm concentration and motility, abnormal morphology, sperm DNA fragmentation, and impaired sexual function.

Stress-Related Brain Alterations and Their Reproductive Relevance

Chronic stress also produces structural and neurochemical changes in brain regions involved in

emotional processing and endocrine regulation. Sustained glucocorticoid exposure has been associated with hippocampal atrophy and impairment of synaptic plasticity and neuronal survival (Zhu et al., 2014). Amygdala hypertrophy has also been reported and may contribute to increased emotional reactivity during prolonged stress exposure (Moisan & Le Moal, 2012; Terburg et al., 2018).

At the neurochemical level, stress can alter neurotransmission involving dopamine, serotonin, GABA, and glutamate (Godoy et al., 2018). Elevated cortisol may also adversely affect hippocampal neurons by disrupting energy metabolism and promoting apoptosis (Bremner, 2006).

Neuroinflammation represents another component of the central response to chronic stress. Microglial activation can increase production of IL-1β, IL-6, and TNF-α, thereby affecting neuronal communication and synaptic plasticity (Liu et al., 2017). In addition, excessive cerebral ROS production may cause oxidative injury to neuronal lipids, proteins, and DNA (Salim, 2017).

Chronic stress has also been associated with reduced hippocampal neurogenesis and decreased brain-derived neurotrophic factor (BDNF) levels, which are important for neuronal growth, differentiation, and survival (Bahls et al., 2017; Leschik et al., 2021). Because central neural pathways regulate both the stress response and reproductive endocrine activity, these brain alterations may indirectly contribute to reproductive dysfunction by altering HPG-axis regulation, psychological state, and sexual behavior.

Clinical and Therapeutic Implications

The multidimensional mechanisms involved in stress-related reproductive dysfunction suggest that clinical management may require more than one therapeutic strategy. Psychological interventions represent one potential approach because they target the stress response itself. Cognitive-behavioral therapy (CBT) has been associated with reductions in anxiety and psychological distress as well as improvements in seminal parameters (Ilacqua et al., 2018). Relaxation techniques, yoga, meditation, and psychological support have also been used to reduce stress and its emotional impact in men experiencing infertility (Jadhav et al., 2024).

Lifestyle modification may provide additional benefits. Moderate physical activity, improved sleep hygiene, and reductions in tobacco and alcohol consumption have been associated with improvements in spermatogenesis and semen quality (Jóźków & Rossato, 2017). Such approaches may be particularly important because lifestyle factors can simultaneously influence psychological stress and reproductive health.

Pharmacological approaches targeting erectile function and reproductive hormonal regulation include phosphodiesterase type 5 inhibitors, clomiphene citrate, and human chorionic gonadotropin (hCG). Clomiphene promotes gonadotropin secretion by reducing estrogen-mediated negative feedback, whereas hCG stimulates Leydig cells via LH-like activity, thereby increasing testosterone production (Sofikitis et al., 2021). These interventions may therefore have a role in selected patients with specific hormonal or sexual-function abnormalities.

Antioxidant therapy has also attracted considerable interest because oxidative stress is an important mechanism of male reproductive dysfunction. Vitamin C, vitamin E, zinc, coenzyme Q10, omega-3 fatty acids, and L-carnitine have been investigated for their ability to reduce ROS-mediated sperm damage and improve semen parameters. Vitamin C contributes to membrane protection, whereas vitamin E and coenzyme Q10 participate in antioxidant defense and cellular energy metabolism (Kallinikas et al., 2024). Nevertheless, the clinical evidence remains heterogeneous and sometimes contradictory because studies differ in antioxidant doses, treatment combinations, populations, and outcome measures.

Several phytotherapeutic agents have also shown potentially beneficial effects on reproduction or stress. Ashwagandha has been associated with anxiolytic activity, increased testosterone, and improvements in sperm quality and concentration (Ambiye et al., 2013). Ginseng has been investigated for adaptogenic and circulatory effects and may improve testicular blood flow and sperm motility (Leung & Wong, 2013). Rhodiola rosea has been associated with reduced fatigue, increased stress resilience, and regulation of cortisol responses (Jówko et al., 2018). Ginger has demonstrated antioxidant and anti-inflammatory properties and has been associated with improvements in sperm motility and quality (Banihani, 2019; El-Naggar et al., 2020).

Despite these promising findings, robust clinical evidence for many phytotherapeutic interventions

remains limited, and well-designed randomized controlled trials are required to establish their long-term effectiveness and safety.

Evidence regarding cannabidiol (CBD) is also insufficient to support clinical recommendations for stress-related male infertility. Although preclinical investigations have described potential anti-inflammatory and antioxidant properties, studies of cannabis-derived products have also reported potentially adverse reproductive effects (Hsiao & Clavijo, 2018). CBD should therefore remain an area of investigation rather than an established therapeutic intervention.

Overall, the available therapeutic evidence supports a potentially multifaceted approach in which psychological support, lifestyle management, reproductive assessment, and appropriate targeted interventions are considered together. However, differences among patients in neuroendocrine status, oxidative balance, psychological condition, and reproductive abnormalities suggest that management should ultimately be individualized.

Limitations

This review has several limitations. First, as a narrative review, it did not include a formal risk-of-bias assessment or quantitative meta-analysis. Therefore, the methodological quality of individual studies could not be systematically weighted within the overall synthesis.

Second, substantial heterogeneity exists among the reviewed studies in methods for assessing psychological stress, fertility-related outcomes, study populations, and therapeutic protocols. This heterogeneity limits direct comparison of results and may contribute to inconsistencies across the available literature.

Third, much of the mechanistic evidence originates from animal and in vitro studies. Although these studies provide important information regarding biological pathways, differences between experimental models and human reproductive physiology limit their direct clinical translation.

Fourth, most human studies examining stress and male reproductive outcomes are observational. Their design limits the ability to establish definitive causal relationships between psychological stress and male infertility. The relationship may also be bidirectional, because psychological stress may negatively affect reproductive function, while infertility itself can generate considerable psychological distress.

Finally, evidence concerning several therapeutic approaches, particularly antioxidant and phytotherapeutic interventions, remains heterogeneous. Differences in dose, duration of therapy, treatment combinations, participant characteristics, and outcome measures currently prevent the establishment of standardized therapeutic recommendations.

Recommendations and Future Directions

Future studies should prioritize prospective longitudinal designs to establish the temporal relationship between exposure to psychological stress and subsequent reproductive alterations. Standardized measures of psychological stress should be used alongside biological indicators, such as cortisol dynamics, to improve comparability across studies.

Future research should also employ harmonized semen-analysis protocols and incorporate outcomes extending beyond conventional sperm concentration, motility, and morphology. Assessment of sperm DNA fragmentation, oxidative stress markers, inflammatory mediators, hormonal profiles, and other reproductive biomarkers may provide a more complete characterization of stress-related reproductive dysfunction.

Multi-omic approaches, including genomics, proteomics, and metabolomics, may help identify early biomarkers and biological profiles associated with susceptibility to stress-induced testicular dysfunction. Investigation of emerging mechanisms, including the gut–brain–testis axis and the microbiome, may further clarify interactions between psychological stress, systemic inflammation, endocrine regulation, and reproductive health.

Randomized controlled trials evaluating psychological stress-reduction interventions and their effects on reproductive outcomes are particularly needed. Clinical trials should also clarify the effectiveness, safety, optimal dose, and appropriate patient populations for antioxidant and phytotherapeutic interventions.

Ultimately, personalized therapeutic approaches based on individual neuroendocrine, oxidative, inflammatory, psychological, and reproductive profiles

may provide a more effective strategy for managing stress-related male reproductive dysfunction.

In conclusion, current evidence suggests that psychological stress may contribute to male reproductive dysfunction through complex interactions involving neuroendocrine dysregulation, oxidative stress, inflammation, and behavioral factors. Experimental studies provide substantial mechanistic support for these associations, whereas human evidence remains predominantly observational and does not yet establish definitive causality. Although several therapeutic approaches, including stress-management interventions, lifestyle modifications, and antioxidant strategies, appear promising, their effectiveness in stress-related male infertility requires further validation through well-designed clinical studies.

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Declaration of Interest

The authors of this article declared no conflict of interest.

Ethical Considerations

The study protocol adhered to the principles outlined in the Declaration of Helsinki, which provides guidelines for ethical research involving human participants. Ethical considerations in this study were that participation was entirely optional.

Transparency of Data

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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Authors' Contributions

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