Stress and Infertility: Biological Mechanisms and Management

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***Abstract*-** Infertility significantly affects about 48 million couples globally, presenting a major issue in reproductive biology concerning the potential impact of psychological stress on pregnancy rates. Those experiencing difficulty in conceiving often encounter substantial emotional distress, increasing their risk for psychological issues. There is a mutual reinforcement between stress and infertility, where stress might contribute significantly to infertility. Moreover, infertility treatments can elevate stress levels and negatively affect treatment outcomes. The biological connections between stress and infertility involve hormonal actions in the brain, specifically affecting the hypothalamic-pituitary- adrenal (HPA) axis, which in turn influences hormone secretion by reproductive organs and pregnancy outcomes. Sex hormones are crucial in both reproductive and general physiology, creating the conditions necessary for pregnancy. This review explores how stress impacts reproductive success and the role of sex hormones in infertility. It also discusses strategies to manage stress and identifies scenarios that may lead to stress.

I. Introduction

Stress is an unavoidable aspect of contemporary life, manifesting as an uncomfortable state of mental and physical arousal when individuals perceive threats or harm to their well-being. As lifestyles and social systems evolve, managing stress and mitigating its effects is crucial for maintaining a balanced and healthy life. The nature, duration, and severity of stress responses can disrupt homeostasis and significantly impact the body, sometimes resulting in severe health issues or even death.

Infertility, affecting approximately 186 million people worldwide, is a significant global health issue causing substantial psychological distress. Personal stress, marital pressures, social networks, family dynamics, and educational levels negatively influence infertility. Although not life-threatening, infertility is a profound life-altering problem where achieving a clinical pregnancy is challenging. Traditionally, infertility workups have primarily focused on female factors, with male factors contributing to about 50% of cases and uniquely accounting for 20% of instances.

Both men and women experiencing mental health issues, including stress, depression, sleep, and eating disorders, are often considered at risk for unexplained (idiopathic) infertility.

The understanding of the link between stress and infertility is not widely accepted. However, stress is frequently identified as a contributing factor to unexplained reproductive disorders. A significant challenge lies in correlating emotional factors with reproductive outcomes. The inability to conceive naturally can lead to feelings of shame, guilt, and low self-esteem, increasing psychological vulnerability and potentially resulting in depression, anxiety, distress, and a diminished quality of life. This review aims to clarify the impact of stress on infertility and reproductive outcomes, explore the role of hormones in stress and fertility rates, and examine various stress-related conditions leading to infertility. For this review, international databases (PubMed, Scopus, Web of Science) and Google Scholar were searched for articles published between 2000 and February 2023, using keywords such as “stress”, “depression”, “infertility”, and “reproductive hormones”. The articles were reviewed based on their titles, abstracts, and full texts.

Potential Causes of Infertility

Stress is often seen as a failure to achieve genetic potential and adapt to one's environment. Diagnostic and therapeutic methods can negatively impact sexual health and increase stress among infertile couples. Stress can be classified as acute or chronic. Acute stress usually occurs in emergencies, like in a fight, and triggers changes in brain chemicals that activate the emotional and cognitive system, helping individuals make stress-coping decisions. This type of stress can be beneficial by boosting infection resistance and reducing the body’s immune response. In contrast, chronic stress is linked to many diseases, including professional stress and unique adversities, causing insomnia, gastrointestinal problems, anxiety, depression, and increased risks of heart disease, cancer, and mental illness, as well as negatively impacting fertility. Chronic stress also disrupts immune cell migration to infection or inflammation sites. Psychological stress, often preventable, is a primary infertility cause. Other related stresses include metabolic and oxidative stress, which are connected to psychological stress.

2.1 Psychological Stress

Psychological stress is prevalent among infertile women, often presenting as chronic stress. If untreated, it can lower pregnancy success rates and hinder fertility treatments. Psychological stress leading to a cytokine storm can induce oxidative stress, disrupting the blood-testis barrier and causing abnormal semen. This stress delays fertility attempts, negatively affecting a couple’s reproductive potential. Severe reductions in testicular function are frequently attributed to psychological stress, which is also linked to high levels of female infertility, resulting in repeated implantation failures and miscarriages. Psychological

distress can directly cause endometrial dysfunction by disrupting hormone secretion and regulation. Long-term psychological distress leads to higher rates of discontinued medically assisted reproduction. Psychological stress is a critical environmental factor affecting fertility, causing various health issues and contributing to infertility as a chronic condition.

2.2 Emotional Stress

Emotional stress is another significant consequence of infertility and is widely recognized. Many individuals suffer emotional pain due to an inability to conceive, creating a vicious cycle where infertility causes emotional stress, which in turn affects fertility by altering hypothalamic-pituitary pathways, leading to conditions like tubal spasms, decreased libido in men, and frigidity. Although the biological connection between emotional stress and infertility lacks extensive research, it is crucial to address it. Maternal stress is often blamed for infertility due to miscarriages, late pregnancy complications, and reduced fetal growth. Alleviating infertility stress in women can improve overall stress levels and potentially enhance pregnancy chances without biological interventions.

2.3 Metabolic Stress

Recently, evaluating metabolic risk factors has become essential in understanding reproductive disorders, particularly in identifying causes of idiopathic infertility to improve treatment outcomes. Metabolic stress contributes to disorders like obesity, osteoporosis, amenorrhea, or the athlete triad (an eating disorder leading to being underweight). The imbalance between reproduction and metabolism is mainly due to PCOS, often causing ovarian dysfunction and metabolic syndrome in women. Obesity can lead to permanent infertility, with higher BMI reducing serum adiponectin and increasing insulin, triggering hyperandrogenemia and risks of menstrual irregularity, PCOS, acne, and hirsutism. Women with higher BMI show lower fertility despite undergoing many ART treatment cycles. Women with the athlete triad experience menstrual dysfunction, increasing infertility risk.

2.4 Oxidative Stress

Oxidative stress imbalance can severely affect female reproduction and conditions like PCOS, endometriosis, and preeclampsia. The imbalance between reactive oxygen species (ROS) and antioxidants damages sperm motility due to scrotal heat, metabolite reflux, and testicular hypoxia. Oxidative stress can be caused by metals, organic solvents, and ionizing radiation, worsening obesity, insulin resistance, vitamin D deficiency, and immune dyscrasia in PCOS, a significant infertility risk factor. Oxidative stress regulates several cellular mechanisms, inhibiting sex hormone-binding globulin expression and secretion by downregulating HNF-4α in vitro, promoting hyperandrogenemia in PCOS. Abnormal oxidative stress levels are found in women with PCOS, regardless of being overweight. Oxidative stress indicates functional inflammation markers like seminal interleukin levels in men with fertility issues.

2.5 Preconception Stress

Preconception stress is common among reproductive-age men and women, affecting fertility, pregnancy, and neonatal outcomes. Annually, approximately 23 million miscarriages occur globally, equating to 44 pregnancy losses per minute. Preconception stress may stem from marital conflict, bereavement, or psychiatric disorders. Routine mental health screening for parents is crucial to mitigate maternal depression's impact on children. Stress disrupts the HPG axis, reducing steroidogenesis and spermiogenesis, increasing infection and inflammation risks, and worsening semen quality. Maternal stress significantly affects pregnancy outcomes, leading to preterm births, miscarriages, small gestational age development, and low birth weight.

Reproductive Hormonal Changes during Stress and Infertility Conditions

Hormones regulate and coordinate human sexual development, sexuality, reproduction, and developmental plasticity throughout life, including follicle formation and ovulation. Key hormones such as LH and Follicle-Stimulating Hormone (FSH) operate in different parts of the body, including the hypothalamus, pituitary gland, and reproductive organs, as shown in Table 1. Hormonal imbalances are responsible for about 10% of infertility cases. Stress affects hormone levels, leading to increased salivary cortisol and changes in voice pitch, vocal tract resonances (formants), and speech speed. Hormones produced under stress can cause long-term neuroendocrine changes that affect female fertility. Normally, during the estrogen cycle's follicular phase, the hypothalamus releases gonadotropin-releasing hormone (GnRH), prompting the pituitary gland to secrete luteinizing hormone (LH). Stress can disrupt hormone production, leading to an irregular estrogen cycle and conception failure. Prolonged stress exposure may result in harmful endocrine disorders that negatively affect conception.

3.1. GnRH

Under stress, the primary reproductive hormone, gonadotropin-releasing hormone (GnRH), is reduced. Neurons synthesizing GnRH serve as control points for modulating reproductive function and represent stress responses in reproduction by monitoring physiological status. Stress activates the hypothalamus-pituitary-adrenal (HPA) axis and inhibits the hypothalamus-pituitary-gonadal (HPG) axis, affecting GnRH secretion. Stress can disrupt any HPG axis level, impacting reproductive function. Gonadotropin production and action impairment lead to LH and FSH deficits, affecting gametogenesis and steroid synthesis in gonads, reducing fertility, and lowering estradiol levels.

3.2. Inhibin

Inhibin, a gonadal hormone, negatively regulates FSH secretion from pituitary gonadotropin cells. Identified in 1986, activins are ovarian hormones increasing FSH secretion, with activin A being the most valuable isoform in humans. Activin A functions beyond reproduction, acting as a hormone, growth factor, and cytokine. Inhibin B is a potential oxidative stress biomarker in Sertoli cells, the primary inhibin B production site.

3.3. Testosterone

Testosterone, an androgen, is crucial for growth, reproduction, and health. Spermatogenesis is regulated by endocrine and paracrine systems, with FSH and LH involved through testosterone produced by Leydig cells in the testis. Few studies focus on stress's effect on testosterone synthesis and male infertility. Psychological stress reduces serum testosterone levels, affecting semen quality by lowering motility, count, and normal sperm function. The Endocrine Society recommends T replacement therapy for symptomatic hypogonadism in men. Intratesticular testosterone is vital for spermatogenesis, virility, and male fertility, measurable only through invasive testicular biopsy.

Transdermal testosterone pretreatment enhances ovarian sensitivity to FSH and increases follicular response in low-responder IVF individuals compared to the mini-dose GnRH agonist protocol. Studies report reduced body weight, serum testosterone levels, and genital index after 21 days of unintended chronic stress in adult male rats.

3.4. FSH

FSH, a dimeric glycoprotein gonadotropin hormone, and its receptor are vital for follicle generation and steroidogenesis regulation in ovaries and spermatogenesis in testes. Produced by the anterior pituitary gland, FSH targets gonadal cells and coordinates with LH through G protein-coupled receptors (GPCRs) to regulate reproduction. Disrupted pituitary gland hormone secretion leads to infertility and testicular dysfunction, with gonadotropin deficiency accounting for 0.5% of male infertility. FSH interacts with Sertoli cell receptors, triggering nutrient secretion for germ cell maturation, with germ cell concentration dependent on Sertoli cell volume. Extensively used in assisted reproductive technologies (ART), FSH binds to granulosa and Sertoli cell receptors, with receptor gene polymorphism linked to infertility, ovarian failure, and amenorrhea in women. Stress lowers serum FSH levels, affecting sperm motility and function.

3.5. LH

LH is crucial for spermatogenesis, secondary sexual characteristics, and various bodily functions. LH abnormalities affect spermatogenesis, leading to infertility. In men with hypogonadotropic hypogonadism-related infertility, sperm restoration is achieved with HCG or hMG. High BMI affects seminal plasma and reproductive hormone concentrations, increasing oxidative stress and impairing sperm quality, linked to male infertility. Infertility duration, women's age, and weight gain elevate stress hormone levels, reducing antioxidant activity and potentially causing infertility. GABA signaling in the MePD suppresses stress-induced pulsatile LH secretion, suggesting a critical MePD GABAergic projection to the hypothalamic GnRH pulse generator.

Chronic stress reduces kisspeptin content in the Anteroventral Periventricular Nucleus and GnRH in the preoptic area in females, disrupting the LH surge, estrous cycle, and fertility, reducing pregnancy and embryo numbers. The GnRH-p62-OXPHOS (Ndufa2)-Ca2+/ATP-LH pathway, influenced by p62 deficiency, exhibits abnormal pituitary LH secretion via mitochondrial OXPHOS signaling, posing an infertility risk in females.

3.6. Prolactin

Prolactin, a polypeptide hormone, is essential for male reproduction, secreted by lactotrophs. Treating elevated prolactin has positive metabolic effects, such as glycemic control. Men under long-term psychological stress show higher prolactin levels, which are not observed in women. Infertile men with oligo- and azoospermia, impaired movement, and hypogonadotropic hypogonadism have significantly increased serum prolactin and seminal plasma levels, with chronic serum prolactin affecting spermatogenesis in infertile men.

3.7. Estrogen

The presence of estrogen in males has been debated, with early studies suggesting it harms male reproduction due to abnormal outcomes from exogenous treatments. However, estrogen synthesis in the testis and high 17- oestradiol levels in testis fluid are considered crucial for healthy male reproduction. Based on species, estrogen receptors such as ESR1 (ER-alpha) and ESR2 (ER-beta) are expressed in certain testis cells and epididymal epithelium. The testis secretes estrogen through the aromatase enzyme, with Leydig cells, immature germ cells, and spermatozoa expressing biologically active aromatase. ESR1 and ESR2 are found in spermatozoa and germ cells, with spermatozoa containing a truncated ESR1 form, suggesting estrogen involvement in male germ cell development. Estrogen is vital for energy metabolism, mineral balance, stress responses, and sexual development. It is a powerful vasodilator, increasing blood flow in various organs, notably the uterus.

3.8. Progesterone

Progesterone is a steroid hormone essential for female reproductive function, aiding mature ovary release into the uterus. During pregnancy, it facilitates implantation and suppresses myometrial contraction to support uterine growth. Progesterone hormone effects are mediated by intracellular progesterone receptors (PRs), composed of a central DNA-binding domain (DBD), C-terminal ligand-binding domain (LBD), and amino-terminal domain (NTD) with intrinsically disordered (ID) proteins. PR protein, expressed in two isoforms—progesterone receptor-A and progesterone receptor-B—was identified in the 1970s. AF1 and AF2 are functional transcriptional domains in PR, with AF1 in NTD and AF2 in LBD. Progesterone receptor-A expression is crucial for ovulatory response to progesterone, often inhibiting progesterone receptor-B, a strong co-activator regulating progesterone target gene response. Impaired PR endometrial expression during implantation causes infertility. Progesterone is the primary hormone in the luteal phase, orchestrating and sustaining the uterus for potential gestation. Luteal phase deficiency in assisted reproduction therapies necessitates supplementation for optimal implantation and pregnancy outcomes.

3.9. Anti-Mullerian Hormone (AMH)

The Anti-Mullerian hormone (AMH) is produced by small developing follicles in the ovary by granulosa cells. It is a homodimer glycoprotein involved in the transforming growth factor-B (TGFB) superfamily, serving as an ovarian reserve marker on chromosome 19's short arm. It quantifies the ovarian

reserve's quality and quantity of primordial follicles. After puberty, primordial follicles undergo atresia by FSH when the HPG endocrine axis activates. AMH produces a 140 kDa disulfide-linked homodimer, covalently bonded as a 560 amino acid monomer. AMH exists as a 25 kDa dimer active form and a 110 kDa N-terminal pro region, known for assessing ovarian reserve and PCOS. AMH has two distinct receptors, AMHRI and AMHRII, involved in signal transmission relating to Suppressor of Mothers Against Decapentaplegic (SMAD) proteins, effectively transducing intracellular signals through nuclear and physiological binding to AMH. AMH exhibits a vital prenatal gonadal sex differentiation function by developing mullerian ducts in males, produced by immature Sertoli cells in the testes until 2 years post-natal, declining over pubertal years, and ultimately becoming untraceable in adults due to high testosterone concentrations. Low AMH levels in males lead to the growth of male and female genitalia. In females, serum AMH levels with autoimmune disease are associated with infertility.

Biological Mechanisms Linking Stress to Infertility

Stress adversely affects reproductive health, although the specific mechanisms remain unclear. Cadmium buildup can produce free radicals (Cd2+), acting as a complex II non-competitive inhibitor, resulting in reactive semi-ubiquinone, which can cause cell necrosis and apoptosis through prolonged ROS (reactive oxygen species) production. This process can lead to infertility or poor pregnancy outcomes due to high ROS levels and inadequate antioxidants like glutathione, impacting both men and women. The activity of alpha-amylase and salivary amylase concentrations via the sympathetic-adreno-medullary (SAM) axis reduces fertility by interacting with catecholamine receptors and altering blood flow in the fallopian tubes, affecting gamete transfer. Oxidative stress-induced DNA damage is a significant cause of sperm dysfunction, leading to congenital malformations and neuropsychiatric disorders. Due to low antioxidant levels, spermatozoa are susceptible to DNA damage, and ROS-mediated sperm destruction affects sperm motility and the genetic integrity of embryos. ROS levels are inversely correlated with sperm DNA integrity. Superoxide dismutase (SOD) protects against oxidative stress, and low seminal catalase activity is linked to male infertility. Another antioxidant, glutathione peroxidase (GPX), in combination with mercapto-succinate, significantly increases sperm lipid peroxidation.

Inflammatory responses under Th1-lymphocyte and M1-macrophage responses regulate cytokines, adipokines, and myokines, leading to obesity- related inflammation that disrupts the hypothalamic-pituitary-gonadal (HPG) axis, preventing the release of hypothalamic GnRH and subsequent FSH and LH release. This disruption causes oxidative damage to spermatozoa through increased lipid peroxidation, with excess ROS formation affecting reproduction. The stress hormone cortisol can inhibit estradiol-17 production in the ovary, leading to amenorrhea, anovulation, and menstrual irregularities. Reproductive activities in humans and animals are primarily controlled by the HPG axis, and stress reduces GnRH action, resulting in lower gonadotropin levels. Nutritionally induced oxidative stress from excessive macronutrient intake can cause oxidative stress and inflammation through NF-B-driven cell signaling pathways, leading to outcomes like nutritional deficiency, viral infection, and genotoxic stress. The shift towards excess ROS can cause oocyte aging, reducing oocyte number and quality, and leading to embryo fragmentation and developmental defects, which are major causes of spontaneous and recurrent miscarriages.

Oxidative stress-related reproductive disorders include polycystic ovary syndrome (PCOS), endometriosis, and preeclampsia. Preeclampsia is linked to fetal morbidity and mortality, monitored using markers like F2-isoprostanes.

Endometriosis and preeclampsia can impair embryo implantation by increasing reactive oxygen and nitrogen species. The microbiota, a community of microorganisms in mucosal tissues of the gut, reproductive tract, and skin, is essential for maintaining mucosal barrier integrity, pathogen defense, and immunomodulation. Disruptions in the microbiota can reduce microbial diversity and increase pathogenic organisms. The gut and intestinal microbiota may influence male and female fertility through their effects on inflammatory conditions. Oxidation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH- S) resulting from H2O2 generation has been shown to reduce sperm motility and inhibit GAPDH-S activity.

Stress and Other Reproductive Disorders

Conditions like varicocele, metabolic syndrome, sexually transmitted diseases, tobacco use, alcohol consumption, bacterial prostatitis, microbial infections, mutations, and viral infections can all lead to oxidative stress (OS) and inflammation. Improving sperm quality after varicocelectomy doesn't always result in spontaneous conception. Stress and its mechanisms can also cause immune dysregulation in reproductive health. Physical and emotional stress can lead to puberty issues and, during reproductive years, can impair oogenesis and spermatogenesis, resulting in temporary sterility in women and permanent infertility in men. Corticotropin-releasing hormone (CRH), present in both male and female reproductive systems, regulates steroidogenesis and inflammatory processes in the ovary, endometrium, and placenta. Abnormal CRH levels can lead to conditions like preeclampsia, restricted endometrial growth, abnormal placental invasion, and preterm delivery. Prolonged stress- induced glucocorticoid secretion can cause ongoing reproductive dysfunction.

Melatonin, important for reproduction, counteracts oxidative stress and acts as a ROS scavenger. Stress can suppress HPG axis activity at multiple levels through various HPA axis components. Gonadotropin-inhibitory hormone (GnIH) is a key negative regulator of reproduction. Polycystic Ovary Syndrome (PCOS) PCOS affects 7 to 15% of women of reproductive age and is a metabolic gynecological disorder leading to clinical hyperandrogenism, biological dysovulation, and infertility. It is associated with symptoms like glucose intolerance, diabetes, atherogenic dyslipidemia, systemic inflammation, non- alcoholic fatty liver disease, hypertension, coagulation disorders, severe acne, neuroendocrine changes, hirsutism, insulin resistance, elevated androgen levels, adiponectin levels, adiposity, menstrual irregularities, and ovarian abnormalities. In PCOS, the OS index remains high even after adjusting for BMI. Women with lower BMI and PCOS experience less emotional distress compared to

obese patients. Women with PCOS show abnormal OS biomarkers and lower antioxidant levels such as catalase and ferroxidase.

Reducing oxidative stress with d-chiro-inositol, vitamin D, and probiotics can be effective for women with PCOS. Depression is common in PCOS patients, severely impacting their quality of life, and is three times more prevalent in PCOS women than non-PCOS women. Depression is strongly linked to insulin resistance, acting as a physiological mediator. Electroacupuncture can help treat PCOS, improving depression symptoms and quality of life.

Endometriosis

Endometriosis is a condition where endometrial-like tissue is present outside the uterus, causing chronic inflammation; many affected women show no symptoms. About 35-50% of women with endometriosis experience infertility. OS is closely linked to endometriosis prognosis, with increased ROS production causing damage and proliferation, affecting functions like ovulation, implantation, oocyte maturation, luteolysis, and maintaining the luteal phase during pregnancy, partly explaining infertility. Antioxidant supplementation, such as Vitamin C and E, melatonin, etc., can treat endometriosis-related infertility. Impaired gonadotropin hormone secretion in endometriosis patients correlates with disease severity.

Effects of Psychosocial Stress on Reproductive Health

Stress is associated with decreased reproductive success, caused by lifestyle changes, job stress, or psychological factors. Disruption of the HPG axis by stress has long-term effects on health and fertility. Psychological stress affects reproduction by disturbing the HPA axis, leading to altered hormone levels and impaired reproductive function. Women experiencing high levels of psychosocial stress have lower conception rates, as stress can alter gonadotropin levels and menstrual cycles. Men under chronic stress may experience reduced sperm quality and quantity, impacting fertility. Assisted reproductive technology (ART) treatments can cause significant stress, lowering their success rates. Managing psychosocial stress in couples undergoing infertility treatments is vital for improving reproductive outcomes.

6.1. Psychological Stress and Female Infertility

High levels of stress can negatively impact women's reproductive health by disrupting menstrual cycles and hormonal balance. Stress-related changes in the HPA axis and cortisol levels can affect gonadotropin secretion, leading to anovulation, irregular menstrual cycles, and infertility. Chronic stress can also result in lifestyle changes, such as poor diet and lack of exercise, further impacting fertility. Stress management techniques, such as mindfulness, cognitive-behavioral therapy, and relaxation exercises, can improve menstrual regularity and increase the chances of conception.

6.2. Psychological Stress and Male Infertility

Stress can also negatively affect male fertility by reducing sperm quality and motility. Chronic stress can cause hormonal imbalances, such as decreased testosterone and increased cortisol levels, impairing spermatogenesis. Men under high stress may also engage in unhealthy behaviors like smoking, alcohol consumption, and poor diet, further reducing fertility. Stress management and lifestyle changes, including regular exercise, healthy eating, and relaxation techniques, can improve sperm quality and enhance the likelihood of conception.

6.3. Psychosocial Stress and Assisted Reproductive Technology (ART)

Couples undergoing ART treatments often experience high levels of psychosocial stress, which can affect the success rates of these procedures. Stress can lead to poor treatment adherence, reduced ovarian response, and lower implantation rates. Providing psychological support and stress management interventions for couples undergoing ART can improve treatment outcomes. Techniques such as counseling, support groups, and stress reduction strategies can help couples cope with the emotional burden of infertility and increase their chances of successful conception.

Conclusion

Couples facing infertility often endure significant stress and depression. Infertility is a prevalent yet often unspoken issue, with diagnosis and treatment imposing heavy burdens. The effect of stress on infertility is a contentious topic; nonetheless, it is established that stress, anxiety, and depression can influence reproductive rates. This review emphasizes that stress can be a major factor in infertility and can affect treatment success rates, concerns about fertility, and hormonal roles in reproductive outcomes. Stress might be a contributing factor to infertility in contemporary times. Further research into the hormonal pathways connecting stress and infertility could improve our understanding of the relationship between common symptoms, stress, and infertility.

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