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# Fertility treatment-induced oxidative stress and reproductive disorders

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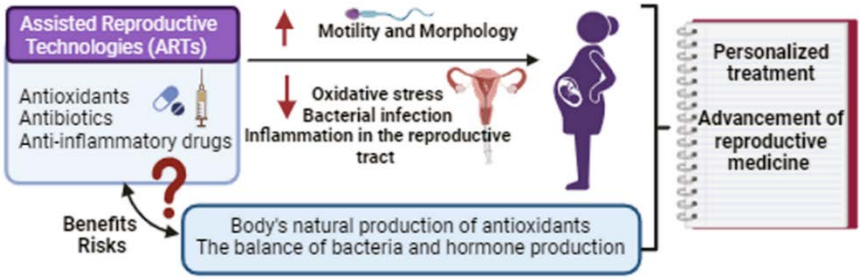
Review

## ABSTRACT




Rising global infertility rates have amplified the dependence on assisted reproductive technologies (ARTs) for conception. This necessitates a thorough examination of fertility drug effects on reproductive health. This review explores the impact of fertility drugs, such as antioxidants, antibiotics, and anti-inflammatory agents, on oxidative stress (OS), reproductive irregularities, and treatment outcomes. While antioxidants can potentially improve reproductive outcomes by modulating OS, excessive consumption can lead to the 'antioxidant paradox' — a delicate balance between external antioxidant intake, OS reduction, and its effects on fertility. Moreover, some antibiotics and anti-inflammatory drugs can intensify OS, possibly exacerbating reproductive issues. The article emphasizes the complex relationship between fertility drugs and ovarian stimulation, highlighting the need for personalized treatments and careful weighing of the advantages and drawbacks of fertility interventions. This review emphasizes the intricate relationship among fertility drugs, ovarian stimulation, and semen quality, advocating for personalized treatment plans and a thorough assessment of the benefits and drawbacks of fertility interventions. The comprehensive insights obtained from this extensive review aims to aid clinical protocols and support informed decisions in reproductive medicine.

*Keywords: antibiotics; antioxidants; assisted reproductive technologies; erectile dysfunction; infertility; NSAIDS; ovulation; pregnancy*

## INTRODUCTION

Fertility is an essential characteristic vital for the continuation of the human species. Notably, a rising number of couples globally are experiencing challenges with infertility.[1] This has prompted a surge in the pursuit of treatments to address this issue. While fertility interventions have proven efficacious for many couples in facilitating conception, they can also introduce potential complications, including oxidative stress (OS) and reproductive disturbances.[2-5]

In the realm of reproductive medicine, fertility interventions encompassing in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), ovarian stimulation, and a myriad of therapeutic strategies targeting infertility—namely, anti-inflammatory, antibiotic, and anti-oxidant treatments—have been identified to be associated with various physical and psychological stressors.[6-8] Such interventions invariably expose gametes (both spermatozoa and oocytes) and embryos to multifarious stress factors. These include hormonal treatments, cryopreservation techniques, and modifications performed *in vitro*.[9-11] Such exposures can potentiate the production of reactive oxygen species (ROS) whilst simultaneously attenuating the body's innate antioxidant defense mechanisms, consequently precipitating OS.[11-13]

OS is typified by a disequilibrium between the ROS generation and the body's antioxidant defense capacities. As byproducts of routine metabolic processes, ROS are inherently reactive entities. They are pivotal in modulating several physiological mechanisms, encompassing signaling cascades and immunological reactions. Nevertheless, an excessive accumulation of ROS can inflict detrimental alterations on cellular constituents, such as DNA, proteins, and lipids.[14, 15] Such alterations can compromise cellular functionality, culminating in cell death. Evidently, a surge in OS

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levels has been documented to exert deleterious implications on both male and female reproductive health.[5, 16] In the male population, oligospermia has the potential to induce impairment in sperm function, leading to diminished sperm count, motility, and morphology. Furthermore, it has the potential to induce harm to the genetic material of sperm, hence resulting in the manifestation of genetic defects in subsequent generations.[17] OS may result in follicular dysfunction, ovulation difficulties, endometriosis, polycystic ovarian syndrome (PCOS), and implantation failure in females. It may also cause premature ovarian failure, which occurs when the ovaries cease working before the age of 40.[18] Endometriosis is a pathological disorder characterized by the ectopic growth of endometrial tissue, which typically lines the inner surface of the uterus, beyond its anatomical boundaries. This aberrant growth manifests clinically as chronic pelvic discomfort, excessive menstrual bleeding, and impaired fertility. Research findings indicate that individuals diagnosed with endometriosis have elevated levels of OS in comparison to those who do not present this medical disease.[19] PCOS is a hormonal disorder that affects women of reproductive age and causes irregular menstrual cycles, acne, and excessive hair growth. PCOS is a significant contributor to female infertility. Comparative studies have indicated that women diagnosed with PCOS exhibit elevated levels of OS in comparison to their non-PCOS counterparts.[20]

To counteract the detrimental effects of OS on reproductive health, multiple strategies have been proposed and implemented. Notably, antioxidants, which are capable of neutralizing ROS, play a pivotal role in safeguarding cells from oxidative damage. Consequently, their incorporation as an adjunctive therapy in fertility interventions has been suggested to enhance the likelihood of successful outcomes.[21] Empirical evidence underscores the efficacy of certain antioxidants, including vitamins C and E, in mitigating OS levels among individuals undergoing reproductive procedures.[21, 22]

Addressing OS precipitated by fertility treatments and understanding its implications for reproductive disorders remain critical areas of focus within reproductive medicine. It is essential to fully understand the underlying mechanisms and develop effective strategies to prevent and treat these conditions. This article aims to explore the potential mechanisms and consequences of OS on the reproductive system following fertility treatments, and thereby to raise awareness of the potential risks associated with fertility treatments and highlight the importance of various strategies, such as antioxidant therapy in reducing OS and improving reproductive outcomes. Therefore, it is essential to conduct further research on fertility treatment-induced OS and reproductive disorders.

## COMMON REPRODUCTIVE ISSUES IN MEN AND WOMEN

Reproductive health pertains to the state of the male and female reproductive systems during all phases of life. The provision of reproductive health services is considered an essential entitlement inherent to all individuals, constituting a fundamental human right. It is crucial for the overall welfare of individuals, families, and the broader societal framework. The prioritization of reproductive health within society may contribute to the promotion of physical and mental well-being, the advancement of gender equality, the mitigation of poverty, and the facilitation of social and economic progress.[23] Investments in sexual and reproductive healthcare are of utmost importance as they enhance the well-being of people and enable them to exercise their rights pertaining to sexual and reproductive matters.[24] Evidence shows that an increasing number of environmental contaminants are harming men's sperm quality, women's menstrual cycles and fertility potential. One contaminant may work via a number of distinct pathways, but these have yet to be completely defined in human studies, and further study is needed to discover the mechanisms through which contaminants exert their pathophysiological effects.[25] There are several reproductive problems that may affect people of either gender and need accurate diagnosis and treatment in order to be resolved.

### *Reproductive disorders in men*

Numerous concerns pertaining to the male reproductive system are often seen as socially uncomfortable, perhaps contributing to their underdiagnoses and inadequate attention within the realm of general medical practice. This chapter encompasses an examination of many prevalent illnesses affecting the male reproductive system, with an exploration of contemporary treatment modalities (**Table 1**).[26, 27]

Erectile dysfunction (ED) is a common medical disorder defined by the inability to generate or maintain a satisfactory erection for sexual intercourse.[28] It may afflict males of all ages, although its incidence rises as they become older. Depending on the community investigated and the terminology employed, the prevalence of ED varies greatly. The prevalence of ED diagnosis or treatment increased as individuals advanced in age; nonetheless, those in the most advanced stages of old age exhibited a decline in the likelihood of being diagnosed with or seeking therapy for ED. The decline in the diagnosis and treatment of ED in very old age can be attributed to several factors. These include the lack of a sexual partner, diminished interest in sexual activity, insufficient concern about the condition to seek medical attention, the presence of other concurrent health conditions, and the reduced likelihood of medical practitioners inquiring about ED in elderly men. The prevalence of ED diagnosis or treatment grew from age 18–29 years (0.4%) to age 60–69 years (11.5%), then fell in the 7th decade (11.0%), the 8th decade (4.6%), and the 9th decade (0.9%). Males who had been diagnosed with or were receiving treatment for ED had a significantly greater frequency of any and all comorbid conditions than men who did not have ED (63.1% vs 29.3%).[29] This percentage is likely to be underestimated since many men do not seek medical assistance for this disease. ED may be caused by physical, psychological, or a combination of both factors.[30]

Hypertension, atherosclerosis, and diabetes are all examples of cardiovascular diseases that may impair blood flow.[31] Multiple sclerosis, Parkinson's disease, and stroke are examples of neurological illnesses that may impact the nerves and brain. Physical injury to the penis or pelvic nerves, arteries, or veins.[32] Peyronie's disease is characterized by the development of fibrous tissue inside the penile shaft, resulting in an abnormal curvature or bending of the penis during the erect state.[33] Fear, worry, and stress may all produce performance anxiety, making it harder to develop or sustain an erection. Furthermore, sentiments of melancholy,

pessimism, and worthlessness might obstruct sexual desire and arousal.[34] Problems with conflict or communication with a partner, as well as excessive pornographic intake, may desensitize the brain to sexual impulses, making it harder to feel aroused in real-life sexual circumstances.[35] Drug and alcohol usage may impair sexual function by altering the nerve system and blood flow.[36]

Ejaculation happening within one minute of penetration is often characterized as premature ejaculation (PE).[37] Approximately 90% of male individuals seeking therapeutic intervention for lifelong PE had ejaculation within a minute of engaging in sexual intercourse. The remaining 10% of individuals ejaculated between 1 and 2 minutes after penetration.[38] PE is a common male sexual disorder that is defined by the inability to defer ejaculation during sexual activity, generating suffering or unhappiness in both parties.[39] With a global frequency of over 30%, PE is probably the most frequent sexual problem among males. Until recently, the absence of a broadly accepted definition of PE has hindered its investigation and study in clinical and research settings. PE can be categorized as lifelong (primary) or acquired (secondary).[40]

PE may be caused by either psychological or physiological factors, or by a mix of the two. PE may be exacerbated by poor communication or unresolved disputes with a spouse. Low levels of the hormone serotonin, which helps regulate mood and behaviour, have been connected with PE.[41] Prostate gland inflammation may produce pain and discomfort during ejaculation.[42] Multiple sclerosis and spinal cord injuries are examples of conditions that disrupt the nerves that govern ejaculation.[43] PE may be genetically predisposed in some males. The polymorphism in the serotonin transporter-linked polymorphic region (5-HTTLPR) gene has been the subject of the most research (11 studies), with 7 demonstrating a significant association with PE and 4 refuting such a relationship. Six studies looked at polymorphisms in 5-HT receptors and discovered a significant association. A strong connection between polymorphisms in the dopamine transporter (DAT) gene (DAT1) and PE was discovered by four separate investigations. Androgen receptor (AR) gene polymorphisms were investigated in three studies, of which two discovered a significant association and one did not. One study discovered an association between oxytocin receptors (OXTR) gene polymorphisms. Eventually, a study discovered a significant correlation between tryptophan hydroxylase 2 (TPH2) gene polymorphisms and schizophrenia.[44]

Two conditions that might potentially affect men's sexual health are low libido, which refers to a decrease in sexual desire, and low testosterone levels. Assessing the incidence of diminished sexual desire in males presents challenges due to its subjective nature and susceptibility to several influencing factors, including but not limited to age, relationship status, and mental and physical well-being.[45, 46] Diabetes, heart disease, and cancer are among chronic conditions that may reduce sexual desire.[47] Antidepressants have been linked to a reduction in sexual desire.[48] In males with low testosterone, testosterone treatment boosts libido. Testosterone replacement therapy as a standalone intervention has been shown to potentially enhance erectile function in males exhibiting mild E), although its efficacy seems to be limited in persons presenting with moderate or severe ED. The potential enhancement of responsiveness to PDE5 inhibitors in males with low testosterone levels who exhibit insensitivity to PDE5 medicines might be achieved by the normalization of testosterone levels.[49]

Hypogonadism, or low testosterone, is a medical disorder defined by low amounts of the hormone testosterone. Low testosterone prevalence rises with age and other variables such as obesity and type 2 diabetes.[50] A comprehensive study and meta-analysis found that more than 20% of men in their 60s and 30% of those in their 70s have low testosterone levels.[51, 52] Some drugs, such as opioids and glucocorticoids, have the potential to lower testosterone levels. Several systematic reviews and meta-analyses found that testosterone levels are lowered in males who use opioids, independent of the kind of opioid or the rationale for usage. These discoveries might have significant therapy implications. Those with a history of opiate use are likely to have considerably reduced testosterone levels.[53] Low testosterone levels may be caused by injury to the testicles or pituitary gland. Low testosterone levels may be caused by rare genetic illnesses such as Klinefelter syndrome.[54]

Varicocele affects roughly 20% of adults and adolescents, as well as 19-41% of males seeking infertility therapy. It is connected with a reduction in sperm count, motility, and morphology.[55, 56] Varicocele is more prevalent in young males and is often diagnosed during adolescence or early adulthood. Varicocele is often discovered via a physical examination and confirmed with an ultrasound. Varicoceles are pampiniform vein dilations inside the spermatic lead. This has a deleterious influence on the testicular environment and may decrease male fertility by lowering sperm quality and DNA fragmentation rates. They may also cause soreness and a lack of testosterone.[57] Varicocele has the potential to diminish fertility in certain male individuals due to its detrimental impact on the testicles or its interference with sperm production. It is the predominant etiology of surgically treatable infertility in adult males, whereby surgical intervention has been seen to enhance semen parameters in 60% - 80% of individuals and elevate the probability of achieving pregnancy in up to 60% of cases. Nevertheless, the justification for doing varicocele surgery in juvenile patients remains uncertain. Although most individuals with varicocele may not have any symptoms, a subset of males may present with scrotal pain, discomfort, or swelling.[58]

Chlamydia is a bacterial infection that may cause penile discomfort and discharge. It is the most prevalent sexually transmitted diseases in the United States, with an estimated one in every 20 sexually active young men infected.[59] Men may get gonorrhea from a bacterial infection that causes discharge and uncomfortable urinating. The bacterium *Neisseria gonorrhoeae* causes gonorrhea, a sexually transmitted illness with a worldwide yearly incidence of 86.9 million individuals.[60]

Syphilis is a bacterial infection that may cause genital sores and redness, as well as flu-like symptoms. It is less prevalent than chlamydia and gonorrhea, although its incidence has recently increased.[61] Herpes is a viral illness that may cause oral or genital sores. Genital herpes, a chronic life-long viral infection, is very widespread around the globe and is one of the most frequent sexually transmitted illnesses in the reproductive age range. Both herpes simplex virus type 1 (HSV-1) and herpes simplex virus type

2 (HSV-2) infections may be primary or recurring. HSV-2 is the most common cause of recurrent genital herpes.[62]

The human papillomavirus (HPV) infection is responsible for the development of genital warts and has been associated with many types of cancer.[63] Regarding the distribution of HPV types, there is a growing body of evidence suggesting that high-risk HPV16 exhibits a higher prevalence in male anogenital areas, prostate, bladder, and oropharynx.[64,65] HPV16 was the most prevalent type in sperm, accounting for almost one-fifth of HPV-positive samples from both the general population and fertility clinic attendance.[66] The human immunodeficiency virus (HIV) infects the immune system. Although it is less frequent than other sexually transmitted diseases, it is a major health problem that may lead to AIDS. It is estimated that one in every 270 sexually active males has HIV.

***Reproductive issues in women***

Fertility is often defined as the capability of a couple to successfully sustain pregnancies till completion, while fecundity refers to a woman's biological potential to engage in reproduction, as determined by the monthly probability of conception. Clinical infertility is characterized as the inability to conceive after a period of 12 months of engaging in unprotected sexual intercourse. This condition may arise due to several circumstances, such as hormone imbalances, anatomical abnormalities, advanced age, and lifestyle-related influences.[74] Despite toxicological studies clearly demonstrating that several poisons affect the female reproductive system both directly and/or indirectly, exposure to chemicals in the environment and diet has gotten significantly less attention (**Table 2**).[75]

The prevalence of PCOS varies depending on the diagnostic criteria that are employed, however it is believed to afflict between 5-15% of reproductive-aged women, which is defined as women between the ages of 18-44.[76, 77] A majority of women diagnosed with PCOS actively pursue infertility treatments, while a significant proportion, ranging from 70%-80%, have either oligomenorrhea or amenorrhea..[78] Several often seen signs of PCOS include irregularities in menstrual periods, the presence of acne, excessive hair growth (hirsutism), weight gain, and difficulties in conceiving. Women diagnosed with PCOS may potentially face an increased susceptibility to the development of type 2 diabetes, hypertension, and several other health complications.[79, 80]

Endometriosis refers to the existence of tissue resembling the endometrium beyond the confines of the uterine cavity. The evolution of this predominantly anatomical idea has been facilitated by clinical and molecular advancements throughout the last two decades. Endometriosis is a complex clinical condition characterized by a persistent inflammatory process that mostly impacts pelvic tissues and is influenced by estrogen. This new description highlights the intricate nature of the illness.[81] Heavy menstrual flow is the most prevalent presenting symptom, which might result in anemia, exhaustion, or painful periods. Lower back discomfort, pelvic pressure or pain, and pain during intercourse are also potential symptoms. Pressure on the bladder or intestines caused by fibroids larger than a particular size may result in increased micturition frequency or retention, discomfort, or constipation. Uterine fibroids may also be linked to reproductive issues including infertility, recurrent pregnancy loss, and poor obstetric outcomes.[82-84]

The response of fibroids to estrogen and progesterone is a common trait. Fibroids may hinder gamete transport and obstruct the fallopian tubes, resulting in infertility. The current evidence suggests that a significant factor contributing to this phenomenon is the deformation of the endometrial cavity, leading to abnormal endometrial receptivity, hormonal environment, and modified endometrial growth.[85] The predominant changes seen in fibroids include four categories: MED12 mutations, FH inactivation, COL4A6-COL4A5 deletions, and HMGA2 overexpression.[86, 87]

Menstrual irregularities refer to changes in the length, duration, or frequency of menstrual periods. The prevalence of menstrual irregularities varies depending on the specific condition, but it is estimated that up to 5%-35.6% of women, depending on age, occupation, and the country of residence may experience some type of menstrual irregularity at some point in their lives and impacting

**Table 1.** Various male reproductive disorders and their causes

| Reproductive disorder | Causes | References |
|---|---|---|
| Erectile dysfunction | Physical causes: cardiovascular disease, neurological diseases, hormonal imbalances, Peyronie's disease, trauma or injury. | 31, 33, 67-69 |
| | Psychological causes: Anxiety, depression, pornography addiction, substance abuse or relationship issue. | |
| Premature ejaculation | Psychological variables, including anxiety, stress, and depression. The topic of concern is to the correlation between interpersonal relationships and neurological disorders. Low serotonin, prostatitis, erectile dysfunction and genetic inheritance. | 42-44, 70, 71 |
| Low libido | Psychological variables, including anxiety, stress, and depression, are being considered. Relationship issues, medicines, and medical ailments. The lifestyle element. | 72 |
| Low testosterone | Aging, medication and medical conditions, trauma and genetic disorder. | 49, 52, 54 |
| Sexually transmitted infections | Chlamydia, gonorrhea, syphilis, herpes, *Human papillomavirus* and *Human immunodeficiency virus*. | 60, 73 |
| Varicocele | Abnormal valves in the veins, anatomic variations, increased pressure in the veins, genetic inheritance. | 56, 57 |

female fertility.[88] Amenorrhea may be classified into two distinct categories: primary amenorrhea, characterized by the absence of menstruation by the age of 16, and secondary amenorrhea, characterized by the cessation of menstruation for a duration exceeding three months in women who previously had regular menstrual cycles.[89]

Endometritis, salpingitis, fallopian tube and ovarian abscesses, and pelvic peritonitis are the most prevalent signs of pelvic inflammatory disease (PID). Inflammation may be localized or spread to several locations at once. Pelvic inflammation is categorized into two types: acute and chronic. As acute pelvic inflammation progresses, it may lead to extensive peritonitis, sepsis, and septic shock. In severe cases, it might be lethal. If it is not completely treated during the acute phase, it will proceed to chronic pelvic inflammatory disease, which may last a long time and repeat. It may lead to infertility, tubal pregnancy, and chronic pelvic pain, wreaking havoc on women's health and increasing the financial burden on families and society.[90] If PID is left untreated, it may result in the formation of scar tissue and the development of infected fluid-filled pockets, known as abscesses, inside the reproductive system. This can lead to long-term detrimental effects.

**Table 2.** Various female reproductive disorders and their causes.

| Reproductive disorder | Causes | References |
|---|---|---|
| Polycystic ovary syndrome (PCOS) | Obesity, insulin resistance, genetic inheritance. | 78, 96 |
| Endometriosis | Genetic inheritance, hormonal imbalances, and immune system dysfunction. | 97 |
| Fibroids | Hormonal imbalances, somatic stem cells and genetic factors. | 98 |
| Pelvic inflammatory disease | Sexually transmitted infections such as chlamydia or gonorrhea, or by non-sexually transmitted bacteria. | 90 |
| Premature ovarian failure | Genetic factors, autoimmune disorders, or certain medical treatments such as chemotherapy. | 99 |
| Menstrual irregularities | Hormonal imbalances, stress, weight changes, medications, and medical conditions such as thyroid disorders or polycystic ovary syndrome. | 88, 89 |
| Amenorrhea | Hormonal imbalances, thyroid diseases, pharmaceutical interventions, significant fluctuations in body weight, intense physical activity, psychological stress, and medical illnesses such as polycystic ovary syndrome or premature ovarian failure. | 88 |
| Ovarian and cervical cancer | Family history, age, and hormonal imbalances, human papillomavirus (HPV). | 100, 101 |

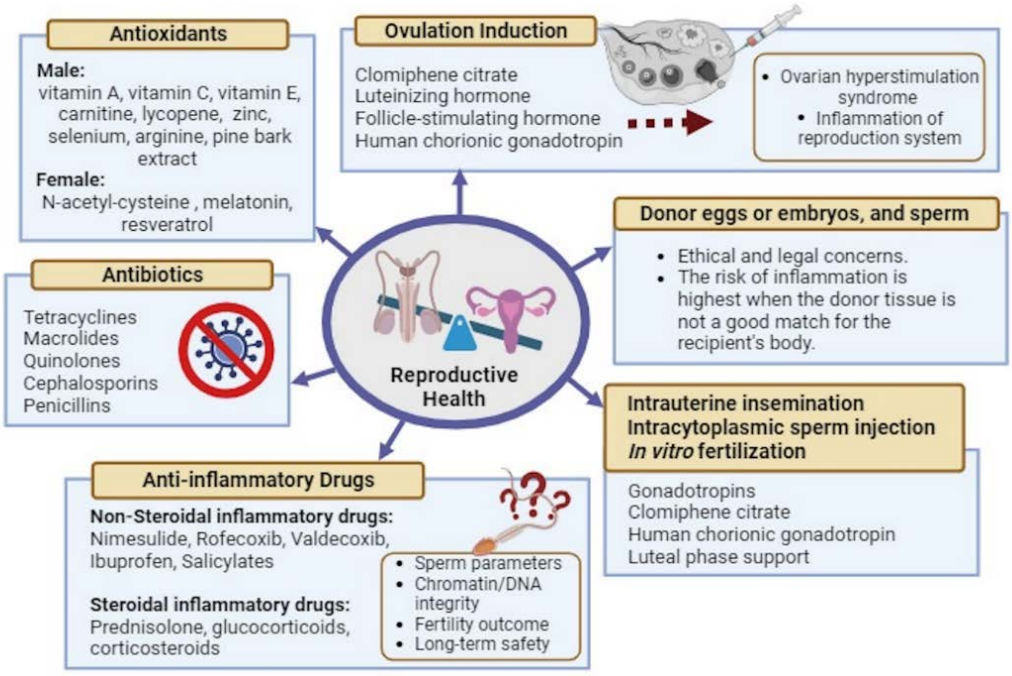


**Figure 1.** Common treatments for improving reproductive health, from lifestyle changes to assisted reproductive technologies.

The clinical ovarian dysfunction spectrum includes primary ovarian insufficiency (POI). Overt POI develops as oligo/amenorrhea and hypergonadotropic or hypogonadism at the age of 40. Overt POI include chronic physical issues such as increased morbidity and mortality associated with estradiol deficiency and the resulting osteoporosis and cardiovascular disease, as well as psychosocial and mental difficulties associated with reproductive hormone loss and infertility.[91] Women diagnosed with premature ovarian failure(POF) may encounter several symptoms, including but not limited to hot flashes, changes in mood, and vaginal dryness. The potential course of treatment may include hormone therapy as well as fertility therapies.[92]

Ovarian cancer is a malignancy that arises in the ovaries, which are the female reproductive organs responsible for oogenesis. Common manifestations of ovarian cancer are stomach distension, bloating, and pelvic discomfort.[92] The potential course of treatment may include surgical intervention, administration of chemotherapy, or use of radiation therapy. The inclusion of both ovarian cancer treatment and fertility preservation in therapy regimens is of utmost importance, especially for young women diagnosed with ovarian cancer. Given that the ovary serves as both the origin of reproductive capability and the primary site of malignancy in these individuals, the task at hand involves the eradication and elimination of cancerous cells, while simultaneously safeguarding and maintaining the viability of healthy oocytes.[93] Cervical cancer is a malignancy that arises in the cervix, which is the inferior segment of the uterus. Cervical cancer may manifest with symptoms such as atypical vaginal bleeding, pelvic discomfort, and dyspareunia.[94] Given that this illness is fully avoidable, conventional measures for preventing cervical cancer, such as administering HPV vaccine that covers a wide range of genotypes, conducting screening using a highly accurate test, and promptly treating cervical precancerous lesions, have the potential to prevent a significant proportion of cervical cancer instances.[95]

## COMMON TREATMENTS OF REPRODUCTIVE ISSUES

### *Antioxidants to mitigate OS-induced reproductive disorders*

OS-induced reproductive diseases, as previously described, arise when ROS levels in the reproductive system rise and exceed the body's antioxidant defense systems, causing harm to reproductive tissues and cells. Antioxidants are chemicals that may reduce OS-induced reproductive problems by scavenging ROS and lowering OS levels in reproductive organs.[21, 102] Intrinsic antioxidants can be either enzymatic, including catalase, superoxide dismutase (SOD), and thiol peroxidase, or nonenzymatic, such as glutathione.[21]

Male infertility is often idiopathic, whose underlying mechanisms are mostly associated with induction of OS.[103] The presence of ROS in seminal plasma that exceeds the capacity of endogenous antioxidants may have a detrimental influence on semen parameters. ROS may harm sperm DNA, membrane lipids, and proteins, resulting in reduced sperm count, motility, and morphology.[103] This may be the reason why antioxidants have a significant role in the management and treatment of idiopathic male infertility.[104] In such scenarios, exogenous antioxidants, which can be consumed through diet or supplements, including micronutrients such as vitamin A, vitamin C, vitamin E, carnitine, lycopene, and trace elements like zinc and selenium, can be used.[105-107] The addition of antioxidant supplements has been shown to have a significant impact on the quality of semen and the likelihood of achieving conception in men with infertility (**Figure 1**).[104, 108, 109]

ED is a prevalent reproductive disorder that has been linked to oxidative stress (OS). Reactive oxygen species (ROS) have the potential to induce endothelial dysfunction, damage smooth muscle cells, and hinder the synthesis of nitric oxide (NO). Consequently, these disruptions can result in diminished blood flow to the penis, culminating in ED. Previous studies have shown that the presence of antioxidants, including as vitamin E, arginine, and Pycnogenol, might effectively enhance erectile function by diminishing levels of ROS and augmenting the bioavailability of NO. In a recent randomized controlled trial, it was demonstrated that the administration of antioxidant supplements significantly enhanced erectile function in men with mild-to-moderate erectile dysfunction.

OS has been associated with various female reproductive disorders such as PCOS, endometriosis, and POF[110, 111] ROS are implicated in causing DNA damage, lipid peroxidation, and mitochondrial dysfunction, which subsequently contribute to follicular atresia, ovarian dysfunction, and infertility.[11,19,112] Various antioxidants, including N-acetyl-cysteine (NAC), melatonin, and resveratrol, have exhibited beneficial effects in improving ovarian function and elevating pregnancy rates in women diagnosed with PCOS and POF. Moreover, the intake of antioxidant supplements has been associated with enhanced oocyte quality and an increased clinical pregnancy rate in women undergoing IVF treatments.[113, 114]

### *Anti-inflammatory drugs to treat inflammatory reproductive issues*

Anti-inflammatory medications are commonly prescribed for the treatment of inflammatory reproductive disorders such as endometriosis, pelvic inflammatory disease, and uterine fibroids.[115] These agents function by attenuating inflammation, thereby mitigating associated symptoms like pain and swelling. Nonetheless, while these drugs offer therapeutic benefits, they may also present potential adverse effects (**Figure 1**).[115, 116]

Inflammatory reproductive disorders, such as endometriosis, pelvic inflammatory disease, and prostatitis, afflict a considerable fraction of the global populace, leading to manifestations like chronic pain, diminished fertility, and compromised sexual function.[117] The multifactorial etiology of these disorders underscores inflammation as a pivotal determinant in their associated infertility pathophysiology. As a result, anti-inflammatory medications have been posited as promising therapeutic strategies for these ailments.[118]

The pathogenesis of inflammatory processes in these reproductive disorders encompasses an array of cytokines, prostaglandins, and other inflammatory mediators, which collectively facilitate tissue injury and pain.[5] Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a widely prescribed class of drugs that adeptly inhibit the function of cyclooxygenase (COX) enzymes. This action subsequently reduces the production of prostaglandins, attenuating the inflammatory cascade.[119] Among

NSAIDs, COX-2 selective agents like nimesulide not only offer analgesic properties but also exhibit superoxide anion scavenging activities. Studies suggest nimesulide may not be spermatoxic at regular doses but could be toxic at higher doses in rats. In prostatovesiculitis patients, nimesulide improved inflammatory signs and sperm morphology but not count or motility. Rofecoxib and valdecoxib improved sperm motility and morphology in assisted reproduction patients. However, leukocytospermia treatment needs more research.[120-122] Ibuprofen may alter sperm parameters and chromatin/DNA integrity in mice, and cause compensated hypogonadism in young men by disrupting the endocrine system.[123, 124] Salicylates have been shown to be associated with reduced sperm motility as depicted by a preliminary study after administering 650 mg of salicylate four times a day for 72 hours to four healthy males.[125, 126] Among the steroidal anti-inflammatory drugs, prednisolone can be used to treat accessory gland inflammation, and glucocorticoids have been found to improve sperm parameters in oligozoospermic patients with accessory gland inflammation.[127] Glucocorticoids can also be beneficial in treating infertility related to antisperm antibodies (ASA), which have been shown to affect sperm motility and concentration.[128] Corticosteroids, a distinct category of anti-inflammatory medications, function by inhibiting the secretion of cytokines and other pro-inflammatory agents.[129] Therefore, the efficacy of anti-inflammatory medicines in alleviating pain and reducing inflammation in reproductive problems has been shown, while their influence on fertility results remains uncertain.[104, 130] Further investigation is required to provide a comprehensive understanding of the enduring safety and effectiveness of anti-inflammatory medications in relation to reproductive problems, as well as to determine the most advantageous approaches for managing these particular ailments.

### *Antibiotics in the treatment of reproductive tract infections*

Antibiotics are the primary therapeutic agents used to treat bacterial infections in the reproductive system [131-133]. This article elucidates the diverse classes of antibiotics utilized in the treatment of reproductive tract infections (RTIs) in both males and females, highlighting their therapeutic benefits and potential implications for fertility. Antibiotic regimens have proven effective in addressing RTIs and male accessory gland infections (MAGI).[134, 135] The selection of an appropriate antibiotic should be predicated upon the specific microorganism identified and its corresponding antibiogram profile, ensuring a tailored treatment approach. Different antibiotic classes are equipped to tackle infections that impede fertility. It is essential to note that most of these microorganisms are sexually transmitted, necessitating the avoidance of sexual contact during treatment and the monitoring and treatment of female partners for infections, as needed.[104]

Several classes of antibiotics are utilized in the treatment of reproductive infections in both males and females:

*Tetracyclines:* Doxycycline is the most commonly prescribed tetracycline for the treatment of sexually transmitted infections such as *Chlamydia trachomatis* and *Ureaplasma urealyticum*. Its efficacy can be attributed to its broad-spectrum activity and its proficient tissue penetration.[136, 137]

*Macrolides:* Azithromycin, a macrolide antibiotic, is commonly administered as a single-dose regimen for the treatment of Chlamydia trachomatis and Mycoplasma genitalium infections. Owing to its extended half-life and pronounced anti-inflammatory characteristics, it stands as a preferred choice for managing these infections.[138] Studies indicate that azithromycin exhibits efficacy rate of 85-95% against infections that are susceptible to macrolides. An extended treatment regimen may further enhance the likelihood of successful outcomes. The escalating prevalence of macrolide resistance, primarily attributed to the widespread administration of a single 1 g azithromycin dose without a test of cure, is significantly diminishing the cure rate. Moxifloxacin may serve as an alternative second-line therapy, though resistance is also on the rise.[139]

*Quinolones:* Fluoroquinolones, such as ciprofloxacin and levofloxacin, are employed in the treatment of gonorrhea (*Neisseria gonorrhoeae*) and PID caused by various bacteria. They are broad-spectrum antibiotics with excellent tissue penetration, making them suitable for treating complex infections.[140]

*Cephalosporins:* Third-generation cephalosporins like ceftriaxone are the first-line treatment for gonorrhea, particularly in cases of antimicrobial resistance.[141] They are also used to treat PID in combination with other antibiotics. The updated 2020 European guidelines advise a combination of two antimicrobial therapies, which involve intramuscular injection of 1 g ceftriaxone along with a single oral dose of 2 g azithromycin, or solely 1 g ceftriaxone by intramuscular injection if laboratory testing has indicated no resistance to ceftriaxone. It is mandatory to conduct a test of cure, and if there is a possibility of *Chlamydia trachomatis* infection, then doxycycline regimen is recommended.[142]

*Penicillins:* Ampicillin and amoxicillin are often used in the treatment of infections induced by Gram-positive bacteria, including group B *Streptococcus* and *Listeria monocytogenes*. These bacterial strains have the potential to give rise to significant difficulties in pregnant women if not promptly addressed. The etiology of urinary tract infection in pregnant women is mostly attributed to *Escherichia coli*. The bacteria in question continues to be susceptible to the antimicrobial agents ceftriaxone and nitrofurantoin. Gram-positive bacteria, including Group B *Streptococcus*, are widely distributed, and penicillin remains efficacious in their treatment. Conversely, *E. faecalis* is sensitive to ampicillin. Regular monitoring is crucial in light of the evolution of antimicrobial resistance, since it allows for the timely updating of guidelines about the empirical use of antibiotics.[143, 144]

## OTHER FERTILITY TREATMENTS

There are many different fertility therapies accessible, and these treatments are available for both infertile women and men. The therapy that is most suitable will be determined by the underlying reason for infertility, and a healthcare practitioner may assist in determining the treatment plan that will be most appropriate.

### *Ovulation induction*

Ovulation induction is a type of fertility treatment that is used to stimulate the ovary to produce one or more eggs, with the goal of increasing the chances of conception. Ovulation induction may be used to treat infertility in women who do not ovulate regularly or who have irregular menstrual cycles.[145] There are several

medications that can be used for ovulation induction, including clomiphene citrate and gonadotropins. Clomiphene citrate is an oral medication that is usually taken for 5 days early in the menstrual cycle. The medication works by blocking the action of estrogen in the body, which signals the brain to produce more follicle-stimulating hormone (FSH). FSH stimulates the ovary to produce follicles, which contain the eggs. An 8-day regimen for individuals who did not ovulate after 5 days of medication was shown to be beneficial in more than half of instances. Patients who did not react to clomiphene were usually treated with gonadotropins. The usual FSH dose increased the likelihood of multiple gestations and ovarian hyperstimulation syndrome. As a result, various organizations recommended for a low-dose strategy.[146, 147]

Gonadotropins, on the other hand, are injectable medications that contain FSH and luteinizing hormone (LH). They are used to stimulate the ovaries to produce multiple follicles and eggs. Gonadotropins are usually given daily for several days, and the dose may be adjusted depending on the woman's response. The intricate interplay of FSH, LH, and their complementing actions is required for optimal follicle formation and subsequent ovulation. Insufficient endogenous LH production may result in a poor ART outcome. Exogenous LH may help people with hypogonadotrophic hypogonadism and people over the age of 35 who are trying to get pregnant. Nevertheless, the amount of LH is essential since high LH may have a negative impact on ART. Hence, optimizing FSH dosage in different patient populations and supplementing LH in various subgroups outlined above may enhance ART outcomes.[148] During ovulation induction, the woman's response to the medication is closely monitored using blood tests and ultrasound scans to determine when the follicles are mature and ready for ovulation. When the follicles are mature, a trigger shot of human chorionic gonadotropin (hCG) is given to trigger ovulation.[149] The integration of ovulation induction with other reproductive interventions, such as intrauterine insemination (IUI) or IVF, might enhance the likelihood of achieving pregnancy.[150]

In men, elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) have the potential to induce heightened testicular activity, resulting in greater production of testosterone and sperm. Human chorionic gonadotropin (hCG) is a hormone that is endogenously synthesized during gestation. However, it may also be used exogenously to elicit testosterone synthesis and enhance sperm production and motility in males.[151]

***Intrauterine insemination (IUI)***

In the realm of ARTs, IUI is widely recognized as the primary approach for couples with infertility or reduced fertility. The preference for IUI as a fertility treatment is largely due to its simplicity, reduced care needs, limited adverse effects, and relative cost-effectiveness.[152] IUI is a procedure that entails tracking a woman's menstrual cycle to ascertain ovulation timing. Sperm, either from the male partner or a donor, is harvested, cleaned, and concentrated to exclude impurities or non-viable sperm cells. This concentrated sperm sample is subsequently introduced into the uterine cavity using a thin catheter, typically within 24 hours post-ovulation. The success rate of IUI can vary, influenced by factors such as the cause of infertility, age of the participants, and the quality and quantity of sperm used. When juxtaposed with IVF, IUI stands out due to its reduced invasiveness and affordability.[152]

For male patients, IUI serves as a remedy for infertility issues stemming from low sperm count, suboptimal sperm motility, or other seminal fluid anomalies. It is especially instrumental for couples grappling with moderate male factor infertility, which is defined by sperm morphology of 4% or less and a progressive motile sperm count between 5 to 10 million. [153] Regarding female patients, IUI acts as a countermeasure for infertility induced by conditions such as ovulatory disorders, cervical factor infertility, endometriosis, unexplained infertility, and other associated reproductive challenges. It's worth noting that in instances of unexplained infertility among couples, IUI is rarely administered without the support of adjunct treatments like clomiphene citrate or gonadotropins.[153]

***In vitro fertilization (IVF)***

IVF is a form of assisted reproductive technology (ART) wherein oocytes and sperm are united in a laboratory setting to produce embryos. These embryos are subsequently transferred to a woman's uterus. The efficacy of IVF is influenced by multiple variables, such as the age of the couple, the underlying cause of infertility, and the quality of embryos utilized. Common indications for IVF include tubal occlusion, endometriosis, male factor infertility, idiopathic infertility, and other conditions impeding natural conception.[154] IVF might be pursued when other fertility interventions, like intrauterine insemination (IUI), have not yielded success.

The IVF procedure encompasses multiple stages: ovarian stimulation to yield numerous oocytes, oocyte retrieval, sperm acquisition and processing, in vitro fertilization, and uterine embryo transfer. In certain scenarios, adjunctive techniques like intracytoplasmic sperm injection (ICSI) or pre-implantation genetic testing (PGT) may be advised to augment the likelihood of a positive outcome. [154, 155] While IVF offers a potential treatment avenue for individuals contending with infertility, consultation with a fertility specialist is pivotal to ascertain if IVF aligns as the optimal therapeutic strategy for specific cases.

***Intracytoplasmic sperm injection (ICSI)***

The use of ICSI is a specialized technique within ART designed to address infertility issues in individuals of both genders. Specifically, ICSI is commonly employed within the framework of IVF. The procedure involves the direct injection of a single spermatozoon into an oocyte to facilitate fertilization. ICSI is particularly beneficial in cases of pronounced male factor infertility characterized by low sperm count, compromised sperm motility, or abnormal sperm morphology. Moreover, ICSI is recommended when previous IVF attempts have been unsuccessful or when other complicating factors, such as unexplained infertility or advanced maternal age, are present.[156, 157]

The procedure of ICSI consists of numerous stages, including ovarian stimulation to create multiple eggs, egg retrieval, sperm collection and preparation, and the injection of a single sperm into each egg. Each stage is followed by the next stage in the process. After the eggs have been fertilised, they are cultivated in the laboratory for many days until they are ready to be implanted into the uterus of the lady. ICSI involves immediately microinjecting

the fertilising spermatozoon into the ooplasm after it has been immobilised. This ensures that neither the cumulus-corona radiata complex nor the ZP are skipped in the process of fusing the metaphase II egg with the spermatozoon. Immobilisation is a necessary micromanipulation that must be performed in order to make the sperm membrane permeable and permit the release of "sperm cytosolic components," both of which are essential for the activation of the oocyte.[158] After sperm microinjection, the release of calcium cortical vesicles causes the oocyte membrane to depolarize, which may be seen. *In vitro* embryonic development in IVF-fertilized oocytes and ICSI-fertilized oocytes is comparable, with the two pronuclei emerging and disappearing at the zygote stage.[159] The efficacy of ICSI is contingent upon several circumstances, including the age of the individuals involved, the calibre of the eggs and sperm used, and the proficiency of the embryologist executing the technique.

### *Donor eggs or embryos, and sperm*

The use of donor eggs or embryos and sperm in infertility therapy is a viable alternative for couples facing challenges in conceiving owing to various circumstances, including but not limited to advanced maternal age, reduced ovarian reserve, male factor infertility, or genetic illnesses.[160]

Donor eggs or embryos can be used when a woman is unable to produce viable eggs or has genetic conditions that she does not want to pass on to her child. The eggs or embryos are donated by a young, healthy woman who has undergone ovarian stimulation and egg retrieval.[161] Sperm donation is used in cases when the male partner exhibits diminished sperm count, impaired sperm motility or quality, or harbours genetic abnormalities that he wishes to prevent from being inherited by his offspring. The acquisition of donor sperm involves the procurement of gametes from a young and healthy male individual, which are afterwards used for the purpose of fertilising either a donor egg or the recipient's own egg.[162]

In some circumstances, the use of both donor eggs or embryos and donor sperm may be employed when both individuals in a partnership have infertility or possess genetic abnormalities. Utilizing donor ova or embryos in combination with sperm can potentially augment the probability of successful fertilization and subsequent healthy gestation. However, the employment of donor gametes necessitates meticulous consideration of both ethical and legal dimensions, encompassing issues related to anonymity, disclosure, and informed consent. It is imperative for prospective parents to seek guidance from their healthcare professional and a reproductive specialist to determine the suitability of this specific intervention and to comprehensively understand its potential benefits and risks.[163]

## FERTILITY TREATMENT INDUCED OS AND REPRODUCTIVE DISORDERS

### *Excessive antioxidants in OS and reproductive disorders*

Antioxidants possess the potential to ameliorate OS-induced reproductive dysfunctions by diminishing ROS concentrations in reproductive tissues. Nevertheless, the specific roles of antioxidants in both the prevention and treatment of distinct reproductive disorders have yet to be comprehensively understood. It is imperative to conduct additional studies to ascertain the ideal dosages of antioxidants that promote reproductive health, since excessive supplementation might lead to detrimental outcomes. A plausible explanation for these negative effects could be the perturbation of redox signaling cascades, which orchestrate cellular functions such as gene transcription and cell proliferation. By neutralizing ROS that act as signaling entities, antioxidants may inadvertently disrupt these cascades, potentially intensifying the damage induced by OS.[164] In several scientific investigations, there is evidence suggesting that an overabundance of antioxidant supplementation can potentially exert pro-oxidant effects, consequently resulting in the production of ROS and subsequent oxidative damage.[165] This counterintuitive occurrence, termed the "antioxidant paradox," is postulated to transpire when antioxidants surpass optimal levels, thereby overpowering the cellular antioxidant defense systems, which in turn facilitates the accumulation of ROS. Furthermore, the use of antioxidants to mitigate OS-induced reproductive disorders may interfere with normal physiological processes, such as sperm capacitation and oocyte maturation, which rely on ROS signaling. Excessive antioxidant supplementation may disrupt these processes and impair fertility.[164]

The inadequate identification of OS in male infertility limits the appropriateness of administering antioxidants. In some instances, this may result in excessive usage and the initiation of reductive stress as mentioned above. Additionally, the correlation between inflammation and OS can establish a detrimental cycle that causes damage to male reproductive tissues. This ultimately exacerbates cellular harm and compromises the function of male reproductive tissues. Therefore, the deficiencies of antioxidant therapy in addressing male infertility arise from the lack of targeted interventions that simultaneously address inflammation and OS, which represent crucial mechanisms of male infertility.[166]

### *Anti-inflammatory drug induced OS and reproductive disorders*

NSAIDs are often used in the management of inflammatory conditions and analgesia. The broad use of NSAIDs, including both traditional non-selective NSAIDs and selective cyclooxygenase (COX)-2 inhibitors, is primarily attributed to their anti-inflammatory and analgesic characteristics. NSAIDs play a crucial role in pain management due to their ability to modulate the COX pathway, which is involved in both the generation of inflammation and the biochemical perception of pain. The enzyme cyclooxygenase competitively inhibits the bioconversion of arachidonic acid to inflammatory prostaglandins. NSAIDs are known to inhibit COX.[167] Nevertheless, some investigations have shown that these pharmaceutical substances have the potential to elicit OS, characterised by a disruption in the equilibrium between the generation of ROS and the organism's capacity to eliminate them. ROS are generated as a result of the production of free radicals induced by NSAIDs. The generation of ROS leads to OS, which has been associated with cellular apoptosis. The toxicity of several NSAIDs has been associated with OS as a broad underlying mechanism.[168, 169]

OS may cause cell and tissue damage and has been related to a variety of health conditions, including reproductive difficulties. OS arises when there is an imbalance between the creation of free

radicals and the capacity of the cells to eliminate them. For example, an excess of peroxynitrite and hydroxyl radicals may cause lipid peroxidation, which harms lipoproteins and cell membranes. As a consequence, malondialdehyde (MDA) and conjugated diene molecules, both of which are known to be cytotoxic and mutagenic, would form. Because lipid peroxidation is a radical chain reaction, it spreads quickly and damages a large number of lipidic molecules. Proteins, in addition to being damaged by OS, may undergo structural alterations that impair their capacity to operate as enzymes.[170, 171] Studies have found that NSAIDs can disrupt testicular function and reduce testosterone production in men. In men, LH plasma levels were linked to ibuprofen plasma levels, and the testosterone/LH ratio fell. Using adult testis explants that were either treated or not treated with ibuprofen, we demonstrate that the endocrine functions of testicular Leydig and Sertoli cells, including testosterone production, were suppressed through transcriptional repression. This effect was detected in a human steroidogenic cell line as well. Ibuprofen alters the human testicular endocrine system by producing compensatory hypogonadism via selective transcriptional repression.[172] In women, NSAIDs may interfere with ovulation and reduce fertility. In women with minor musculoskeletal discomfort, diclofenac, naproxen, and etoricoxib substantially decrease ovulation. Researchers noticed a substantial drop in progesterone, a hormone required for ovulation, across all therapy groups after only ten days of medication, as well as functioning cysts in one-third of patients.[173]

Long-term NSAID usage has also been linked to an increased risk of cardiovascular disease, gastrointestinal issues, and renal damage. Therefore, it is important to use these drugs as directed and only when necessary.[174]

In scientific terms, it is crucial to underscore that not all anti-inflammatory agents precipitate OS. Conversely, some may exert antioxidant properties. Specifically, curcumin, the principal bioactive compound in turmeric, has demonstrated both anti-inflammatory and antioxidant activities, suggesting potential advantages for reproductive health.[175] Overall, more research is needed to fully understand the relationship between anti-inflammatory drugs, OS, and reproductive disorders. It is important for individuals to speak with their healthcare provider before taking any medications and to discuss any potential risks or concerns.

### *Antibiotics in production of OS and fertility disorders*

The use of antibiotics has been associated with several health complications, including OS and reproductive disorders. Notably, certain antibiotics, such as aminoglycosides, fluoroquinolones, and beta-lactam classes, can induce oxidative stress, leading to cellular damage in specific host tissues, including the renal cortex and tendons.[176-178] Antibiotics have the potential to upset the equilibrium of the microbiome in the gut, which may result in an increase in the number of pathogenic bacteria and a reduction in the number of helpful bacteria. This may result in a rise in the generation of ROS as well as a fall in the antioxidant capacity, which can lead to OS.[179]

OS has been linked to various health problems, including cardiovascular disease, cancer, and neurodegenerative disorders. It can also affect fertility by damaging the DNA of sperm and eggs and reducing their quality. ROS/RNS serve a key role in regulating various intracellular signaling pathways, immunological and mitogen responses, and maintaining cellular homeostasis at moderate levels. Elevated quantities of ROS, conversely, have the potential to induce oxidative harm to cellular components such as proteins, lipids, and nucleic acids (DNA, RNA), so compromising cellular integrity. In order to preserve redox equilibrium and mitigate potential damage to biological systems, a complex network of antioxidant molecules has been devised.[180, 181] In addition to OS, antibiotic use has also been linked to fertility disorders. The gut microbiome plays a crucial role in regulating the body's hormonal balance, and disruptions to the microbiome can lead to hormonal imbalances that can affect fertility.[182] The use of antibiotics in general has been shown to have a correlation with fecundity. However, it is important to note that the impact on fecundity may vary depending on the specific kind of antibiotic used and the reasons for its administration. Multiple variables, such as medical history, underlying health condition, inflammatory reactions, and the microbiome of the reproductive tract, are presumed to play a role in the aforementioned disparities. However, when conducting stratified analyses, it becomes evident that the utilisation of antibiotics might be marginally more inclined to be linked with reduced fertility in younger women, smokers, and individuals with a reproductive health background.[183]

The impact of antibiotics on male fertility may manifest via the disruption of testosterone and other hormone synthesis, resulting in diminished sperm count and quality. In general, while antibiotics has the potential to save lives in the management of bacterial infections, it is essential to exercise caution and oversight in their administration to mitigate the occurrence of adverse consequences, such as OS and disruptions in reproductive capacity. The judicious use of antibiotics and the implementation of measures to promote the well-being of the gut microbiome, such as the consumption of a diet abundant in fiber and probiotics, are of paramount importance.

## OTHER FERTILITY TREATMENT INDUCED OS AND REPRODUCTIVE ISSUES

OS has been identified as a significant component that might significantly impact the results of assisted reproductive procedures owing to an imbalance between ROS and antioxidants.

During IVF and ICSI, the process of fertilization occurs outside of the body in a laboratory setting. This process involves the use of medications to stimulate the ovaries and increase the number of eggs that are produced. Despite advancements in ART methods, gametes and embryos are exposed to a variety of possible ROS-inducing variables when handled, prepared, and manipulated during ART operations. The probability of OS development *in vitro* is higher than *in vivo*[184], and its harmful effect may be increased owing to a lack of physiological defense systems, the absence of natural antioxidants, and the existence of several potential ROS sources.[185] The sources of ROS seen during ART procedures might originate either endogenously from gametes or externally from environmental factors.[112] However, unless proactive measures are taken to mitigate the creation of ROS, which may originate from

both internal and external sources, OS will inevitably occur, significantly impacting fertility rates and pregnancy outcomes.

Furthermore, the induction of ovarian stimulation in conjunction with the manipulation of eggs and sperm during IVF and ICSI may also result in OS. The assessment of light exposure is conducted by considering the metrics of light intensity, measured in lux, or irradiation level, measured in W/m2. The use of low light levels (specifically, 100 lux from the microscope and 20 lux from the ceiling) during the manipulation of human embryos in IVF-ET procedures, together with other tactics aimed at minimizing OS development in vitro, yielded a notably elevated rate of blastulation in a total of 110 IVF cycles.[186] Blue light, which falls within the wavelength range of 400-500 nm, is considered to be more deleterious compared to visible light with longer wavelengths. This heightened harmfulness may be attributed to its potential to generate hydrogen peroxide and interfere with the normal functioning of enzymes in the respiratory chain.[187] Blue light exposure inhibited blastocyst development, increased blastomeric apoptosis, and increased ROS generation in morula.[188] The use of light filters on inspection microscopes, namely those that effectively block light at a wavelength of 500 nm, together with the utilization of low illumination levels that do not hinder visual examination, and the reduction of inspection periods, may serve as potential strategies to alleviate the aforementioned impacts.[186]

There is a clear correlation between the composition of the medium used to culture human oocytes and pre-implantation embryos and the quality of the embryos produced by ART.[189] The presence of metallic ions (iron and copper) in culture medium may cause ROS-generating processes inside cells[190], and the rate of ROS generation varies with culture media composition.[190] The presence of EDTA may minimize ROS generation, while additional supplements such as albumin may produce an increase in oxygen load.[112] Antioxidants (e.g., ascorbic acid, alpha-tocopherol) added to culture medium may help mitigate the negative effects of ROS on gametes.[191,196-200]

OS has been shown to have detrimental effects on the viability and functionality of both eggs and sperm, hence impairing their capacity to successfully fertilize and develop into a viable embryo. This phenomenon has the potential to result in a decline in the efficacy of reproductive interventions. Cryopreservation refers to the technique of subjecting gametes/embryos and whole ovarian or testicular tissues to freezing temperatures, followed by subsequent thawing, with the purpose of using them in ART treatments..[192] While cryoprotectants and customized procedures seem to increase cell viability, the freeze-thaw process is an intensive stressor that may affect the structure and integrity of the cell, such as the spermatozoa plasma membrane.[193] Cryopreservation freeze-thaw procedures enhance DNA oxidative damage and fragmentation, resulting in reduced motility and viability in post-thaw spermatozoa.[194]

In addition to OS, fertility treatments can also increase the risk of reproductive issues. For example, the use of medications to stimulate the ovaries can increase the risk of ovarian hyperstimulation syndrome, which can cause abdominal pain, nausea, and other symptoms.[195] Overall, while fertility treatments can be effective in helping couples conceive, their use should be carefully considered and monitored to minimize potential side effects. It is essential to work closely with a healthcare provider to establish the best course of therapy and to take efforts to promote reproductive health, such as keeping a healthy diet and participating in regular physical exercise. It is also important to work closely with a healthcare practitioner to decide the best course of treatment.

## CONCLUSION

In conclusion, the present literature review elucidates the complex and multifaceted relationship between fertility drugs and ovarian stimulation. It underscores the importance of weighing the therapeutic benefits against potential drawbacks. While antioxidants present a potential strategy for mitigating OS and improving fertility outcomes, excessive use might lead to the "antioxidant paradox." This emphasizes the nuanced interaction between redox homeostasis and gametogenesis. Furthermore, specific antibiotics and anti-inflammatory medications might intensify OS, thereby possibly leading to reproductive anomalies.

Future research directions should emphasize uncovering the molecular mechanisms underlying the interplay between fertility drugs and OS and pinpointing biomarkers that can signal early manifestations of OS-induced reproductive impairments. Moreover, research efforts should be directed towards developing personalized treatment approaches that consider patients' individual genetic makeup, hormonal profiles, and medical histories to optimize the use of fertility medications while minimizing potential risks. Rigorous evaluation of the safety and efficacy of these medications will be crucial in informing clinical practice and policy decisions.

Ultimately, a comprehensive understanding of the effects of fertility medications on OS will pave the way for novel therapeutic interventions, facilitating the development of more targeted and efficacious treatments. This knowledge will empower clinicians and patients alike to make informed decisions in the pursuit of optimal reproductive health, ultimately contributing to the advancement of assisted reproductive technologies and addressing the growing global challenge of infertility.

### Conflict of Interest

The authors declare that none of them has any conflict of interest.

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