A Review on Male Infertility - Environmental Factors, Pathophysiological and Oxidative Stress

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ABSTRACT

Male infertility is one of the rising global problems with an increasing decline in male semen quality among men living in Asia, Europe, Africa and North America. Infertility is defined as the failure of conception after at least 12 months of unprotected intercourse. Globally 70 million people are affected by infertility. Environmental, occupational and modifiable lifestyle factors may contribute to this decline of male fertility. Various factors associated with male infertility include smoking cigarettes, alcohol intake, use of illicit drugs, obesity, genetic factors, heavy metals, psychological stress, exposure to pesticides and industrial chemicals, poor nutrition intake, oxidative stress, sedentary lifestyle, advanced paternal age, diet and coffee consumption.

KEY WORDS

Infertility, Antioxidant, Environmental Factors, Endocrine Factors.

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BACKGROUND

Infertility is a global medical and social issue. Although infertility results from a male partner's abnormality in nearly 50 percent of cases, considering infertility as a problem for female partners is a common prejudice. In many cases, the underlying pathological basis of qualitative and quantitative sperm defects which lead to fertilization defects is not clear. Infertility is a major clinical issue that medically and psychosocially affects people. Infertility is defined as the inability to conceive after at least 12 months of unprotected intercourse. In the United States, about 15 percent of couples suffer from infertility. In India, it has been reported that one in six couples suffer from infertility.¹⁻³

Numerous factors can impact a couple's fertility. The factors responsible for male infertility are, however, conveniently classified into pre-testicular, testicular and post-testicular factors.^{4,5} The pre-testicular factors are related to hormonal imbalance and poor general health, and the important pre-testicular causes are hypogonadism, drugs, alcohol, smoking, psychological stress, genetic abnormalities, chemotherapy and various types of medication such as anabolic steroids, cimetidine, spironolactone, phenytoin, sulfasalazine and nitrofurantoin. On the other hand, the testicular factors refer to conditions where despite hormonal support, the testes produce semen of low and poor quality. Age, chromosomal abnormality, seminoma, idiopathic oligospermia, varicocele, hydrocele and mumps are among the testicular causes of male infertility.⁶ Post-testicular factors decrease male fertility by affecting the male genital system after testicular sperm production and include genital tract defects as well as ejaculation problems. Some important post-testicular factors are blockage or absence of vas deferens, prostatitis, antisperm antibodies, retrograde ejaculation, obstruction of the ejaculatory duct, hypospadias and impotence. Even so, in several cases, it is quite difficult to identify the exact factor responsible for male infertility and the mechanism of the underlying poor semen quality deficiencies remain obscure. Consequently, potential non-conventional factors have been sought for the pathogenesis of male infertility, and recent studies have suggested that oxidative stress may have a profound role in male infertility.⁷

Spermiogenesis

Spermiogenesis is a complex process involving many changes in morphology, physiology and biochemistry. These changes include nuclear condensation, nucleus shaping, acrosome formation, cytoplasm elimination, development of a flagellum, and mitochondrial arrangement into the middle sperm piece. The nucleus contains decondensed chromatin at the beginning of spermiogenesis and is believed to be active transcription. But the nucleus replaces lysine and histidine-rich histones with a series of basic proteins during the later stages of spermiogenesis. These are initially transitional proteins, and ultimately basic protamines rich in arginine and cysteine the spermatids becomes highly condensed. Replacement of nuclear histones during spermiogenesis by protamines and nuclear condensation involves a series of interactions mediated by the transition proteins.

Two major classes of transitional proteins TP1 and TP2 are found.⁸ As a result of this arrangement, mammalian

sperm nuclear DNA becomes 6 times more condensed than somatic cell DNA (in an ordered process starting at the anterior end of the nucleus and proceeding towards the tail, making sperm nuclear DNA known as the highest condensed eukaryotic DNA).⁹ The formation of disulphide cross-links in the nucleus is an important change to the sperm during epididymal transit. Protamine, rich in cysteine, contains groups of sulfhydryl (S-H) that participate in the formation of covalent bonds in and between the molecules of protamine that provide a highly stable keratin nature.¹⁰ Human nuclear proteins at the end of the epididymal passage contain a limited amount of nonoxidized protamine and cysteine. These free amino groups of cysteine and arginine and free thiol may be chelated by reversible binding of zinc ions and further condensing of the sperm nucleus. Zinc in the sperm nucleus is thought to hinder the premature exchange of thiol disulphide and thereby decreases the vulnerability of sperm chromatin to chemical attack during transfer to the ovum.¹¹ Until ejaculation, the storage of fully mature sperm occurs primarily in epididymis cauda. Sperm can remain viable in the epididymis for about 4 to 6 weeks.¹² During this period, sperm may become exposed to toxicants. If such chemicals subvert the normal condensation mechanism to protect the nucleus, they may have a detrimental effect on the integrity and function of nuclear sperm.¹³

CAUSES OF MALE INFERTILITY

Environmental, occupational and modifiable factors in lifestyle may contribute to male infertility. Male infertility related lifestyle factors include cigarette smoking, alcohol intake, illicit drug use, obesity, psychological stress, advanced paternal age, diet and coffee consumption. Testicular heat stress, intense cycling training, insomnia and exposure to electromagnetic radiation from mobile phones are other factors associated with male infertility.¹⁴

Cigarette Smoking

Cigarette smoke exposure generates high oxidative stress levels, directly increasing both seminal leukocyte concentration and seminal ROS generation,¹⁵ and decreasing seminal levels of the antioxidant enzyme SOD. Men who smoke also have lower sperm quality measures including reduced sperm counts, motility and morphologically normal sperm counts. Smoking has been noted to decrease the concentration of seminal antioxidants vitamin C and E, thereby reducing the spermatozoa and seminal fluid's oxidant scavenging capacity.¹⁶

Alcohol Intake

Alcohol can affect male infertility by altering sperm count, shape, motility and size of sperm. Heavy drinking of alcohol affects fertility by lowering testosterone levels, follicle-stimulating hormones and luteinizing hormones and raising estrogen levels, which reduce sperm production. It has also been shown that high amounts of alcohol intake increase systemic levels of oxidative stress, and the effect of oxidative stress can be further exacerbated by the low-nutrient diet that usually accompanies this high intake of alcohol.¹⁷

Industrial Compounds

Industrial waste products have a broad impact on human and environmental health and several groups have been investigating the impact of these compounds on fertility. The compound phthalate, for example, is found in a wide range of plastics used in food packaging, as well as beauty products and exposure to these chemicals can occur via oral, skin, or inhalation routes. Exposure to phthalates has been shown to cause sperm DNA damage, as well as impaired spermatogenesis.^{18,19} Heavy metals such as cadmium and lead, have been shown to increase testicular oxidative stress and increased infertility and miscarriage rates have been noted in welders as well as paint workers, and battery manufacturers.²⁰ Men in these industries may be exposed to heavy metals and are recommended to take aggressive steps to avoid further exposure. Several pesticides, including lindane, methoxychlor and herbicide dioxin-TCDD, have been linked to increased testicular oxidative stress in rodent models. It has been noted that the almost ubiquitous food preservative sulphur dioxide directly increases intratesticular oxidative stress, and it has been shown that diesel exhaust particulates powerfully activate the production of leukocyte ROS.^{21,22}

Male Infertility

1. Impairment of Spermatozoa in Humans

Defective sperms are one of the main causes of infertility. It has been reported that the nucleohistone sperm compartment containing histone bound DNA sequences such as telomeres and gene promoters for embryonic development is often at high risk of oxidative stress, leading to infertility.²³ The relative decrease in protamine 2 levels also results in infertility in the ratio of protamine 1: protamine 2, at mRNA and protein rates. Once, gene mutations encoding protamines induce structural changes in the composition of the sperm chromatin, leading to infertility.²⁴

2. Sperm Dysfunction

The mechanism of sperm dysfunction is related to oxidative stress, which induces distortion of sperm DNA integrity by destroying the lipids and protein present in the sperm cells. This has a negative effect on sperm cell membrane fluidity and permeability which results in infertility.²⁵

3. Sperm DNA Fragmentation (SDF)

Many researchers say that SDF is regulated by free radicals.²⁶ Once again, the underlying SDF mechanism includes single and double-strand breaks, DNA fragmentation, abasic site entry, purine, pyrimidine modifications and DNA cross-linking resulting in gene transcription induction, signal transduction pathways induction; accelerated telomeric RNA depletion, replication defects, genomic instability, and GC to TA transmissions.²⁷ Given that these mechanisms are also known to be the causes of carcinogenesis, this may explain a link between infertility and cancer. Male infertility is also closely associated with DNA damage caused by ROS, which in turn accelerates the apoptosis of the germ cells, leading to a decrease in sperm count.²⁸

4. Physiologic Role of Reactive Oxygen Species (ROS)

Depending on the type and concentration of ROS, and the length and location of ROS exposure, it has adverse effects on sperm function.²⁹ Sperm gradually acquires the capacity to travel during epididymal motion. However, they gain the capacity to fertilize in the female tract by a series of physiological changes, called "Capacitation".³⁰

Antioxidants and Infertility

ROS has both physiological and pathological functions, and antioxidants maintain a stable state of ROS in seminal plasma. Antioxidants serve as free radical scavengers, to shield ROS sperm. Such antioxidants are superoxide dismutase (SOD), catalase and glutathione peroxidase (GPX). However, semen contains a variety of non-enzymatic antioxidants such as Vitamin C and E, pyruvate, glutathione and carnitine, which decrease endogenous mechanism of repair and enzymatic defence.³¹ The production of reactive oxygen species may result in the breakage of the DNA strands and chromosomal rearrangements. 8-OHdG is a sensitive marker of oxidative stress, many studies have shown a higher level of 8-OHdG in ejaculated sperm of infertile males.

Seminal Malondialdehyde

Lipid peroxidation of the sperm membrane is the main mechanism of ROS-induced sperm damage that leads to infertility. Malondialdehyde, a by-product of lipid peroxide, reflects the level of lipid peroxidation.³² Numerous studies have shown that lipid peroxidation affects sperm concentration, motility, morphology and poor sperm quality.

Glutathione

Glutathione is one of the most abundant non-thiol proteins in mammalian cells.³³ Glutathione deficiency can lead to mid-piece instability, leading to deficient motility.³⁴ It protects the plasma membrane from lipid peroxidation, and superoxide prevents the formation of O₂. Glutathione peroxidase (GPx) is a major contributor to the reduction of hydrogen peroxide and organic peroxide involving phospholipids peroxides. Selenium occurs in the GPx active site in the selenocysteine. It is contained in the mitochondrial sperm matrix but a nuclear portion of GPx is associated with the protection of sperm DNA from oxidative disruption. The nuclear process has also been documented to play a part in condensing chromatin. The appearance of GPx in seminal plasma indicates that its source may be the prostate.³⁵

Superoxide Dismutase

Superoxide dismutase (SOD) scavengers both extracellular and intracellular superoxide anion and prevent the lipid peroxidation of the plasma membrane.³⁶ SOD also prevents the premature hyperactivation and pre-ejaculation capacitation of superoxide radicals.³⁷ Superoxide dismutase or superoxide reductase catalyzes the conversion of superoxide anions to dismutation. These also occur for both extra- and intracellular forms which are otherwise known as metalloenzymes.

The two intracellular forms in their active centre and the organelle where they are located are separated by the metal. The first intracellular component in the active centre contains copper and zinc (SOD-1) and is mainly contained in the cytoplasm, while the second component present with manganese in the active centre of mitochondria is called SOD-2. In extracellular space (SOD-3), the SOD functions as an extracellular shape. This is connected to the surface of polysaccharides although it can be found in a free form.³⁸ SOD is one of the key elements of seminal plasma. Superoxide anion scavenging capacity and several investigators have reported a reduction of SOD activity in the semen of infertile males.

Catalase

Catalase catalyzes the splitting of H₂O₂ into H₂O and O₂; H₂O₂ is one of the reactive oxygen species involved in oxidative stress; catalase helps detoxify both intracellular and extracellular H₂O₂ into water and oxygen. However, it triggers nitrous oxide (NO) sperm capacitation, a complex process involving H₂O₂.³⁹

Vitamin E

Vitamin E is a powerful antioxidant that is found in the cell membrane. It inhibits lipid peroxidation and scavenges free radicals produced during univalent molecular oxygen reduction and normal oxidative activity. The formation of these radicals leads to phospholipid peroxidation in the mitochondrial sperm resulting in low motility⁴⁰ Suleiman et al. (1996) found that supplementation with vitamin E could significantly reduce lipid peroxidation in seminal plasma, improve sperm motility and improve the incidence of pregnancy.⁴¹

Vitamin C

Vitamin C is a keto-lactone containing six carbons that are biosynthesized in the liver. Nevertheless, human inability to synthesize vitamins necessitates its inclusion in the diet or as a supplement. Vitamin C is a cofactor enzyme, which helps in the metabolic folic acid, tyrosine, and tryptophane processes.⁴²

Endocrine Factors of Male Infertility

1. Hypothalamic Dysfunction (Kallmann Syndrome)

The normal endocrine reproductive system functions as a prerequisite for normal male fertility. Any disruption of the delicately coordinated interaction between the hypothalamic-pituitary-testicular axis components may result in hypogonadism or infertility. The objective of the clinical evaluation is to determine whether the patient has an abnormality and whether hormone therapy will correct infertility. Based on a careful history, the physician will determine whether the patient's hypogonadism is (1) prepubertal or postpubertal onset; (2) the result of an abnormality in the hypothalamic-pituitary axis, the tests or the androgen receptor; or (3) the result of another underlying medical condition. This

information will place the patients in one of the four diagnostic categories: hypogonadotropic hypogonadism, testicular failure, deficiency of 5 α - reductase, or resistance to androgen disorders with identifiable pathogenic mechanism fall within each category.⁴³

2. Pituitary Failure (Tumour, Radiation, Surgery)

The failure of the pituitary to secrete the follicle-stimulating hormone and luteinizing hormone results in testicular disruption and infertility. Measurement of serum FSH is of paramount importance, providing a useful index of the seminiferous epithelium state when the concentration is related to sperm density: high concentration associated with severe oligospermia or azospermia usually denotes untreatable infertility. In about 30 % of men with severe degrees of testicular damage, elevated LH and low testosterone levels are indicative of interstitial cell failure. Measurements of prolactin are most likely linked to impotence rather than infertility. Hormonal treatment is often indicated for male infertility. Androgen injections of testosterone suppress spermatogenesis, so sperm count will rebound to a concentration greater than pretreatment levels once treatment is stopped. Those endocrine factors can potentiate testicular damage and are postulated as indicators of seminiferous tubular disruption resulting in spermatogenesis disruption, based on FSH measurement.⁴⁴

3. Hyperprolactinemia (Drug, Tumour)

Hyperprolactinemia causes infertility in around 11 % of oligospermic males. Hyperprolactinemia inhibits the pulsatile secretion of the gonadotrophin-releasing hormone, which causes the decreased pulsatile release of follicle-stimulating hormone, luteinizing hormone, and testosterone, which in turn causes spermatogenic arrest, impaired sperm motility, and altered sperm quality. It later produces secondary hypogonadism and infertility. Hyperprolactinemia also directly influences spermatogenesis and steroidogenesis by acting on prolactin receptors present in Sertoli cells and Leydig cells in testes and produces primary hypogonadism and infertility. It is seen that oligospermia or azospermic patients with normal serum levels of gonadotrophins show relatively higher serum levels of prolactin, proving a role of prolactin in gametogenesis, which is independent of gonadotrophins. Many studies are suggesting that hyperprolactinemia has a definite role in male infertility, and is one of the reversible causes of infertility. It can be managed medically with simple medication, such as bromocriptine and cabergoline, which normalize serum prolactin levels, restoration of gonadal function, reversing infertility caused by hyperprolactinemia and induce a reduction in the prolactinoma size in the majority of patients.⁴⁵

4. Exogenous Androgens

Exogenous androgens should only be prescribed if hypogonadism has been established by appropriate investigation, and preferably the patient does not intend to father a child. There are alternative

medications or combinations of medications, that can be used if hypogonadism is present and fertility is desired. It is somewhat counterintuitive that testosterone treatment will decrease or abolish fertility. Exogenous testosterone inhibits spermatogenesis by removing the feedback response to low testosterone at the hypothalamus and pituitary. This results in reduced synthesis and secretion of gonadotropins required to stimulate endogenous testosterone production and to support spermatogenesis. It is important to realize that the normal testicular levels of testosterone are approximately 100 times the concentration in circulation. These high levels are required locally to support spermatogenesis. So even with circulating androgen levels within the normal range, spermatogenesis fails due to insufficient gonadotropin and local testosterone support. Androgenic herbal supplements and illicit use of anabolic steroids have contributed to this serious challenge in the treatment of infertile men. Most men will recover normal spermatogenesis after cessation of exogenous testosterone treatment, but this requires 6 months or more in most men. In rare cases, fertility is permanently impaired.⁴⁶

5. **Thyroid Disorders**

Thyroid dysfunction can impair semen quality, and decrease sperm motility and/or concentration. In addition, it is described as an association between TAI and asthenozoospermia. After patients achieved euthyroidism, alterations in semen were reversible. The impact of thyroid dysfunction on the semen is primarily due to an effect on the central (luteinizing hormone / follicle-stimulating hormone) and peripheral gonadal function and binding proteins via sex hormone.⁴⁷

6. **Adrenal Hyperplasia**

The presence of testicular adrenal rest tumours (TARTs) in adult patients with congenital adrenal hyperplasia (CAH) is an important cause of gonadal dysfunction and infertility.⁴⁸

7. **Testicular Failure**

Testicular or spermatogenic insufficiency is the most serious form of male infertility. Typical testicular failure phenotype in severely impaired spermatogenesis results in azoospermia or severe oligozoospermia (sperm density as low as 5 or 106 ml⁻¹). A range of conditions can cause testicular failure, both congenital and acquired. Even after a complete diagnostic workup, aetiology remains unknown in about 40-50 percent of primary testicular failure.⁴⁹

Anatomic

1. Congenital absence of vas deferens.
2. Obstructed vas deferens.
3. Congenital abnormalities of the ejaculatory system.
4. Varicocele.
5. Retrograde ejaculations.

Abnormal Spermatogenesis

1. Unexplained azoospermia.
2. Chromosomal abnormalities.
3. Mumps orchitis.
4. Cryptorchidism.
5. Chemical or radiation exposure.

Abnormal Motility

1. Absent cilia (Kartagener syndrome)
2. Antibody formation.

Psychosocial

1. Unexplained impotence.
2. Decreased libido.⁵⁰

CONCLUSIONS

Antioxidants such as vitamin C, coenzyme Q, vitamin E and glutathione have been reported to be beneficial in male infertility management. Several defence mechanisms are critical in the living system, including antioxidant enzymes, vitamins and biomolecules. In essence, normal spermatozoa function may require a balance between ROS and antioxidants. Although natural antioxidants and phytochemicals have been shown to play a beneficial role in spermatogenesis. Infertility can be stressful for you as well as your partner. There are so many complications of male infertility like surgery or other procedures to treat low sperm count underlying causes or other reproductive problems, costly, involving reproductive techniques, stress and relationship difficulties associated with the impossibility of having a child. Almost all kinds of male infertility can't be prevented. You can however avoid certain known causes of male infertility. Nonetheless, healthy living, regular exercise and stress-free jobs can help reverse sperm dysfunction. For instance, don't smoke, limit alcohol intake, keep off weight, do not have a vasectomy, avoid things that cause the testicles to get prolonged heat, cut back on stress and avoid exposure to pesticides, heavy metals and other toxins and a healthy diet rich of antioxidants should be taken for the reversal of damage caused by reactive oxygen species.

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