Review Article

Increasing Prevalence of Male Infertility and Stress Factors: An Overview

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Abstract
Infertility is a social problem adding to the woes of marital life. Sex is the most powerful drive and instinct of all living beings including human. Infertility may be due to decrease in number of sperms, absence of sperms or increased in abnormal form of sperms in male semen and failure of the sperm to move with sufficient vigour towards ovum. Reactive oxygen species (ROS) are responsible for infertility. These ROS have beneficial as well as detrimental effect on sperm functions, depending on the nature and the concentration of the ROS involved. Hydrogen peroxide (H2O2) is a main toxic ROS for human spermatozoa, in low concentration, causes sperm immobilization. High concentration of H2O2 induces lipid peroxidation, which causes cell death. On the other hand, the superoxide anion (O2-) appears to play an important role in the process of sperm hyperactivity and capacitation.

Keywords: Male infertility, ROS, metal exposure, azospermia, oligospermia.

Introduction:
Infertility is the most common problem in present environment. It can be defined as failure to conceive after 12 months of unprotected sexual intercourse. It is classified as primary infertility and secondary infertility. If no previous pregnancies have occurred then it is primary infertility and if it occurs after one or more pregnancies then it is termed as secondary infertility. Approximately 15% of couples attempting their first pregnancy meet with a failure, and another 10% face secondary infertility. Data available over the past 20 years reveals that in approximately 30% cases of infertility, the pathology is abnormal in the man alone, and in another 20% cases, the pathology is abnormal in both the male and the female. Therefore, the male factors are partly responsible for infertility in approx 50% of cases. In an earlier study, pathology was found in 28.6% cases alone in male, while 30% cases showed abnormality in both the man and the woman. Male fertility depends upon an intact hypothalamo-pituitary- testicular axis to initiate and maintain quantitatively and qualitatively normal spermatogenesis, which maintain normal secondary sex glands and sexual functions. Up to 20% of male infertility can be attributed to endocrine disorders.

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fact, endocrine disorders which are associated with significant medical pathology remains, an important factor to be considered in the etiology of male infertility, because they are amenable for treatment.

The hormones initially evaluated for infertility in males include follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone and prolactin. For further studies, evaluation of oestradiol, sex hormone binding globulin, thyroid function tests can be done, depending on the clinical scenario and the results of the initial studies. Based on the results of the hormonal studies, a precise endocrinological diagnosis such as hypergonadotropic hypogonadism can be done and the patients are managed accordingly. The aim of this review is to conclude the entire factors responsible for male infertility and to re-conclude the role of oxidative stress and their effect on male infertility.

**Free radical and infertility:**
Infertility is one of the most stressful conditions amongst married couples. Male factor infertility is implicated in almost half of these cases. Recent advances in the field of reproductive medicine have focused the attention of many researchers to consider ROS as one of the mediators of infertility causing sperm dysfunction. Spermatozoa like any other aerobic cells are constantly facing the “oxygen paradox”. \( \text{O}_2^- \) is essential to sustain life as physiological levels of ROS, necessary to maintain normal cell function. Although, ROS is involved in many physiological functions of human spermatozoa, their excess production results in oxidative stress. Low level of ROS has been shown to be essential for fertilization, acrosomal reaction, hyperactivation, motility and capacitation. ROS is a major source of defective spermiogenesis. During spermatogenesis, a defect of the cytoplasmic extrusion mechanism results in release of spermatozoa, from germinal epithelium carrying surplus residual cytoplasm. The resulting spermatozoa are thought to be immature and functionally defective. Studies have suggested that retention of residual cytoplasm by spermatozoa is, in fact, positively correlated with ROS generation via mechanisms that may be mediated by the cytosolic enzyme glucose-6-phosphate dehydrogenase. The generation of ROS by spermatozoa has been proposed to occur in two ways: (i) nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system at the level of the sperm plasma membrane, and (ii) NADPH-dependent oxidoreductase (diphorase) at the mitochondrial level.

ROS causes damage to the spermatozoa DNA, resulting in increased apoptosis of these cells. Gomez *et al.* (1998) demonstrated that levels of ROS produced by spermatozoa were negatively correlated with the quality of sperm in the original semen. A study reported that levels of antioxidants in seminal plasma from infertile men were significantly lower than levels in fertile controls. However, pathological levels of ROS detected in semen of infertile men are more likely a result of increased ROS production rather than reduced antioxidant capacity of the seminal plasma. Various endogenous antioxidants belonging to both enzymatic and non-enzymatic groups can remove the excess ROS and prevent oxidative stress. The production of ROS is greatly enhanced under the influence of various environmental and life style factors such as pollution and smoking. An effective scavenging system is essential to counteract the effects of ROS. Since, ROS is essential for the normal sperm physiology, rationale use of antioxidants is advocated.
Effect of Lead on infertility:

Lead’s adverse effects on male reproductive function, particularly at low levels (<10µg/dl), has still not been adequately reviewed. Experimental data from both epidemiological and animal research suggests that lead in different concentrations has a wide spectrum of toxicity on the male reproductive system, including spermatogenesis, sperm functional parameters and reproductive hormones. Although unfavorable reproductive effects usually occur at relatively high levels of lead exposure, lower doses for longer time periods may also alter the male reproductive system in a manner similar to that previously reported at higher doses for shorter periods. Furthermore, regarding dosage level and duration of exposure, there are other potential factors to consider such as individual differences, social conditions, and various environmental factors.

Studies on occupationally lead-exposed men showed multiple sperm parameters, affects seminal plasma or rises blood lead concentrations, usually at levels of >40µg/dl, but sometimes even at levels of <10µg/dl. For instance, reduction in sperm count, sperm concentration or density, decreased volume of ejaculation as well as correlations with asthenospermia, hypospermia, and teratospermia (53µg/dl) have been reported in male workers.

Furthermore, higher percentages of immature and abnormal sperms seen in lead exposed workers have been reported in both high (40µg/dl) and low (<15µg/dl) blood lead levels. Low lead concentrations in the testes, seminal fluid and epididymis have demonstrated that, blood testicular barrier may protect testicular cells from direct exposed to the high levels blood lead. Macroscopic changes in accessory sex organs such as diminished weight of testes, seminal vesicles, epididymis, and ventral prostate have been demonstrated in various studies using experimental animals. Microscopic, histological and macroscopic changes, have been induced by increasing level of lead, in lead exposed male rats including changes in the testicular tissues morphology, and decreased germ cells layer population. In addition, two studies conducted on lead exposed mice demonstrated seminiferous tubule degeneration, and seminal abnormal cytology. Similarly, electron microscopic analysis has revealed that lead-exposed monkeys, when exposed during infancy, can induce testicular alterations, which persist in later life even when blood lead concentrations have been decreased considerably.

The results of experimental studies in rats have shown that the effects of lead involve multiple sites on male reproductive hormones although the most important part of these disorders probably occurs in the hypothalamic-pituitary-testosterone (HPT) axis.

Despite such finding it has not been easy to definitely ascertain the correlation between lead exposure, male fecundity and probable mechanism of infertility, because high level of lead exposure might affect many organs in various ways, aside from reproductive system.
Effect of occupational exposure on male fertility:

The knowledge existing today regarding the influence of chemical, physical and emotional factors on male fertility is limited. The main categories known to adversely affect male fertility include heavy metals (lead and selenium), solvents, pesticides and other agricultural materials, radiation, heat and welding. In addition to these factors, psychological stress is also a responsible factor for infertility and may also cause decreased fertility.

Carlsen et al. analyzed a total of 61 studies including 14, 947 men from the years 1938 to 1991, for mean sperm density and mean seminal volume. The results show a significant decline in mean sperm density from 113 million/ml in 1940 to 66 million/ml in 1990 with p value < 0.001. It was observed that seminal volume decreased (1940-1990) from an average of 3.40 ml to 2.75 ml (p= 0.027). This demonstrates a 20-percent decline in volume and a significant 58-percent decline in sperm production over the last five decades. Van Waeleghem et al. also reported a possible link between a decline in sperm quality and selenium deficiency, although in combination with other dietary factors.

Expanding knowledge about materials and exposures that could adversely affect male fertility has great importance in maintaining a worker’s health, his family life and the health of his progeny. In addition, learning about exposures that could negatively impact the male reproductive system is particularly important because of the relatively short time period before the damage becomes evident (in contrast to, for example, cancer). As such, protecting workers from exposures that could impact their fertility will generally protect them from other negative health effects, which could ultimately result from such exposures.

Azoospermia:
The causes of Azoospermia such as failure of spermatogenesis and obstruction of the ductal system particularly the vas deferens have been investigated. Emokpae et al., 2006 reported that hormonal abnormalities, underlying testicular pathology were common in infertile Azoospermia males. They also reported 40% Azoospermia males had abnormal hormone levels, the pattern of abnormalities varies. This indicates testicular failure in which there is loss of negative feed back by testicular product. Defect in testes despite increased level of FSH and LH. Marked elevation of FSH in the Azoospermia patients strongly suggest testicular failure and a poor prognosis.

Spermatogenic arrest, testicular atrophy and hypospermatogenesis were the most common testicular abnormalities. Testicular failure is also a responsible factor for decrease in sperm count. Defect in testes can not produce adequate quality sperm cells.

The high prevalence rates of AZFc deletions among the Caucasian populations suggest that this region of the Y chromosome consists of one or more important genes that are responsible for normal spermatogenesis. The DAZ gene, which clusters at the AZFc region, is one of the most frequently deleted genes in patients with severe male-factor infertility. This gene is expressed specifically in the testis and encodes an RNA-binding protein.
Although its precise biological function is not yet known, the DAZ protein is believed to play a role in male germ-cell development. The same AZFc micro deletion was detected in the oligospermic father and his ICSI-derived baby.\textsuperscript{38}

**Oligospermia:**
Oligospermia is an important clinical condition. There may be many responsible factors for oligospermia, including endocrine inter-relationship, testicular function, genetic factors or conditions of the vas and genital tract, the seminal vesicles, pH of the vaginal fluid and the motility and general health of the spermatozoa in the seminal fluid and their viability in the female genital tract. Madan and Madan in 1985\textsuperscript{39} reported sperman, to be safer medicine for oligospermia. They concluded that sperman increases sperm count, mobility and bring rapid conversion to spermatogenesis.\textsuperscript{39}

The last decade has seen a phenomenal growth in the field of knowledge about male infertility mainly due to the increased understanding of ROS and OS. This has lead to the development of various antioxidants. Lead and selenium in different concentrations has a wide spectrum of toxicity on the male reproductive system, including spermatogenesis, sperm functional parameters and reproductive hormones.

Unfavorable reproductive effects usually occur at relatively high level of lead exposure, whose lower doses, for longer time period, may alter the male reproductive system in a manner similar to that previously reported, at higher doses for shorter time period. Testosterone, the main male sex hormone, is formed and secreted by leydig cells in testes in response to stimulation by LH. Production of molecules with LH like immunoreactivity, but lesser LH bioactivity due to continuous LH-RH stimulation, suggests that, changes in the pattern of LH-RH stimulation due to lead exposure affects gonadotropin stimulation.

In present review our aim is to conclude all the responsible factors for male infertility such as industrial exposure, infertility due to elevated levels of lead and selenium, effect of ROS, their effect on hormonal disbalance and defective sperm production.

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