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Infertility in male; risk factors, causes and management- A review

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ABSTRACT

The etiology and psychosocial burden of infertility amongst couples especially in Africans has been stressed by various researchers. Male factors have been discovered to account for 20-50% of infertility cases unlike what it used to be when female factors were the only considered factors, thus the need to review the various works done by researchers on male infertility. In this review the contributions of the different etiological factors in male infertility was considered and attempt was also made to update the available information on the management of male infertility. The main aim of this review is to generate information which could act as guideline in the evaluation of male infertility. Laboratory signs suggesting possible sperm oxidative stress as a cause of male infertility include: poor sperm motility, teratozoospermia, increased semen viscosity, poor success in routine in vitro fertilization, and poor blastocyst development in the absence of a clear female factor amongst others. Avoiding tobacco smoking, marijuana, excessive alcoholism, excessive heat to the testes and wearing protective cup and jockstrap when participating in contact sports are suggested good preventive measures to tackle male infertility.

Key words: Male infertility, oxidative stress, mumps, orchitis, life style, testicular factors

INTRODUCTION

Male infertility refers to the inability of a male to achieve pregnancy in a fertile female. Formerly the problem of infertility in couples was ascribed to female alone and hence bears the bulk of the psychosocial effects especially in Africa. This is probably due to cultural believe and inadequate knowledge and clear understanding. Male infertility is considered when identifiable female causes of infertility are excluded and semen quantity and quality fails to fulfill WHO criteria [34]. Researchers had shown that male factors accounts for 40-50% of infertility in human [4, 13]. Male infertility is commonly due to deficiencies in the semen and semen quality is used as a surrogate measure of male fecundity [8].

It is estimated that 60% of married couples having regular unprotected intercourse, achieve pregnancy after 6 months of co-habitation, 90% achieve pregnancy by 12 months and 95% between 18-24 months [1]. In more than 50% of male infertility cases, the etiology remains unknown, and the infertility is thus classified as idiopathic. Idiopathic infertility affects a high percentage of infertile men who cannot be successfully treated by the available therapeutic modalities [30].

Mumps viral infections in adolescent and adult males carry an up to 30% risk that the testes may become infected resulting in orchitis, epididymitis or epididymoorchitis, which can be quite painful; about half of these infections

result in testicular atrophy, and in rare cases sterility can follow [29]. An estimated 20%-30% of cases are asymptomatic [7]. As with any inflammation of the salivary glands, serum amylase is often elevated [31].

Diagnostic test of saliva or blood may be carried out but a newer diagnostic confirmation, using real-time nested polymerase chain reaction (PCR) technology, has also been developed [15].

RISK FACTORS AND CAUSES

Pre-testicular factors

These are conditions that impede adequate support of the testes and include situations of poor hormonal support and poor general health including hypogonadism; drugs such as cimetidine and spironolactone that decrease follicle stimulating hormone (FSH) levels, and nitrofurantoin that decreases sperm motility; adopted life style (chronic alcoholism, marijuana, cigarette smoking); and strenuous activities such as strenuous bicycle riding [17].

Testicular factors

These are factors that affects quality and quantity of semen produced by the testes and include age, genetic defects of the Y-chromosome (Klinefelter syndrome), neoplasm e.g. seminoma, cryptorchidism, varicocele which account for 14% [9], mumps viral infection [18] and may be idiopathic which accounts for 30 % of male infertility [6]. Also, there are defects in USP26 in some cases [35].

Post-testicular factors

Post-testicular factors decrease male fertility due to conditions that affect the male genital system after testicular sperm production and include defects of the genital tract as well as problems in ejaculation: e.g. impotence, Vas deferens obstruction, lack of Vas deferens, infection e.g. proctitis, ejaculatory duct obstruction and hypospadias.

Hypothalamic-pituitary factors

Conditions that affect the hypothalamo-pituitary-axis will eventually affect the gonadotrophin releasing hormone (GRh) and hence the levels of follicle stimulating hormone, luteinizing hormone and prolactin hormone. These conditions include Kallmann syndrome (isolated gonadotropin deficiency), hyperprolactinemia and hypopituitarism. Hyperprolactinemia may be due to diseases affecting the hypothalamus and pituitary gland or secondary to disease of other organs such as the liver, kidneys and thyroid [25] Hyperprolactinemia may cause hypogonadism, erectile dysfunction, decreased libido, gynecomastia and infertility.

Environmental factors

The etiological importance of environmental factors in infertility has been stressed [14].The implication of toxins such as glues, volatile organic solvents, silicones, physical agents, chemical dusts and pesticides in infertility had been established [19]. Radiations and excessive heat to the genitalia have damaging effect on the testicles. Hence individuals having direct contact with or exposure to such chemicals have high chances of having primary or secondary infertility as the case may be. Estrogen-like hormone-disrupting chemicals such as phthalates are of particular concern for infertility in men and for effects on offspring of women. Exposure to phthalates can occur via dietary consumption, dermal absorption or inhalation and has been linked with impaired spermatogenesis and increased sperm DNA damage [12, 24]. The mechanism for this is probably due to increase in the generation of reactive oxygen specie (ROS) within the testis and a concomitant decrease in antioxidant levels, culminating in impaired spermatogenesis as observed in rats [16].

Life style and infertility

The contribution of tobacco smoking and alcohol intake to infertility had been established. Tobacco smoking was observed to damage sperm DNA [10]. Though some of the damage is irreversible, but stopping smoking can prevent further damage [3]. Smokers are 60% more likely to be infertile than non-smokers. Smoking reduces the chances of IVF producing a live birth by 34% and increases the risk of an IVF pregnancy miscarrying by 30% [27]. Smokers have decreased levels of antioxidants such as Vitamin E and Vitamin C, placing their spermatozoa at additional risk of oxidative damage.

Sexually transmitted disease (STD) and infertility

STDs are diseases transmitted through sexual activity with an infected partner caused by viruses, bacteria, or parasitic microorganisms. STDs are a leading cause of infertility. They are often asymptomatic but may display few symptoms, with the risk of failing to seek proper treatment in time to prevent decreased fertility [3]. Some of the

identified STDs (such as syphilis, trichomoniasis, chancroid, chlamydia, gonorrhoea, herpes simplex virus, human papilloma virus, lymphogranuloma venereum) are treatable while many are not and may eventually lead to death.

Urinary Tract Infection and infertility

The urinary tract has a relative anatomical association with the reproductive tract. *Escherichia coli* and *Staphylococcus aureus* are reputed to be the most prevalent Gram negative and Gram positive organisms implicated in UTI respectively [20].

Structural obstruction and infertility

Vas deferens and ejaculatory duct obstruction could be an important cause of infertility as they affect ejaculation. Hypospadias may also be of etiological importance. Obstructive azoospermia may result from previous vasectomy; epididymal, vassal, or ejaculatory duct pathology relating to genitourinary infection; iatrogenic injury during inguinal or scrotal surgery and congenital anomalies [2].

Spermatozoa and infertility

Azoospermia (low sperm counts), abnormal spermatozoa morphology (shape) and low sperm motility are usually asymptomatic conditions to most males but of great etiological importance. Most cases of low sperm counts are "idiopathic" but may be associated with varicocele and chronic testicular diseases. The quality and the total number of spermatozoa are a reflection of the testicular state, plasma testosterone level and the patency of the post-testicular duct system. The total seminal fluid volume is contributed by the various accessory glands and is thus a function of the secretory activity of the accessory glands. The quality of the spermatozoa (count, vitality, motility and morphology) and the composition of seminal fluid are also important index of sperm function. It is well recognized that sperm DNA can be damaged oxidatively by oxidative stress [24] and nonoxidatively by mechanisms such as aberrant apoptosis and incomplete sperm protamination [26].

Chemotherapy and infertility

Studies have shown that the antral follicle count decreases after the third series of chemotherapy, whereas follicle stimulating hormone (FSH) reaches menopausal levels after the fourth series; inhibin B and anti Mullerian hormone levels decrease following chemotherapy [28]. Drugs with high risk of infertility include procarbazine, cyclophosphamide, ifosfamide, busulfan, melphalan, chlorambucil and chlormethine; drugs like doxorubicin, cisplatin and carboplatin have medium risk while therapies with plant derivatives (such as vincristine and vinblastine), antibiotics (such as bleomycin and dactinomycin) and antimetabolites (such as methotrexate, mercaptopurine and 5-fluorouracil) have low risk of gonadotoxicity [5].

Microorganisms and infertility

Microbial infections have been reported to reduce sperm viability. *Staphylococcus aureus* is the most prevalent Gram positive organism, while *Escherichia coli* is the most prevalent Gram negative organism isolated in the semen of males with primary infertility [21]. Chronic epididymitis secondary to *Chlamydia trachomatis* infection had been shown to blockage of the epididymis and thus obstructive azoospermia [23]. However, *Ureaplasma urealyticum* infections induces leukocytospermia and consequently lead to sperm damage, decrease sperm counts and invariably impaired sperm motility [33].

Herpes simplex virus (HSV) was reported to have been found in the semen of some infertile men and was related to low sperm count and poor motility [22]. Mumps viral infections in adolescent and adult males carry about 30% risk of developing orchitis or epididymitis, which can result in testicular atrophy and sterility [29].

Diagnosis

Medical History and Physical Examination

Adequate medical history should be taken and physical examination of both couple is important in infertility work-up. Generally, Lifestyle issues (cigarette smoking, cannabis, drug and alcohol abuse, and caffeine consumption) and abdominal examination may show liver cirrhosis as a possible etiology. History of any medications being taken and a profile of the patient's general medical and emotional state may help in deciding on appropriate tests.

In investigating the causes of male infertility, history of occupational or therapeutic exposures to radiations, childhood infections in the form of mumps, undescended testes, chronic illnesses (like diabetes, thyroid disease, hypertension, tuberculosis, mumps or other venereal infections), testicular injuries (occupational, trauma), previous

sexually transmitted diseases which may block the ducts, genetic absence of vas deferens, and varicocele should be obtained.

Immunological tests are done to determine the presence of antisperm antibodies in the blood and semen. Antibody infertility blood tests are conducted to detect these antibodies that damage or kill the spermatozoa.

Detection of herpes simplex virus in the semen of infertile men using polymerase chain reaction (PCR) techniques is diagnostic of HSV as a cause.

Prevention

Some strategies suggested or proposed for avoiding male infertility include the following:

- Avoiding tobacco smoking, as it damages sperm DNA [10]. Also, marijuana and alcohol use should be avoided [32].
- Avoiding excessive heat to the testes [32].
- Sperm counts can be depressed by daily coital activity [32] and sperm motility may be depressed by coital activity that takes place too infrequently (abstinence 10–14 days or more)[32].
- Protective cup and Jockstrap should be worn when participating in contact sports (such as football, baseball, cricket, hockey, wrestling, karate, e.t.c.).
- Sexually transmitted diseases can be prevented by abstinence from sex or the practice of “safer sex” strategies for people having multiple sex partners, including mutual monogamy, non-penetrative sex, and consistent use of barrier contraceptive methods, particularly latex male condoms and polyurethane vaginal sheath (female condom).
- Prompt treatment of STDs.

Treatment modalities

This varies according to the underlying etiological factors and the degree of the impairment of the male fertility. Also, the fertility of the female partner should be considered.

1. Pre-testicular conditions are addressed by medical interventions.
2. Testicular-based male infertility is managed by obtaining sperm and using the sperm for intrauterine insemination (IUI), in vitro fertilization (IVF), or IVF with intracytoplasmic sperm injection (ICSI). With IVF-ICSI even with a few sperm pregnancies can be achieved.
3. Obstructive causes of post-testicular infertility can be overcome with either surgery or IVF-ICSI.
4. Ejaculatory factors may be treatable by medication, or by IUI therapy or IVF.
5. Antioxidant such as tocopherols helps counter oxidative stress, which is associated with sperm DNA damage and reduced sperm motility.
6. A hormone-antioxidant combination may improve sperm count and motility [11].

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