

## Understanding Male Infertility and Its Causes: A Review

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### Abstract

Infertility is a distressing condition affecting 60-80 million couples all over the world. Infertility can be due to male factor, female factor or a combination of both of them. The male factor accounts for 40-50% of infertility and affects approximately 7% of all men. This paper covers the various etiologies attributing to male infertility, assessment of male factor and treatment options made available through years of research. The modifiable risk factors like obesity, smoking, alcohol intake and cell phone use should be looked for and addressed. Environmental factors like ionising radiations, pesticides and heavy metals should be avoided. The correctable causes should be identified. Antioxidants help in reducing oxidative stress and improving semen parameters. Surgical retrieval of sperms is an important technique in males with azoospermia and severe oligo asthenospermia.

**Keywords:** Male Infertility, Semen Analysis, Antioxidants, Varicocele, Surgical Sperms Retrieval Techniques, Pretesticular, Testicular, Post-Testicular.

### 1. Introduction

Infertility is defined as the inability to conceive within one year of regular, unprotected coitus [1]. Since the ability to conceive may exist, with another partner or after treatment, the term sub-fertility may be used. Infertility is a distressing condition affecting 60-80 million couples all over the world [2]. Approximately 8-12% of couples in the world are infertile. Infertility is classified as primary or secondary infertility [3]. Primary infertility is the one wherein the couple has not conceived preceding the time of presentation. Secondary infertility is the one wherein the couple has conceived previously (regardless of gestational outcome) but is unable to conceive again [4,5]. Infertility can be attributed to male factor, female factor or a combination of both of them.

The male factor accounts for 40-50% of infertility and affects approximately 7% of all men [6]. The awareness of magnitude and importance of male factor

infertility is relatively recent. The management of male factor infertility requires interdisciplinary approach. A male with infertility may present to gynecologist, a general physician, an urologist, or a dermatologist (sequelae of venereal diseases). Treatment of male factor therefore requires the coordination between these departments including Andrology department. Relevant studies done between 1981 to 2016 have been considered for this review article. The studies considered for this article are available in the various books on subject and research articles printed or hosted over the Internet by reputed online journals.

### 2. Historical Aspect of Male Factor Infertility

The historical aspect of male infertility is given in a chronological order at Table 1.

**Table 1: Chronological Events**

Year	Findings
1677	Leeuwenhoek first saw spermatozoa
1779	Lazzaro Spallanzani described the role of semen in fertilization
1841	Albert von Kolliker described sperms as autologous cells developing from testicular cells
1850	Prevost and Dumas demonstrated that motile sperms are required for fertilization
1949	Chris Polge described cryopreservation of sperms
1953	Bunge and Sherman reported first births from frozen human sperms

Table 1 continue.....	
1985	Temple-Smith human pregnancy by in-vitro fertilization using sperms aspirated from the epididymis
1986	Monash reported successful pregnancy and birth from sperm retrieval operation in case of blocked sperm duct
1988	Microsurgical epididymal sperm aspiration
1988	Successful pregnancy after zona macromanipulation
1992	First pregnancy after Intracytoplasmic sperm injection
1993	First use of Testicular sperm extraction and Intracytoplasmic sperm injection
1997	Detection of DNA fragmentation in sperm and correlation with IVF outcome
2004	Use of In-vitro Maturation and Testicular sperm extraction for successful conception

### 3. Etiology of Male Infertility

The male reproductive system is a complex apparatus involving coordination between the various parts i.e. the hypothalamus, the pituitary, the testes and the ejaculatory system. The defects can occur at any level - pre-testicular, testicular and post-testicular [1]. The details of the Etiologic Factors in male infertility are as under [7]:-

**(a) Pre-testicular**

- (i) Endocrine
  - (aa) Hypogonadotropic hypogonadism
- (ii) Coital Disorder
  - (aa) Erectile Dysfunction

- Psychosexual
- Endocrine, neural or vascular
- (ab) Ejaculatory Failure
  - Psychosexual
  - After genitourinary surgery
  - Neural
  - Drug related

**(b) Post-testicular**

- (i) Obstructive
  - (aa) Epididymal
    - Congenital
    - Infective
  - (ab) Vasal
    - Genetic- cystic fibrosis
    - Acquired –vasectomy
  - (ac) Epididymal hostility
    - Epididymal asthenozoospermia
  - (ad) Accessory gland infection
  - (ae) Immunologic
    - Idiopathic
    - Post vasectomy

**(c) Testicular**

- (i) Genetic
  - (aa) Klienfelter’s syndrome
  - (ab) Y chromosome deletion
  - (ac) Immotile cilia syndrome
- (ii) Congenital
  - (aa) Crypto-orchidism
- (iii) Infective (Orchitis)
  - (aa) Viral
  - (ab) Bacterial
- (iv) Antispermato-genic agents
  - (aa) Heat
  - (ab) Chemotherapy
  - (ac) Drugs

- (ad) Irradiation
- (v) Vascular
  - (aa) Torsion
  - (ab) Varicocele
- (vi) Immunologic
- (vii) Idiopathic

#### 2.1 Pretesticular Causes

Pretesticular causes of male infertility are due to dysfunction in the hypothalamus and/or the pituitary. Hypothalamic diseases present with decrease levels of GnRH, LH, FSH and testosterone along with other signs and symptoms characteristic of the underlying disease [8]. Hypogonadotropic hypogonadism can be congenital or acquired. Acquired causes are due to destruction of hypothalamic tissue secondary to disease process such as metastatic tumors, tuberculosis, sarcoidosis and haemochromatosis[9]. The most important congenital causes of hypogonadotropic hypogonadism are idiopathic hypogonadotropic hypogonadism, kallman’s syndrome, Prader- Labhart- willi syndrome and chromosomal mutation [8,9].

#### 2.2 Post – Testicular Causes

Post – Testicular causes of infertility are either due to obstruction or ejaculatory dysfunction – these can be congenital or acquired. Congenital bilateral absence of the vas presents with azoospermia [1]. Epispadias, hypospadias and bladder extrophy can cause defective semen deposition and retrograde ejaculationv [8]. Acquired causes of obstruction are usually due to infection, trauma or iatrogenic. Epididymal obstructions follow infections, trauma or surgery. Iatrogenic injury to the vas may obstructive infertility for example injury to the vas inguinal herniorrhaphy. The ejaculatory disorders are retrograde ejaculation, premature ejaculation and an ejaculation. Diabetic neuropathy and microangiopathy can cause erectile dysfunction and retrograde ejaculation. Retrograde ejaculation may follow surgeries such as transurethral resection of the prostate, open prostatectomy, and bladder neck surgery. Retrograde ejaculation should be suspected with history of bladder surgery, ejaculate volume less than 1cc, severe oligospermia and alkaline semen [8]. Diagnosis is confirmed by large number of sperms in the centrifuged post ejaculatory urine. Other

causes of ejaculatory dysfunction are multiple sclerosis, spinal cord injury, drugs and sympathectomy [1].

### 2.3 Testicular Causes of infertility

These may be congenital or secondary. The most common cause for testicular infertility is idiopathic which is diagnosed after ruling out all other causes. One of the most common congenital defects is testicular maldescent which has an incidence of two percent in general population [10]. Uncorrected maldescent can lead to infertility and increase risk of malignancy. Kennedy disease is a congenital disorder characterized by excessive CAG repeats in the androgen insensitivity. Klinefelter's syndrome is characterized by 47XXY karyotype, long legs, small and firm testis, gynaecomastia, decrease bearded hair, decreased libido, occasional anti social behaviour, osteoporosis and is almost associated with infertility. Although the seminogram usually shows azoospermia, some patients with mosaicism present with oligoasthenospermia; such patients might benefit from ART. Many structural chromosomal disorders lead to infertility, the most important of which is Y chromosome microdeletions [9].

### 2.4 Testicular Tumors

Testicular Tumors may also present with infertility, this is suspected with new onset oligospermia, sudden seminogram deterioration, differing volume and consistency of testes, pain, inhomogenous lesions on ultrasound, and raised tumour markers such as alpha feto protein, lactate dehydrogenase and beta human chorionic gonadotropin. Diagnosis is confirmed by biopsy. The most common tumors are germ cell tumours of which the most common is seminoma [9].

### 2.5 Varicocele

Infertility due to Varicocele is common although the exact mechanism by which infertility is caused is unknown. It is postulated to be due to increased testicular temperature. Testicular temperature is normally maintained at three to four degrees Celsius lower than the core body temperature. However, oligoasthenoterato-spermia and infertility seen in men with varicocele may persist even after varicocelectomy [1,10]. Other causes of testicular damage are secondary to testicular trauma, torsion or orchitis. Thirty percent testicular torsion later causes abnormal seminograms [10].

### 2.6 Environmental Factors

Many substances are gonadotoxic and interfere with spermatogenesis, either directly or through alteration in the endocrine system [1]. Some examples are exposure to excessive heat, environmental toxins (pesticides like dibromochloropropane), ionizing radiation, organic solvents, heavy metals, medications (sulfasalazine, cimetidine, caffeine, nicotine, alcohol, marijuana and

anabolic steroids). Chronic diseases like renal failure, liver diseases can also result in infertility.

### 2.7 Orchitis

Orchitis is an important cause of infertility. Mumps orchitis is a complication of 25 % cases of mumps parotitis, 10 % of these can result in infertility if it occurs postpubertally [1,10]. Some other causes of viral orchitis are Cox sackie virus, lymphocytic chorio meningitis virus, dengue virus and varicella. Bacterial orchitis is due to tuberculosis, syphilis, leprosy, gonococcus, Chlamydia, pneumococcus and salmonella. Infections of the genital tract may affect fertility in several ways- by damaging sperms, hampering their motility, altering the chemical composition of seminal fluid or producing an inflammatory stricture in the genital tract [11].

### 2.8 Lifestyle Factors

#### (a) Obesity

Men with BMI >25 are at increased risk of infertility due to reduction in sperm concentration and increased DNA fragmentation. Obesity decreases levels of circulating testosterone and increases levels of estradiol [12].

#### (b) Smoking

Smoking has damaging effects on the male fertility. It is significantly co-related with low sperm count, reduced motility and poor morphology. Smoking metalolites act as chemotactic stimuli and induce an inflammatory response leading to the recruitment of leukocytes with subsequent generation of reactive oxygen species resulting in oxidative stress [13]. Smokers also have reduced levels of seminal plasma antioxidants such as vitamin C and vitamin E [14,15].

#### (c) Mobile Radiation

Many studies have found positive correlation between cell phone use and decrease in semen parameters. The radio frequency electromagnetic wave stimulate plasma membrane NADH oxidase in mammalian cells and cause production of reactive oxygen species resulting in decreased sperm motility and viability [16].

## 3. Assessment of Male Infertility

The initial assessment of the male includes a detailed clinical history, physical examination and a semen analysis.

### 3.1 Clinical History

History should include age, occupation, period of infertility, previous pregnancy (if any) either with the present partner or with previous partner. A note of any occupational hazard such exposure to gonadotoxins or thermal heat must be made. Sexual history including history suggestive of impotence, premature ejaculation or retro grade ejaculation and sexually transmitted diseases should be recorded. History of recreational drug abuse,

alcohol intake, smoking, radio therapy, chemotherapy, previous surgeries and chronic drug intake should be considered in detail. Any history of spinal cord injury and chronic medical illnesses such as diabetes, TB should be noted.

**3.2 Examination**

General physical examination including height, weight, and blood pressure should be checked. Secondary sexual characters including Body Habitus, hair distribution and breast development must be checked. A note should be made regarding any lymphadenopathy and thyroid enlargement. Respiratory system, cardiovascular system along with abdominal examination should be done. In addition, detailed examination of the genitalia must be carried out which includes (a) Location of urethral meatus (b) Palpation and size of testes (c) Presence of Varicocele (d) Presence and consistency of both the vasa and epididymides.

**3.3 Semen Analysis**

The single best investigation for male infertility is the seminogram. Male patients should be given clear instruction regarding sample collection. Patient should be instructed to abstain for two to three days prior to sample collection. Semen sample is collected by masturbation in a wide mouth sterile, non plastic container; sample is assessed for volume, pH, liquefaction time, sperm concentration, motility, morphology and pus cells.

The World Health Organisation (WHO) periodically releases manual for laboratory examination of human semem the first one was published in 1980 with subsequent updates in 1987, 1992 and 1999. The WHO published its updated 5<sup>th</sup> edition in 2010 with important differences from previous versions and it is given at Table 2 [17].

**Table 2: World Health Organization- Semen Analysis Criteria**

Semen parameters	WHO 1999	WHO 2010
Volume [mL]	≥2	1.5
Sperm count 10 <sup>6</sup> /mL	≥20	15
Total sperm count [10 <sup>6</sup> ]	≥40	39
Total motility [% motile]	≥50	40
Progressive motility <sup>a</sup>	≥25%[Grade A]	32% [A+B]
Vitality [% alive]	≥75	58
Morphology [% normal]	14	4
Leukocyte count 10 <sup>6</sup> /mL	< 1.0	<1.0

<sup>a</sup>Grade A :rapid linear motility; Grade B : slow or sluggish progressive motility; Grade C: Nonprogressive motility; Grade D : Immotile.

**3.4 Nomenclatures used to describe semen parameters.**

- a) Hemo-spermia - presence of blood in the semen.
- b) Hypospermia- indicate small volume of semen less than 1 ml.
- c) Hyperspermia - semen volume above 10 ml.
- d) Aspermia - absence of ejaculate.
- e) Oligozoospermia - decreased sperm counts.
- f) Asthenospermia - indicates decreased sperm motility,

- g) Teratospermia - indicates abnormal morphology.
- h) Leucocytospermia- indicates increased semen leucocyte counts.
- i) Azoospermia - total absence of sperms in semen.
- j) Necrozoospermia - all dead sperms in semen.

**3.5 Oligoasthenospermia**

Oligoasthenospermia together constitutes nearly 60% of male factor infertility. Azoospermia or the total absence of sperms in semen contributes to 15% of causes of male infertility [1]. The prevalence of leucocytospermia in male infertility patients varies from 2% to 40% and elevated concentrations of pus cells in semen have been associated with reduced sperm function and quality [18].

**3.6 Endocrine Evaluation**

It consists of assessment of serum FSH, LH and testosterone levels. These tests are undertaken if there is oligospermia, azoospermia, impaired sexual function or any endocrinopathy.

**3.7 Tests for Antisperm Antibodies [ASA]**

It is indicated in conditions like ductal obstruction, prior genital infection, testicular trauma and prior vaso-vasostomy or vasoepididymostomy. The Immuno Bead Test (IBT) and Mixed Agglutination Reaction (MAR) test are used to detect the presence of antisperm antibodies.

**3.8 Fructose estimation**

Absence of fructose estimation in the semen sample may indicate bilateral congenital absence of the vas deferens or ejaculatory duct obstruction.

**3.9 Computer assisted Semen Analysis (CASA)**

It involves the evaluation of semen parameters with the help of computer aided systems. The subjective errors in assessing a semen sample can be overcome and motility can be assessed quantitatively.

**3.10 Sperm DNA Fragmentation Test**

This test is indicated in multiple IVF/ICSI failures, poor or arrested embryo development, oligoasthenospermia and unexplained male infertility. DNA fragmentation can be tested by sperm chromatin dispersion test (SCD), sperm chromatin structure assay, sperm nuclear maturity test, comet assay and TUNEL assay.

**3.11 Genetic tests** The three most important genetic tests are:-

- a) Karyotyping for chromosomal abnormality.
- b) Cystic Fibrosis gene mutation test.
- c) Y chromosome microdeletions.

**4. Management of Male Infertility**

**4.1 Antioxidants**

Antioxidants are the chemical compounds that can neutralize or terminate oxidative stress. When high levels of reactive oxygen species are present in the seminal fluid, they can damage sperms by altering their membrane

integrity and thus affecting motility and morphology and can cause sperm cell death [19]. Antioxidants can be classified as catalytic or scavenging agents. Catalytic antioxidants activate certain metabolic reactions that

interfere with Reactive Oxygen Species (ROS) generation and thus protect against toxic effects of ROS. Scavenging antioxidants directly react with oxidant molecules and neutralize them.

**Table 3: Antioxidants in Male Infertility**

Antioxidants	Function	Effect	Dose
Vitamin E	Interrupt lipid peroxidation and enhances scavenging of free radicals	Improves motility and can be added to cryoprotectants during cryopreservation	50-800mg depending on the intake of fruits, vegetables and tea.
Vitamin C	Acts as ROS scavenger, neutralize free radicals and assist in regeneration of vitamin E	Improves motility and viability of sperms. Higher dosages may have damaging pro-oxidant effects.	250-1000mg/day
Carnitine	Role in sperm energy metabolism and increases the levels of antioxidant enzymes	Improves sperm motility and protects sperm DNA and cell membranes from ROS induced damage and apoptosis.	1-4gm/day
N-acetyl Cysteine	Neutralizes hydrogen peroxide, hypochlorous acid and hydroxyl radical	Improves sperm concentration and acrosome reaction	200-500mg upto 3 times/day
Coenzyme Q10	Recycles vitamin E and also involved in energy production.	Increases sperm motility and inhibits hydrogen peroxide formation in seminal fluid.	Therapeutic dose may reach up to 3600mg
Lycopene	It is a carotenoid compound with the highest ROS quenching rate. Found in high concentrations in testes and seminal fluid.	Improves sperm concentration and motility.	2-30mg/day
Selenium	Protects against oxidative sperm DNA damage and required for normal testicular development, spermatogenesis, motility, and function.	Improves sperm motility and morphology.	Recommended daily allowance: 70µg/day for men and 55µg/day for women. Optimal daily allowance: 200µg/day and maximum dose 400 µg/day.
Zinc	It is needed to maintain optimal levels of antioxidant enzymes.	Improves sperm concentration, motility and sperm integrity.	15-35 mg/day
Pentoxifylline	It is a non selective phosphodiesterase inhibitor that raises cAMP levels and reduces inflammation by inhibiting TNFα and leukotriene synthesis	Decreases ROS production and improves sperm motion characteristics.	400mg three times/day

#### 4.2 Electroejaculation

It is used in men with neurological ejaculatory disorders such as spinal cord injury or psychogenic anejaculation, without mechanical obstruction of excurrent ductal obstruction. Electroejaculation is performed with a device called as electroejaculator. An electric probe is inserted into the rectum next to prostate. A current is applied to stimulate the nerves and produce contraction of the pelvic muscles resulting in ejaculation. Electroejaculation allows the retrieval of sperm in more than 90% of patients and up to 40% of couples will achieve pregnancy with IUI or IVF [20].

#### 4.3 Varicocele Ligation

Treatment of varicocele in infertile men aims to restore or improve testicular function. Best practice guidelines recommend that treatment should be offered for couples with documented infertility whose male partner has a clinically palpable varicocele and abnormal semen

analysis [21]. Varicoceles are treated either by surgery (open with/without magnification and laparoscopy) or percutaneous embolization of the internal spermatic vein.

#### 4.4 Hormonal Treatment

In cases of males with oligospermia or azospermia and FSH values in blood < 1mIU/ml, pharmacological treatment with FSH should be indicated. Since FSH acts at the early stages of spermatogenesis and sperm maturation in the testis takes about 70 days, so the duration of treatment should be of at least 3 months.

### 5. Surgical Sperm Retrieval Techniques

These are used in men with severe oligoasthenospermia and azospermia. The sperms retrieved from either epididymis or testis is used to induce conception through assisted reproductive techniques, that is, *in vitro* fertilization with ICSI. Table 4 highlights the same.

**Table 4: Surgical Sperm Retrieval Techniques**

Technique	Procedure
Testicular Sperm Aspiration [TESA]	Percutaneous procedure in which a needle is inserted into testicular parenchyma to sample the seminiferous tubules by aspiration.
Testicular Sperm Extraction [TESE]	Open procedure in which an avascular area is selected in tunica albugenia and incised to expose the seminiferous tubules for sperm extraction.
Microdissection TESE	Advanced version of TESE, the use of microdissection under magnification allows removal of smaller quantity of seminiferous tubules by selecting only the ones which are likely to contain sperms.
Percutaneous Epididymal Sperm Aspiration [PESA]	Sperms are aspirated percutaneously from epididymis using needle.
Micro Epididymal Sperm Aspiration [MESA]	Open procedure in which epididymis is opened by scrotal incision, epididymal tubules are identified microsurgically and micropuncture of each tubule is done and fluid containing sperms is aspirated.

**6. Conclusion**

Male infertility is an important cause of infertility. The awareness of magnitude and importance of male factor infertility is relatively recent. The young male individuals should be addressed about the importance of sexual health. The modifiable risk factors like obesity, smoking, alcohol intake and cell phone use should be looked for and addressed. Environmental factors like ionising radiations, pesticides and heavy metals should be avoided. Focus should be placed on identifying population at risk. The evaluation of male partner is of equal importance as of female. The initial assessment is important to identify conditions that are correctable and helped through assisted reproductive techniques.

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