



Male Infertility

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ABSTRACT

In the last ten years there has been tremendous scientific growth in the field of reproductive medicine. This development in this field was absolutely required, as the incidence of male infertility has gone up by about 15%. One third of all cases of infertility consists of male population, another one third of females and rest of one third both the partners are responsible.

In evaluation of male infertility sexual history, physical examination, semen analysis and hormonal estimation are must, in addition to semen culture, vasography, trans-rectal ultrasonography (TRUS) Doppler study, sperm function testing are important diagnostic tools. In many cases testicular biopsy and X-genetic analysis are critical for all men with azoo-spermia.

In management of male infertility - surgical correction, proper antibiotics to treat gonorrhoea and tuberculosis, hormonal treatment are necessary as per requirement. Hormonal treatment is based on clomiphene testosterone, pituitary hormones and gonadotrophin releasing hormones are helpful in intractable cases.

Artificial Insemination is an effective, non-invasive, relatively simple and cheap method of treatment. Antioxidants improve sperm count, mortality and morphology of sperms.

Psychotherapy and counselling is required in intractable cases.

INTRODUCTION

The last ten years has shown a tremendous sea change in the field of reproductive medicine. The incidence of infertility has gone upto 15%, out of which approximately 30% infertility are caused by males only. Therefore in 50% of all infertile couple, an abnormal male factor contributes to reproductive failure. An analysis of a large number of studies has led to the conclusion that the average sperm concentration has fallen from 113 million/ml in 1938 to 66 million/ml in 1990.

What is Infertility

Infertility is defined as the inability of a couple to achieve a pregnancy after trying for 12 months of "unprotected intercourse".

Reproductive and Hormonal Functions of the Male :

Before going into details of male infertility must review the reproductive and hormonal functions of the male. The reproductive function of the male can be divided into three major subdivisions.

- i. Spermatogenesis : Which means simply the formation of sperm.
- ii. Performance of the male sexual act.
- iii. Regulation of male reproductive functions by the various hormones like testosterone.

I. Physiologic Anatomy of the Male Sexual Organs

The testes are made up of 900 coiled seminiferous tubules, in the wall of which the spermatozoa are formed from the primitive germ cells. This process is known as spermatogenesis. It takes 74 days to form a mature sperm from a primitive germ cell. The sperm then empty into the epididymis, another coiled tube about 6 meters in length. The epididymis leads into the vas deferens, which enters the body of the prostate gland. Two seminal vesicles, one located on each side of the prostate empty into the prostatic end of the vas. From there the content passes into an ejaculatory duct leading through the body of the prostate gland and then emptying into the internal urethra. Finally the urethra is the last connecting link from the testis to the exterior.²⁻³

Spermatogenesis

Spermatogenesis occurs in all the seminiferous tubules during active sexual life as the result of stimulation by anterior pituitary gonadotrophic hormones beginning at an average age of 13 years and continuing through most of the remainder of life span but decreasing markedly in old age.

Hormonal Factors that Stimulate Spermatogenesis

- i. Testosterone - secreted by the Leydig cells which is located in the interstitium of the testis. It is essential for growth and division of the testicular germinal cells which is the first stage in sperm formation.
- ii. Luteinizing Hormone (LH) - secreted by the anterior pituitary gland. It stimulates the Leydig cells to secrete testosterone.
- iii. Follicle Stimulating Hormone (FSH) - also secreted by the anterior pituitary gland, stimulates the Sertoli cells. This helps in the conversion of the spermatids to sperm.
- iv. Estrogens - formed from testosterone by the Sertoli cells. Probably essential for spermatogenesis
- v. Growth Hormone - controls the metabolic functions of the testes. GH promotes early division of the spermatogonia. It is deficient in pituitary dwarfs, causing infertility in them.

II. Male Sexual Act

Stages

- i. **Penile Erection** - Role of parasympathetic nerves - the impulses pass from the sacral portion of the spinal cord through the pelvic nerves to the penis, these nerves secrete nitric oxide and/or vasoactive intestinal peptide in addition to acetylcholine. The nitric oxide especially relaxes the arteries of the penis also smooth muscle fibres in the erectile tissue of the corpora cavernosa and corpus spongiosum in the shaft of the penis.
- ii. **Lubrication**, a parasympathetic function- during sexual stimulation, the parasympathetic impulses, in addition to promoting erection, cause the urethral glands and the bulbo urethral glands to secrete mucus. This mucus flows through the urethra during inter course to aid in the lubrication of coitus.
- iii. **Emission and Ejaculation** - Function of the sympathetic nerves - emission begins with contraction of the vas deferens, wave like increase in pressure in both the erectile tissue of the penis, genital ducts and urethra which ejaculate the semen from the urethra to the exterior, this final process is called ejaculation. This entire period of emission and ejaculation is called the **male orgasm** this last for one to two minutes.

III. Testosterone and Other Male Sex Hormones

The testes secrete several male sex hormones, which are collectively called androgens including testosterone, dihydrotestosterone and androstenedione.

Testosterone is formed by the interstitial cells of Leydig. Only found in adult testes after puberty. In childhood it is absent and where testes secrete almost no testosterone. Testosterone is responsible for the distinguishing characteristics of the masculine body.

PATHOLOGY OF INFERTILITY

Conception depends upon the fertility of both the male and the female. In one third of all cases of infertility, the male is directly responsible, in another one third both partly are at fault and in the remaining third entirely female is responsible.

Faults in Male

Testicular functions depend upon several factors

- i. **Androgens** - are produced in the interstitial cells of the testes as a result of stimulation by the gonadotrophic hormone of the anterior pituitary. Spermatozoa are developed largely under the influence of the anti pituitary gland. For adequate spermatogenesis, the testicle must lie in its correct position in the scrotum where the temperature is slightly cooler than else where in the body. The factors which raise the scrotal temperature can adversely influence spermatogenesis e.g.- person working in blast furnaces, wearing of a tight scrotal support and the presence of a varicocele. The ectopic or undescended testicle provides the best example of the adverse effect of the temperature on spermatogenesis.
- ii. The collecting apparatus of the epididymis may be damaged by trauma or inflammatory disease- notably **gonorrhoea and tuberculosis**.
- iii. The Vas deferens itself may be occluded while doing **herniorrhaphy** iv) **Chronic inflammatory disease** of the prostate and seminal vesicle.
- v. Congenital lesions of the penile urethra such as **hypospadias**, (imperfect insemination)
- vi. A history of **mumps, venereal disease or tuberculosis** may suggest testicular atrophy or obstruction.
- vii. History of **excessive smoking and excessive alcohol consumption** may also suggest poor spermatogenesis.
- viii. **Immunological disorders**- presence of sperm antibodies both in the seminal plasms and in the cervical mucus account for upto 5% cases of male infertility.
- ix. **Accidental or operative trauma** e.g. blow on the testicle with haematoma formation and subsequent atrophy, operation for hernia, varicocele or hydrocele may suggest a degenerative lesion of the testes or obstruction of the vas.
- x. **Role of free radicals** - Idiopathic oligoasthenospermia accounts for almost 24% of all male infertility. Oxidative stress status results in production of excessive reactive oxygen species or free radicals which cause male infertility by affecting the process of conception at various stages like damaging the sperm membrane, DNA and protein, resulting in decreased sperm count, motility, and increased mid-piece defect that impairs sperm capacitation and acrosome reaction. Free radicals can be detected in the semen ejaculate of 40% of infertile men where as none is detected in the semen from fertile men.

EVALUATION OF MALE INFERTILITY

1. History

A detailed history is very important in the evaluation of male infertility.

Table 1 : Normal values of Semen Variables : WHO Guidelines¹¹

Volume	3 ml or more
pH	7.2 to 8.0
Sperm concentration	20 million or more/ml
Total sperm count	40 million or more/ml
Motility	50% or more with forward progression or 25% or more with rapid progression
Morphology	80% or more with normal morphology
Vitality	>75% viable sperm
White blood cells	Less than 1 million per ml.
Immunobead	Negative

- a. **Sexual History:** This includes frequency and timing of coitus, sexual technique, sexual potency, use of lubricants, methods of birth control, duration of sexual relationship, sexual desire and sexual libido, frigidity of female partner's response to sex.
- b. **Family History:** includes hypogonadism, cryptorchidism, congenital midline defects and cystic fibrosis.
- c. **Past History:** Use of drugs, history of occupation and habits, stress conditions, exposure to heat, chemicals, radiation, use of cigarettes, tobacco, alcohol consumption, illicit drugs and anabolic steroids
 - * Surgical procedures undergone like orchidopexy, varicocele, pelvic or scrotal surgery, herniorrhaphy, retroperitoneal surgery.
 - * Medical diseases like recurrent UTI, sexually transmitted diseases, viral orchitis, leprosy, diabetes, epididymitis, tuberculosis, renal diseases, radiotherapy, hypertension, small pox affects male fertility.
 - * History of extramarital sex
 - * Drugs: Use of following drugs affects fertility-lead, marijuana, heroin, phenytoin, H2 blockers, caffeine, arsenic, nitrofurantion, antihypertensives, cancer chemotherapy, ketoconazole, spironolactone and medroxyprogesterone.
 - * Childhood illness like mumps, etc.
- d. **Female reproductive history:** A detail female partner menstrual cycle and reproductive history should be taken.

2. Physical Examination

A detailed male genital examination may reveal critical information pertaining to the etiology of male infertility. Abnormalities like hypospadias or epispadias, peyronies disease, penile curvatures, microphallus, undescended testes, cryptorchidism and varicoceles, epididymitis, spermatic cord agenesis and penile chordae result in male infertility but are surgically correctable. Presence of gynaecomastia in males is suggestive of either an estrogen/androgen imbalance or an excess of prolactin.

3. Semen Analysis

The corner stone of work-up of male infertility is semen analysis. Some simple related terms are:

- a. **Azoospermia:** No dead or alive sperms are identified on three consecutive semen analysis with adequate period of abstinence.
- b. **Oligospermia:** When sperm count is less than 20 million/ml.
- c. **Asthenospermia:** When sperm motility or forward progression movement or both is low i.e. less than 50%.
- d. **Teratospermia:** When defect in sperm morphology is high which may include bifid tail, swollen head, short acrosomal segment. Abnormal morphology of sperm should not exceed 20%.
- e. **Necrospermia:** When only dead sperms are seen on sperm analysis.^{8,9}

The normal values of the parameters involved in semen analysis, as recommended by WHO guidelines are summarised in Table 1:

Collection of Semen

There should be 2-3 days abstinence before each seminal fluid examination. The semen collected should be analyzed within 2 hours of collection. Collection should be done in a wide mouthed clean glass container. The couple is advised intercourse close to ovulation time preferably in the early hours of the morning. The woman presents herself in the clinic within 2 hours of the intercourse. The cervical mucus is aspirated from the cervical canal and spread over a glass slide. Another smear made from the posterior fornix serves as a control.

Small volume of ejaculate may result from ejaculatory duct obstruction, androgen deficiency, retrograde ejaculation, sympathetic denervation, and drug therapy.

Fructose is a normal constituent of the seminal fluid with a concentration of 120-450 mg/ dl. Absence of fructose in sperm analysis indicates congenital absence or obstructed seminal vesicles which is usually associated with CBAVD (congenital bilateral absence of vas deferans).

Azoospermia may be due to hypogonadotrophic hypogonadism, ductal obstructions (congenital/acquired), epididymal obstruction (congenital/acquired), spermatogenetic abnormalities which may result due to viral orchitis, varicocele, torsion of testes, chromosomal abnormalities, gonadotoxins and idiopathic

4. Hormone Evaluation

The incidence of primary endocrine defects in infertile men is less than 3%. A hormone evaluation should be performed when the sperm concentration is low, or when the endocrinopathy is suspected clinically (Table 2). The following hormones are commonly evaluated: follicle stimulating hormone (FSH), leutinizing hormone (LH), testosterone (free and total), prolactin and oestradiol

Table 2 : Hormone Status: Clinical Diagnosis

Clinical Status	FSH (mIU/ml)	LH (mIU/ml)	Testosterone (ng/100 ml)
Normal Men	Normal	Normal	Normal
Germinal Aplasia	Elevated	Normal	Normal / Decreased
Testicular Failure	Elevated	Elevated	Normal / Decreased
Hypogonadotrophic Hypogonadism	Decreased	Decreased	Decreased
Hypergonadotrophic Hypogonadism	Elevated	Elevated	Low Normal or decreased

Adapted from: Lipshultz LI (Guest Editor): Male Infertility. Urol Clin North Am 1994; volume 21, Number 3.

FSH is elevated in primary testicular failure, isolated spermatogenetic failure. It is decreased in hypogonadotrophic hypogonadism.

LH is elevated in primary testicular failure and decreased in hypogonadotrophic hypogonadism,

Serum testosterone begins to decrease at 10 to 12 years of age and remains constant during the reproductive period. Decrease in the level occurs in testicular failure, hypogonadotrophic hypogonadism and in aging males.

Estrogen excess may result from morbid obesity.

Hyperprolactinemia is due to pituitary tumors and this results from low levels of LH-& FSH and hence oligospermia. Serum prolactin should be measured when a patient has a low level of serum testosterone level without an associated increase in LH, as well as symptoms of decreased libido, decreased ejaculate volume, galactorrhea.

5. Antisperm Antibody Titer :

Factors for development of anti-sperm antibodies are vasectomy (60%), CBAVD (33%), acute epididymitis, cryptorchidism and genital trauma, varicocele, STD, chlamydial infection and history of repeated testicular biopsy.

Presence of anti-sperm antibodies results in impairment of cervical mucus penetration, inhibition of sperm capacitation, premature induction of acrosomal reaction and zona binding or fertilization of ova.

6. Semen Cultures

Seminal fluid should be cultured when there is high incidence of leukocytes in semen. Appropriate treatment should be instituted as studies have shown improved pregnancy rate after treatment of infection.

7. Radiological Investigation:

The main purpose of radiological investigation of genital system in infertile males is to identify vas deferens obstruction. The following radiological examinations are usually performed.

a. *Vasography*: Vasography is the simplest radiological examination performed to evaluate obstruction in the vas deferens. The common site at which vasography is performed is at the level of scrotal vas.

b. *Transrecta / Ultrasonography (TRUS)* : TRUS allows good imaging of the anatomy of prostate, seminal vesicle, ejaculatory ducts and ampulla. TRUS is mostly indicated in azoospermic patients suspected of having ejaculatory duct obstruction and seminal vesicle agenesis.

c. *Doppler Study* : are mostly indicated to identify subnormal varicoceles and degree of vein dilatation in varicoceles. Scrotal ultrasonography is done to detect testicular abnormalities and varicoceles.

8. Sperm Function Testing:

a. Sperm Cervical Mucus Interaction (PCT)

A normal test is usually defined as one in which more than 10 to 20 sperm are identified per high field. Progressive cervical sperm, mobility test (PCT) is mostly indicated in hyperviscous semen, unexplained infertility low or high volume semen specimens.

b. Acrosome Reaction :

Fertilization requires sperm to undergo capacitation and acrosome reaction. Transmission electron microscopy clearly defines the status of the acrosome. Normal semen samples demonstrate a spontaneous. Acrosome reaction rate of less than 5% and an induced acrosomal reaction of 15-40%. Acrosome reaction may be considered in unexplained poor fertilization rates.

c. Reactive Oxygen Species :

These oxygen free radicals induce peroxidative damage to the sperm cell lipid membrane which has high concentration of polyunsaturated fatty acids (PUFA) resulting in detrimental effects on sperm metabolism, morphology, motility and fertilizing capacity. Estimation of these free oxygen radicals in serum of infertile males has been found to be of very high concentration.⁶

9. Testicular Biopsy :

Testicular biopsy is only indicated in azoospermic patients with normal hormone levels. Biopsy of testes is done mostly bilateral and the tissues should be preserved in Bouin's solution before histopathological examination.

10. Genetic Analysis:

Karyotype analysis is critical for all men with azoospermia and severe oligospermic patients as 15-20% of them have some chromosomal disorders, most simple being Klinefelter's Syndrome (47 XXY karyotype).^{7,8,9}

MANAGEMENT OF MALE INFERTILITY^{8,10}

- Surgical** - Surgical correction of varicocele and undescended testes improves the semen quality in 60-70% cases. The obstruction of the vas needs vaso-vasal anastomosis.
- Antibiotics** - To treat if infection is there e.g. gonorrhoea and tuberculosis accordingly.
- Hormones**
 - Clomiphene*
Indication - oligospermia and asthenospermia

Dose - 25 mg daily for 25 days in a month for 3 months.

ii. **Testosterone**

Indication - Testicular failure, accidental castration and defective spermatogenesis.

Dose - 120- 160 mg orally daily for 2-3 weeks followed by maintenance dose of 40 - 120 mg daily.

- 25 mg IM twice weekly for 4 -6 weeks.

iii. **Pituitary Hormone (LH-FHS)**

Indication - Defective spermatogenesis, oligospermia, delayed puberty, hypogonadotropic hypogonadism and sterility.

Dose - *Schedule I* - 3 equal doses given on alternate day.

- *Schedule II* - Given daily till response is achieved 75 - 150 I.U.-given I.M.

iv. **Gonadotrophic releasing hormones (GnRH)**

Indication - Spermatogenesis and biosynthesis of sex steroid.

Dose - a. Male hypogonadism - 2000 I.U., twice weekly, IM / SC

b. Cryptorchidism - 500 to 1000 I.U., on alternate day, I.M / SC.

4. **Artificial Insemination :**

It is an effective, non-invasive, relatively simple and cheap method of treatment.

Indications

i. Coital failure

- Ejaculatory failure
- Anatomical (e.g. hypospadias)
- Neurological (e.g. spinal cord injury)
- Retrograde ejaculation
- Psychological (e.g. impotence)
- Vaginismus

ii. Cervical factor

- Cervical mucus hostility

iii. Male subfertility

- Oligozoospermia
- Mild asthenozoospermia
- Teratozoospermia
- Oligoasthenoteratozoospermia

iv. Immunological

- Male antisperm antibodies
- Female antisperm antibodies (Cervical, serum)

v. Unexplained infertility

vi. Dual factors

5. **Antioxidants :** Antioxidants improves sperm count, motility and morphology of sperm

e.g. **CoQ** - Bioenergizer and master antioxidant, increases sperm motility.

Dose - 30 mg daily for 3-6 months (Orally)

LYCOPENE - Improves sperm function.

Dose - 8 mg daily for 3-6 months. (Orally)

6. **Psychotherapy and Counselling :**

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