

# Infertility

## Objectives:

1. To understand definition, causes, and treatment of male infertility.
2. To understand the types of ART.

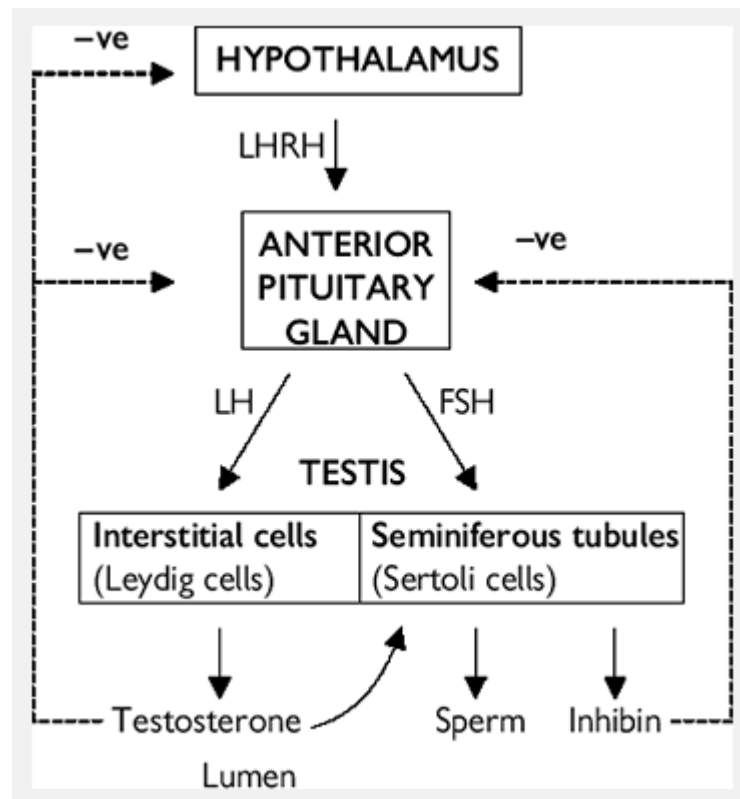
## Definition of infertility

*Failure of conception after at least 12 months of unprotected intercourse.* The chance of a normal couple conceiving is estimated at 20 to 25% per month, 75% by 6 months, and 90% at 1 year.

## Male reproductive physiology

### Hypothalamic, pituitary and testicular axis

The hypothalamus secretes luteinizing hormone-releasing hormone (LHRH), also known as gonadotrophin-releasing hormone (GnRH). This causes pulsatile release of anterior pituitary gonadotrophins, called follicle stimulating hormone (FSH) and luteinizing hormone (LH), which act on the testis. FSH stimulates the seminiferous tubules to secrete inhibin and produce sperm; LH acts on Leydig cells to produce testosterone.



### Spermatogenesis

Seminiferous tubules are lined with Sertoli cells, which surround developing germ cells (spermatogonium) and provide nutrients and stimulating factors, as well as secreting androgen-binding factor and inhibin. Primordial germ cells divide to form primary spermatocytes. These undergo a first meiotic division to create secondary spermatocytes (46 chromosomes), followed by a second meiotic division to form spermatids (23 chromosomes). Finally, these differentiate into spermatozoa. This process takes about 70 days. The non-motile spermatozoa leave the seminiferous tubules and pass to the epididymis, for storage and maturation (until ejaculation). Spermatozoa that are not released are reabsorbed by phagocytosis.

## Epidemiology

Up to 50% of infertility is due to male factors. Up to 25% of couples may be affected at some point in their reproductive years.

## CAUSES OF MALE INFERTILITY

### I- PRETESTICULAR

### II- TESTICULAR

### III- POSTTESTICULAR

#### I- PRETESTICULAR CAUSES: includes:

- Endocrine disorders:
  - **Kallmann's syndrome** (isolated gonadotrophin deficiency causing hypogonadism);
  - **Congenital hypogonadotrophic hypogonadism syndromes:** Prader-Willi syndrome (hypogonadism, short stature, hyperphagia, obesity); Bardet-Biedl syndrome (retardation, retinitis pigmentosa, polydactyly, and hypogonadism)
  - **pituitary gland adenoma, radiation, or infection**
- Hormone excess: excess prolactin (pituitary tumour); excess androgen (adrenal tumour, congenital adrenal hyperplasia, anabolic steroids); excess oestrogens

#### II- TESTICULAR CAUSES:

- **Genetic disorders:** Klinefelter's syndrome (47XXY) involves azoospermia, increased FSH/LH and decreased testosterone; XX male; XYY syndrome
- **Gonadotoxins:** (radiation, drugs (chemotherapy; steroids; alcohol; marijuana; sulphasalazine; smoking))
- **Systemic disease:** (renal failure, liver failure, sickle cell anemia)
- **Testis injury:** (orchitis, torsion, trauma)
- **Cryptorchidism:**
- **Varicocele:** found in 40% of infertile men.
- **Idiopathic:** constitutes 25% of cases of infertility.

#### III- POSTTESTICULAR CAUSES:

##### Reproductive tract obstruction

- **Congenital blockages:** (Congenital absence of the vas deferens (CAVD), Young syndrome, Idiopathic epididymal obstruction, Polycystic kidney disease, Ejaculatory duct obstruction)
- **Acquired blockages:** (Vasectomy, Groin surgery, Infection)
- **Functional blockages:** (Sympathetic nerve injury, Pharmacologic)

##### Disorders of sperm function or motility

- **Immotile cilia syndromes**
- **Maturation defects**
- **Immunologic infertility (antisperm antibodies)**
- **Infection**

##### Disorders of coitus

- **Impotence**
- **Hypospadias**

## -Timing and frequency

### History

- **Sexual:** duration of problem; frequency and timing of intercourse; previous successful conceptions; previous birth control; erectile or ejaculatory dysfunction. Lubricants can influence sperm motility and should be avoided. Commonly used products such as K-Y Jelly, Surgilube, Lubifax, most skin lotions, and saliva significantly reduce sperm motility in vitro. If needed, acceptable lubricants include vegetable, safflower, and peanut oils.
- **Developmental:** age at puberty; history of cryptorchidism; gynaecomastia.
- **Medical and surgical:** detailed assessment for risk factors, recent febrile illness; post-pubertal mumps orchitis; varicocele; testicular torsion, trauma, or tumour; sexually transmitted diseases; genitourinary surgery; radiotherapy; respiratory diseases associated with ciliary dysfunction; diabetes.
- **Drugs and environmental:** previous chemotherapy; exposure to substances which impair spermatogenesis or erectile function; alcohol consumption; smoking habits; hot baths.
- **Family:** hypogonadism; cryptorchidism.

### Examination

Perform a full assessment of all systems, with attention to general appearance (evidence of secondary sexual development; signs of hypogonadism; gynaecomastia). Urogenital examination should include assessment of the penis (Peyronie's plaque, phimosis, hypospadias); measurement of testicular consistency, tenderness, and volume with a Prader orchidometer (normal >20ml; varies with race); palpate epididymis (tenderness, swelling) and spermatic cord (vas deferens present or absent, varicocele); digital rectal examination of prostate.

### Investigation of male infertility

#### Basic investigations

**Semen analysis:** There should be 2 to 7 days of sexual abstinence before collection. Two separate samples at least 7 days apart should be analyzed. Deliver specimens to the laboratory within 1h. Ejaculate volume, liquefaction time, and pH are noted. Microscopy techniques measure sperm concentration, total numbers, morphology, and motility. The mixed agglutination reaction (MAR test) is used to detect antisperm antibodies. The presence of leucocytes ( $>1 \times 10^6$ /ml of semen) suggests infection, and cultures should be requested.

The World Health Organization defines the following reference values (WHO):

**Volume:** 2.0 mL or more

**pH:** 7.2 or more

**Sperm concentration:**  $20 \times 10^6$  or more spermatozoa/mL

**Total sperm number:**  $40 \times 10^6$  or more spermatozoa per ejaculate

**Motility:** 50% or more with grade "a + b" motility or 25% or more with grade "a" motility OR >50% with progressive motility (grades >2); or >25% grade 4

**Morphology:** >30% sperm with normal morphology

**Viability:** 50% or more of sperm viable

**Time to liquefy:** 5-25 min

**WBCs:** Less than 1 million/mL

**Systems used for grading sperm motility:**

**1- Five-point scale:**

**Zero= no motility**

- 1= sluggish or nonprogressive movement;
- 2 = slow, meandering forward progression;
- 3 = sperm moving in a reasonably straight line with moderate speed; and
- 4 = sperm moving in a straight line with high speed

## 2- Four categories scale:

- “A” = rapid progressive motility;
- “B” =slow or sluggish progressive motility;
- “C”= nonprogressive motility; and
- “D”= no motility.

### **Hormone measurement:** Indicated in

- Infertile men with sperm densities of  $<10 \times 10^6$  sperm/mL.
- Evidence of impaired sexual function (impotence, low libido).
- Findings suggestive of a specific endocrinopathy (eg, thyroid).

FSH and testosterone should be measured. Serum LH and prolactin levels may be obtained if testosterone and FSH are abnormal, to help pinpoint the endocrine defect. Raised prolactin is associated with sexual dysfunction, and may indicate pituitary disease.

### **Special investigations**

#### **Chromosome analysis**

Indicated for clinical suspicion of an abnormality (azoospermia or oligospermia, small atrophic testes with increased FSH).

#### **Testicular biopsy**

Performed for azoospermic patients, to differentiate between non-obstructive and obstructive causes. May also be used for sperm retrieval. So it is indicated in men with azoospermia, normal FSH, normal size testes and palpable vasa.

## **Oligospermia , azoospermia, Asthenospermia and Teratospermia**

### **Oligospermia**

Defined as a sperm concentration of less than 20 million/ml of ejaculate.

#### **Aetiology**

Varicoceles; idiopathic; androgen deficiency. It is identified in ~60% of patients presenting with testicular cancer or lymphoma.

#### **Associated disorders**

It is often associated with abnormalities of morphology and motility. The combined disorder is called oligoasthenoteratospermia (OAT) syndrome. Common causes include varicoceles; cryptorchidism; idiopathic; drug and toxin exposure; febrile illness.

**Investigations** Semen analysis: sperm counts  $<5$  million/ml (severe form) require hormone investigation, including FSH and testosterone. Severe oligospermia is associated with seminiferous tubular failure, small soft testes, and increased FSH.

#### **Treatment**

Correct the underlying cause. Idiopathic cases may respond to empirical medical therapy or require assisted reproductive techniques.

### **Azoospermia**

Defined as an absence of sperm in the ejaculate fluid.

#### **Aetiology**

- **Obstructive :** Absent or obstructed vas deferens; epididymal or ejaculatory duct obstruction (related to infection, cystic fibrosis).

- **Non-obstructive:** Hypogonadotrophism (Kallmann's syndrome, pituitary tumour); abnormalities of spermatogenesis (chromosomal anomalies, toxins, idiopathic, varicocele, orchitis, testicular torsion).

### Investigations

- **Hormone assay:** (raised FSH with small testes indicates non-obstructive cause; normal FSH with normal testes indicates increased likelihood of obstruction).
- **Chromosomal analysis:** may be used to exclude Klinefelter's syndrome in patients presenting with azoospermia, small soft testes, gynaecomastia, increased FSH/LH and decreased testosterone.
- **Testicular biopsy:** is performed to assess if normal sperm maturation is occurring, and for sperm retrieval (for later therapeutic use).
- **Transrectal ultrasound scan:** assesses absence or blockage of vas deferens, and ejaculatory duct obstruction.

**Note:** Exclude cystic fibrosis in patients with vas deferens defects.

### Management

Treatment will depend on underlying aetiology.

- **Bilateral absence or agenesis of vas deferens:** Microsurgical epididymal sperm aspiration (MESA), or consider artificial insemination using donor (AID).
- **Primary testicular failure with testicular atrophy:** Testicular sperm extraction (TESE); in vitro fertilization (IVF); or consider AID.
- **Primary testicular failure with normal testis:** TESE; IVF; AID.
- **Obstructive cause with normal testis:** Epididymovasostomy; vasovasostomy.

### Asthenospermia

Defects in sperm movement (asthenospermia) refer to low levels of motility or forward progression, or both.

#### Aetiology

- Spermatozoal structural defects,
- prolonged abstinence periods,
- genital tract infection,
- antisperm antibodies,
- partial ductal obstruction,
- varicoceles, and
- idiopathic causes

A varicocele is the most common surgically correctable abnormality found in infertile men and may be responsible for sperm motility defects as well as defects in sperm count and shape.

### Teratospermia

Defects in morphology are termed *teratospermia*. Teratospermia is often associated with both oligospermia and asthenospermia.

Combined defects in sperm density, motility, and morphology are known as **oligoasthenoteratospermia (OAT)** and are most frequently due to a varicocele effect.

Other causes of multiple sperm defects include cryptorchidism, temporary insults to spermatogenesis such as heat, drugs, or environmental toxins, or idiopathic causes. A heat effect may be either environmental or endogenous due to a fever. If a temporary insult is suspected, several semen analyses over one to two spermatogenic cycles (3 to 6 months) should be obtained once the inciting agent is removed.

### Treatment options for male factor infertility

#### General

Modification of life style factors (reduce alcohol consumption; avoid hot baths).

### **Medical treatment**

Correct any reversible causative factors.

Antibiotics: Treat any positive semen, urine, or urethral cultures with appropriate antibiotics.

#### Hormonal

- **Secondary hypogonadism** (pituitary intact) may respond to human chorionic gonadotrophin (hCG) 2000IU subcutaneously 3 times a week, which stimulates an increase in testosterone and testicular size. If the patient remains azoospermic after 6 months of treatment, FSH is added (human recombinant FSH or human menopausal gonadotrophin). Alternatively, pulsatile LHRH can be administered subcutaneously via a minipump.
- **Testosterone deficiency** requires testosterone replacement therapy.
- **Hyperprolactinaemia** is treated with dopamine agonists.

#### Erectile and ejaculatory dysfunction

Erectile dysfunction may be treated conventionally (oral, intraurethral, intracavernosal drugs; vacuum devices or prostheses). Ejaculatory failure may respond to sympathomimetic drugs (desipramine) or electroejaculation (used in spinal cord injury), where an electrical stimulus is delivered via a rectal probe to the postganglionic sympathetic nerves that innervate the prostate and seminal vesicles.

#### Antisperm antibodies

Corticosteroids have been used, but assisted conception methods are usually required.

### **Surgical treatment**

#### Genital tract obstruction

- Epididymal obstruction can be overcome by microsurgical anastomosis between the epididymal tubule and vas (epididymovasostomy).
- Vas deferens obstruction is treated by microsurgical reanastomosis of ends of the vas, and is used for vasectomy reversal. Highest success rates for finding viable sperm occur in the first 8 years post vasectomy (80-90%).
- Ejaculatory duct obstruction requires transurethral resection of the ducts.

#### Varicocele

Repaired by embolization or open/laparoscopic surgical ligation.

### **Empiric Medical Therapy**

It is used in:

- 1- Idiopathic infertility: no identifiable cause can be attributed to the problem.
- 2- Men in whom a cause of infertility may be identified but no specific therapy is available.

**A. CLOMIPHENE CITRATE:** a synthetic nonsteroidal drug that acts as an antiestrogen and competitively binds to estrogen receptors in the hypothalamus and pituitary. Clomiphene therapy is given for idiopathic low sperm count in the setting of low-normal LH, FSH, and testosterone levels. It is less effective as a treatment for low motility.

**B. ANTIOXIDANT THERAPY:** glutathione or vitamin E. These agents may be useful in a subgroup of infertile men with elevated levels of seminal reactive oxygen species. Non-FDA approved vitamin supplements abound as treatments for male infertility, but well-controlled trials demonstrating their efficacy are scarce. Folic acid and zinc may increase sperm concentration.

## **Assisted reproductive techniques (ART)**

### **Sperm extraction**

Sperm are removed directly from the epididymis by microsurgical epididymal sperm aspiration (MESA) or by percutaneous retrieval (PESA). If these methods fail, testicular sperm extraction (TESE) or aspiration (TESA) may be tried. Sperm undergo cryopreservation until required. Later, they are separated from seminal fluid by dilution and centrifuge methods, with further selection of motile sperm and normal forms using Percoll gradient techniques.

### **Assisted conception**

- **Intrauterine insemination (IUI):** Following ovarian stimulation, sperms are placed directly into the uterus.
- **In vitro fertilization (IVF):** Controlled ovarian stimulation produces oocytes which are then retrieved under transvaginal USS-guidance. Oocytes and sperm are placed in a Petri dish for fertilization to occur. Embryos are transferred to the uterine cavity. Pregnancy rates are 20-30% per cycle.
- **Gamete intrafallopian transfer (GIFT):** Oocytes and sperm are mixed and deposited into the fallopian tubes via laparoscopy. Variations include zygote intrafallopian transfer (ZIFT) and tubal embryo transfer (TET).
- **Intracytoplasmic Sperm injection (ICSI):** A single spermatozoon is injected directly into the oocyte cytoplasm (through the intact zona pellucida). Pregnancy rates are 15-22% per cycle.