Infertility

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Male reproductive physiology

- Hypothalamic pituitary 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.
Testosterone

- is secreted by the interstitial Leydig cells. It promotes development of the male reproductive system and secondary sexual characteristics. At androgen-responsive target tissues, testosterone is converted into a potent androgen, dihydrotestosterone, by intracellular 5-alfa reductase.
Spermatogenesis

- 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 70 days. The non-motile spermatozoa leave the seminiferous tubules and pass to the epididymis, for storage and maturation (until ejaculation).
Mature sperm

The head is composed of a nucleus covered by an acrosome cap, containing vesicles filled with lytic enzymes. The middle piece contains mitochondria and contractile filaments, which extend into the tail to aid motility. After deposition at the cervix, sperm penetrate cervical mucus and travel through the uterus to the site of fertilization in the fallopian tube, during which time they undergo functional maturation (capacitation). Sperm start to penetrate the oocyte, and bind to the zona pellucida, triggering hyperactivated motility and the acrosomal reaction, leading to enzyme release, penetration into the cytoplasm of the oocyte, fusion, and fertilization.
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.

• Up to 50% of infertility is due to male factors.
CAUSES OF MALE INFERTILITY

A: PRETESTICULAR CAUSES:

1. Hypothalamic
   - A. GONADOTROPIN DEFICIENCY
     EX: KALLMANN SYNDROME: there is a disturbance of neuronal migration from the olfactory placode during embryonic development. The clinical features include anosmia, facial asymmetry, microphallus, and cryptorchidism.
   - B. ISOLATED LH DEFICIENCY.
   - C. ISOLATED FSH DEFICIENCY.
   - D. CONGENITAL HYPOGONADOTROPIC SYNDROMES
2. Pituitary Disease

A. Pituitary Insufficiency: Pituitary insufficiency may result from tumors, infarcts, surgery, radiation, or infiltrative and granulomatous processes. In sickle cell anemia, pituitary and testicular microinfarcts from sickling of red blood cells are suspected.

B. Hyperprolactinemia: The most common and important cause of hyperprolactinemia is a prolactin secreting pituitary adenoma. Elevated prolactin usually results in decreased FSH, LH, and testosterone levels and causes infertility. Associated symptoms include loss of libido, impotence, galactorrhea, and gynecomastia.
3. EXOGENOUS OR ENDOGENOUS HORMONES

- **A. Estrogens**—An excess of sex steroids, either estrogens or androgens, can cause male infertility due to an imbalance in the testosterone-estrogen ratio. Hepatic cirrhosis increases endogenous estrogens because of augmented aromatase activity within the diseased liver. Likewise, excessive obesity may be associated with testosterone estrogen imbalance owing to increased peripheral aromatase activity.

- **B. Androgens**—An excess of androgens can suppress pituitary gonadotropin secretion and lead to secondary testis failure. The use of exogenous androgenic steroids (anabolic steroids) by as many as 15% of high school athletes.

- **C. Glucocorticoids**—Exposure to excess glucocorticoids either endogenously or exogenously can result in decreased spermatogenesis. Elevated plasma cortisone levels depress LH secretion and induce secondary testis failure.

- **D. Hyper- and hypothyroidism**—Abnormally high or low levels of serum thyroid hormone affect spermatogenesis at the level of both the pituitary and testis.

- **E. Growth hormone**—There is emerging evidence that growth hormone may play a role in male infertility.
B: TESTICULAR CAUSES :-

1. Chromosomal Causes
   - EX: Klinefelter syndrome is the most common genetic reason for azoospermia. It has a classic triad: small firm testes; gynecomastia; and azoospermia. This syndrome may present with increased likelihood of extragonadal germ cell tumors, and breast cancer (20-fold higher than in normal males).

2. Gonadotoxins
   - A. RADIATION: The effects of radiotherapy on sperm production are well described.
   - B. DRUGS
     - Ketoconazole, spironolactone, and alcohol inhibit testosterone synthesis, cimetidine is an androgen antagonist.
     - Recreational drugs such as marijuana, heroin are associated with lower testosterone levels.
     - Certain pesticides have estrogen-like activity.

3. Systemic Disease
   - A. RENAL FAILURE
   - B. LIVER CIRHOSIS
   - C. SICKLE CELL DISEASE
4. **Defective Androgen Activity**: Peripheral resistance to androgens occurs with 2 basic defects:
   
   (1) a deficiency of androgen production through the absence of 5-alpha-reductase
   
   (2) a deficiency in the androgen receptor.

5. **Testis Injury**
   
   • **A. ORCHITIS**: Inflammation of testis tissue is most commonly due to bacterial infection, termed epididymo-orchitis. Viral infections also occur in the testis in the form of mumps orchitis.
   
   • **B. TORSION**: Ischemic injury to the testis secondary to twisting of the testis on the spermatic cord pedicle.
   
   • **C. TRAUMA**: Because of the peculiar immunologic status of the testis in the body (ie, it is an immunologically privileged site), trauma to the testis can invoke an abnormal immune response in addition to atrophy resulting from injury. Both may contribute to infertility. Trauma to the testis that results in fracture of the testis tunica albugineal layer.

6. **Cryptorchidism**.

7. **Varicocele**: is defined as dilated and tortuous veins within the pampiniform plexus of scrotal veins. (40% of male infertility)
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
- Infection

Disorders of coitus
- Impotence
- Hypospadias
- Timing and frequency
Evaluation of Male infertility

History

- **Sexual**: duration of problem; frequency and timing of intercourse; previous successful conceptions; previous birth control; erectile or ejaculatory dysfunction.
- **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

### seminal fluid analysis (SFA)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Values</th>
</tr>
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<tbody>
<tr>
<td>Semen volume</td>
<td>&gt;2.0 ml</td>
</tr>
<tr>
<td>pH</td>
<td>7.2–7.8</td>
</tr>
<tr>
<td>Total sperm count</td>
<td>&gt;40 $10^6$ / ejaculate</td>
</tr>
<tr>
<td>Sperm concentration</td>
<td>&gt;20 $10^6$ / ml</td>
</tr>
<tr>
<td>Sperm motility</td>
<td>&gt;50% with progressive motility (grades &gt;2); or &gt;25% grade 4</td>
</tr>
<tr>
<td>Sperm morphology</td>
<td>&gt;15% normal forms</td>
</tr>
<tr>
<td>Viability</td>
<td>&gt;75% viable sperm</td>
</tr>
<tr>
<td>Time to liquefy</td>
<td>5–25 min</td>
</tr>
<tr>
<td>White blood cells</td>
<td>&lt;1 $10^6$ / ml</td>
</tr>
<tr>
<td>MAR test (for antisperm Ab)</td>
<td>Negative (&lt;10% with adherent particles)</td>
</tr>
<tr>
<td>Zinc</td>
<td>&gt;2.4 mol / ejaculate</td>
</tr>
<tr>
<td>Semen fructose</td>
<td>120–145 mg/dl</td>
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### Basic investigations:

Hormonal assessment: FSH, LH, S.testosteron, S.estrogen, S.prolactine, thyroid hormon
Imaging

- **Scrotal ultrasound scan** is used to confirm a varicocele and assess testicular abnormalities.
- **Transrectal ultrasound scan** is indicated for low ejaculate volumes, to investigate seminal vesicle obstruction (>1.5 cm width) or absence and ejaculatory duct obstruction (>2.3 mm).
- **Vasography** Vas deferens is punctured at the level of the scrotum and injected with contrast. A normal test shows the passage of contrast along the vas deferens, seminal vesicles, ejaculatory duct, and into the bladder, which rules out obstruction.
- **Venography** used to diagnose and treat varicoceles (embolization).
Special investigations

1. **Chromosome analysis**: Indicated for clinical suspicion of an abnormality (azoospermia or oligospermia, small atrophic testes with ↑ FSH).

2. **Testicular biopsy**: Performed for azoospermic patients, to differentiate between idiopathic and obstructive causes. May also be used for sperm retrieval.

3. **Sperm function tests which include**:
   - **Post coital test**: cervical mucus is taken just before ovulation, and within 8 hours of intercourse, and microscopy performed. Normal results show >10 sperm per high-powered field, the majority demonstrating progressive motility. Abnormal results indicate inappropriate timing of the test; cervical mucus antisperm antibodies; abnormal semen; inappropriately performed coitus.
   - **Sperm penetration test**: a sample of semen is placed directly onto pre-ovulatory cervical mucus on a slide and the penetrative ability of spermatozoa observed.
   - **Sperm-cervical mucus test**: a specimen of semen (control), and one mixed with cervical mucus are placed separately on a slide, and observed for 30 minutes. More than 25% exhibiting jerking movements in the mixed sample (but not the control) is a positive test for antisperm antibodies.
Treatment options for male infertility

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

• **Medical treatment**  
  Correct any reversible causative factors:
  
  1. **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. Alternatively, pulsatile LHRH can be administered subcutaneously via a minipump.  
     
     *Testosterone deficiency* requires testosterone replacement therapy.  
     *Hyperprolactinaemia* is treated with dopamine agonists.

  2. **Empiric medical therapy**
     
     a. **Anti-oestrogens** (clomiphene citrate): are often used empirically to increase LHRH, which stimulates endogenous gonadotrophin secretion.  
     
     b. **Antioxidant**: Vitamine E improve sperm function, zinc and folic acid increase sperm concentration.
3. Correct erectile and ejaculatory dysfunction
4. Antisperm antibodies
Corticosteroids have been used, but assisted conception methods are usually required.
5. Antibiotics to treat any infection

- **Surgical treatment**
  1. Genital tract obstruction
     - Epididymal obstruction can be overcome by microsurgical anastomosis between the epididymal tubule and vas (epididymovasovasostomy).
     - Vas deferens obstruction is treated by microsurgical re-anastomosis of ends of the vas, and is used for vasectomy reversal.
     - Ejaculatory duct obstruction requires transurethral resection of the ducts.
  2. Varicocele
     - Repaired by embolization or open/laparoscopic surgical ligation
  3. Orchidopexy
  4. Pituitary ablation
• **Assisted reproductive techniques (ART)**

• *Intrauterine insemination (IUI)* Following ovarian stimulation, sperm 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.

• *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.
Thank you