# Male Infertility

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# Male reproductive physiology

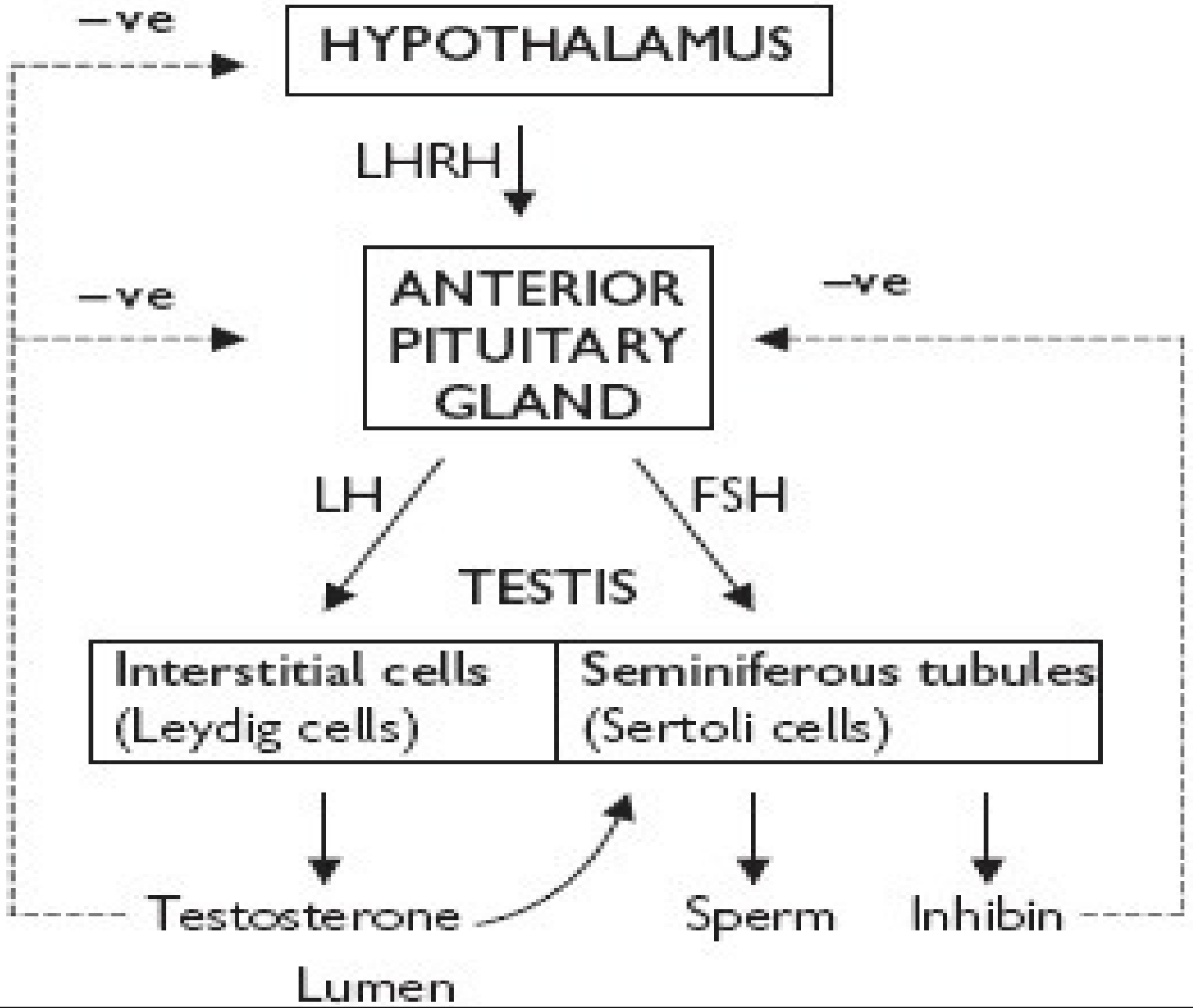
## How Does the Male Reproductive System Function?

The all male reproductive system is dependent on hormones, which are chemicals that regulate the activity of many different types of cells or organs. The primary hormones involved in the male reproductive system are follicle-stimulating hormone, luteinizing hormone, and testosterone

# 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


−ve
HYPOTHALAMUS
LHRH
−ve
ANTERIOR PITUITARY GLAND
−ve
LH
FSH
TESTIS
Interstitial cells (Leydig cells)
Seminiferous tubules (Sertoli cells)
Testosterone
Sperm
Inhibin
Lumen

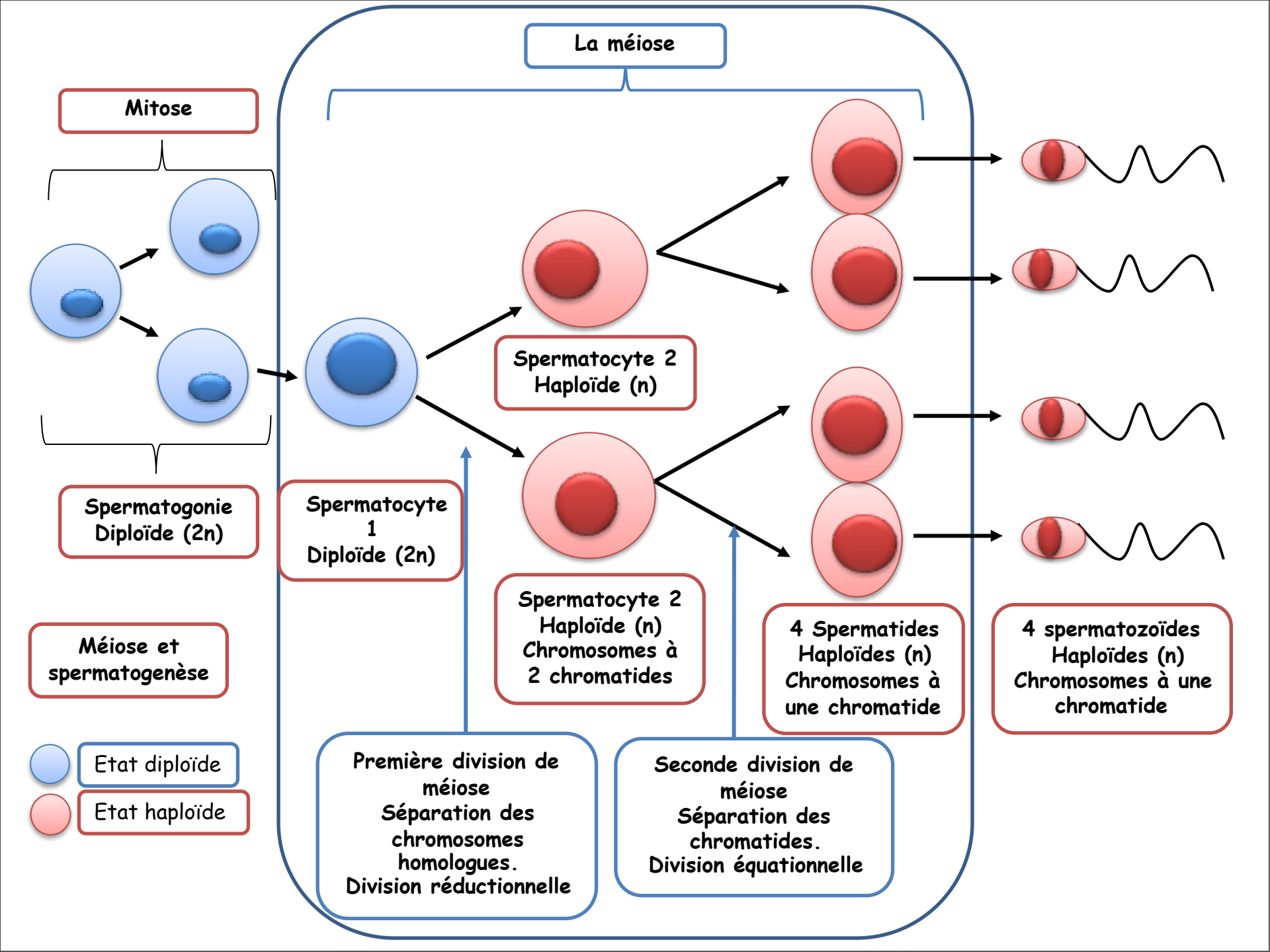
# Spermatogenesis

Seminiferous tubules are lined with Sertoli cells, which surround developing germ cells (spermatogonia) providing nutrients and stimulating factors, as well as secreting androgen-binding factor and inhibin

Primordial germ(spermatogonia) 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.

Spermatogenesis takes 74 days. The nonmotile spermatozoa leave the seminiferous tubules and pass to the epididymis, where they undergo maturation (gain motility and the ability to fertilize). Ductal transit time takes another 2 weeks, so the total time from beginning of spermatogenesis to ejaculation is 3 months.

Motile sperm are stored in the globus minor of the epididymis until ejaculation. Spermatozoa that are not released are reabsorbed by phagocytosis.


La méiose
Mitose
Spermatogonie
Diploïde (2n)
Spermatocyte
1
Diploïde (2n)
Spermatocyte 2
Haploïde (n)
Spermatocyte 2
Haploïde (n)
Chromosomes à
2 chromatides
4 Spermatides
Haploïdes (n)
Chromosomes à
une chromatide
4 spermatozoïdes
Haploïdes (n)
Chromosomes à une
chromatide
Méiose et
spermatogenèse
Etat diploïde
Etat haploïde
Première division de
méiose
Séparation des
chromosomes
homologues.
Division réductionnelle
Seconde division de
méiose
Séparation des
chromatides.
Division équationnelle

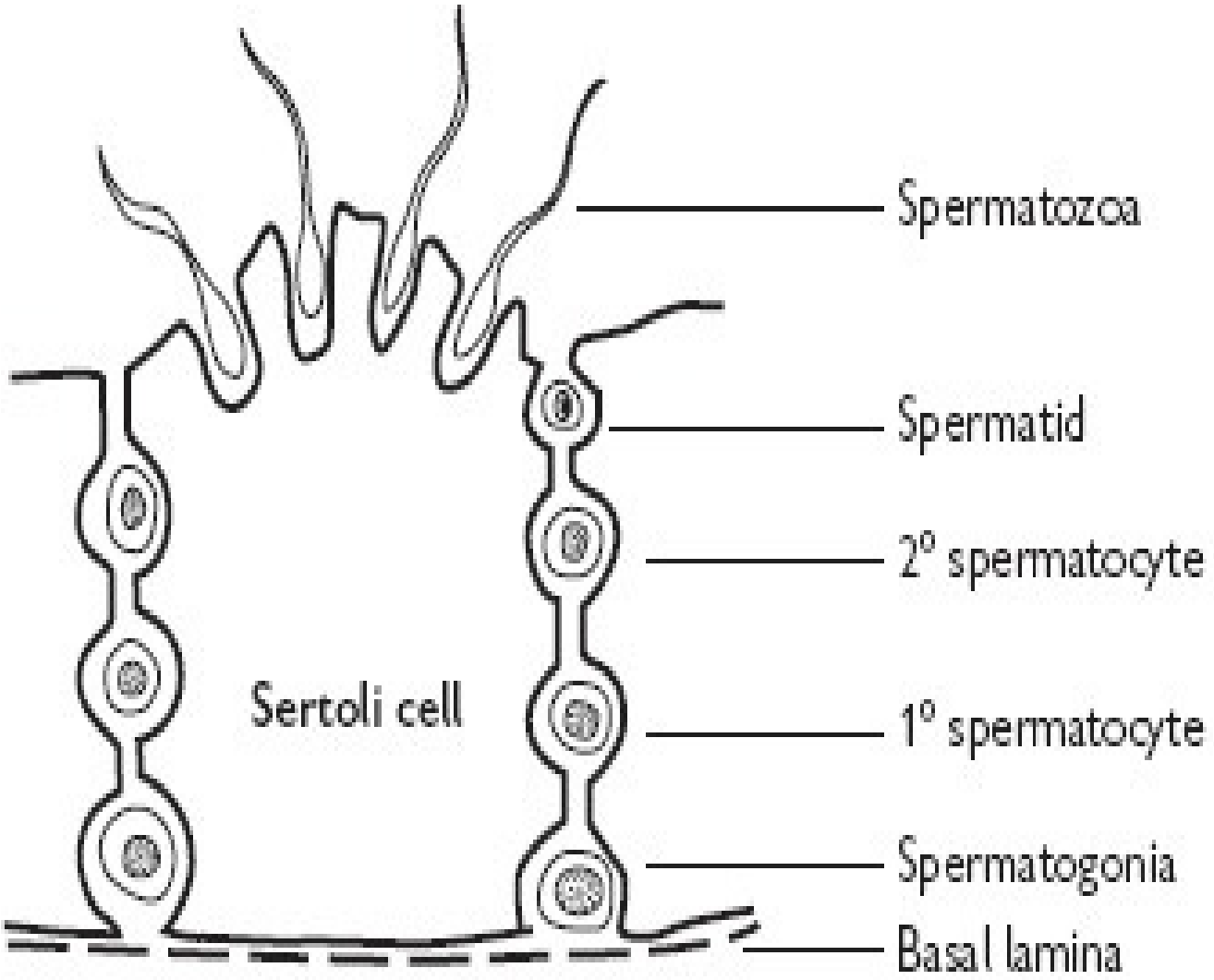
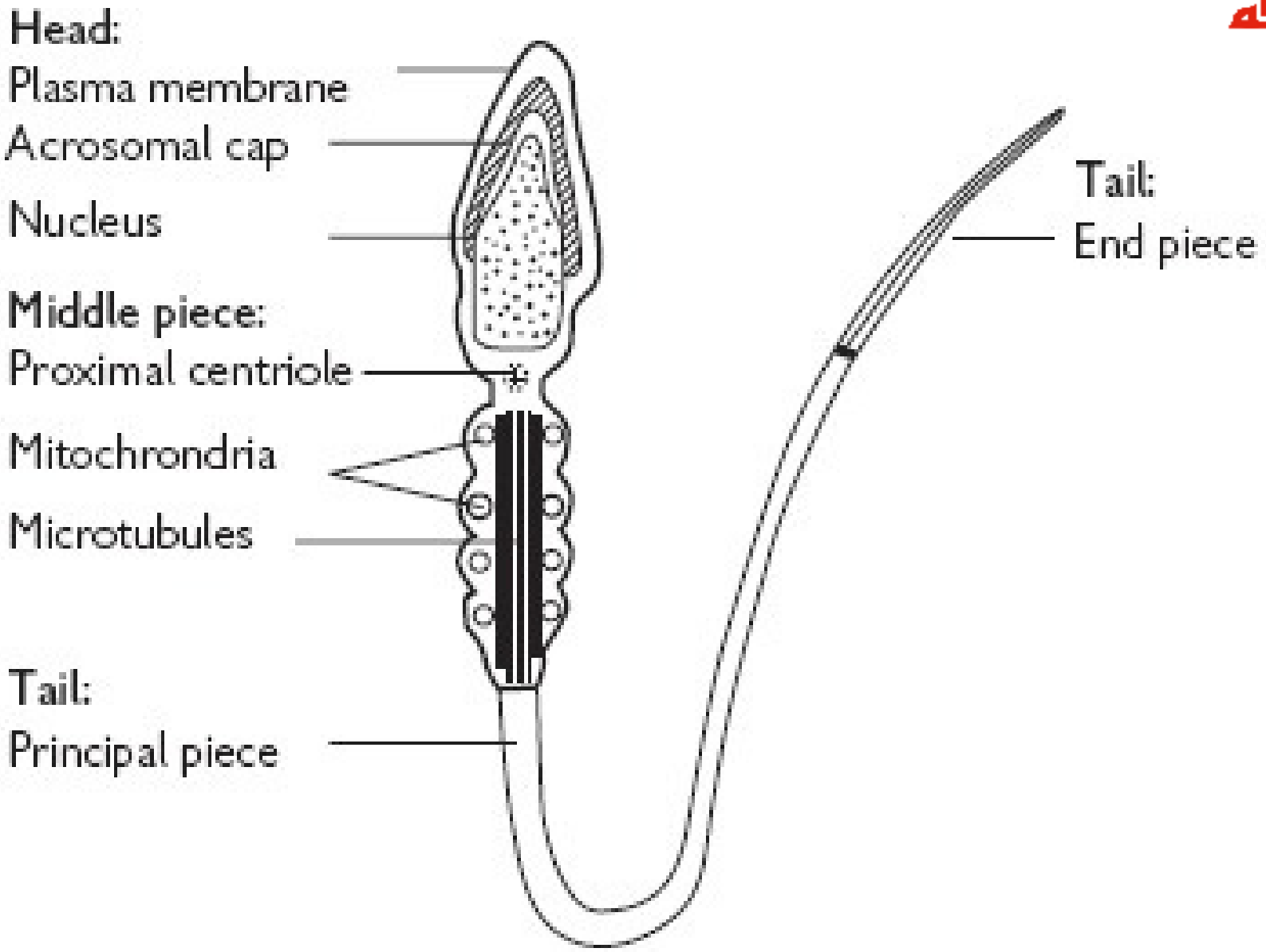



**Figure 11.2** Spermatogenesis in the seminiferous tubules of the testis.

# Mature sperm

Mature sperm have a head, middle piece, and tail . The head is composed of a nucleus covered by an acrosome cap, containing vesicles filled with lytic enzymes that break down the outer layer of the female ovum. The middle piece contains mitochondria and contractile filaments, which extend into the tail to aid motility.


Head:
Plasma membrane
Acrosomal cap
Nucleus
Middle piece:
Proximal centriole
Mitochrondria
Microtubules
Tail:
Principal piece
Tail:
End piece

# Etiology and evaluation of male infertility

**Definition of infertility**

*Infertility is failure of conception after at least 12 months of unprotected* intercourse

. The chance of a normal couple conceiving is estimated at :

20–25% per month, 75% by 6 months, and 90% at 1 year. 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.

# Pathophysiology

Failure of fertilization of the normal ovum is due to defective sperm development, function, or inadequate numbers

. There may be abnormalities :

of morphology (teratospermia) or motility (asthenospermia),

low sperm numbers (oligospermia), combined disorders (oligoasthenospermia), absent sperm (azoospermia).

Abnormal epididymis function may result in defective spermatozoa maturation or transport, or induce cell death.

| Parameter | Lower limit reference |
| --- | --- |
| Sperm volume | 1.5ml |
| PH | => 7.2 |
| Total sperm count | 39x10^6 per ejaculate |
| Sperm concentration | 15x10^6 per ml |
| Motility | 40% progressive + non progressive<br>32% progressive motility |
| Morphology | 4% Normal forms |
| Vitality | 58% live spermatozoa |
| Time to liquefy | 5-25 minutes |
| WBCs | < 1x10^6 per ml |
| MAR test(for anti-sperm antibodies) | <50% motile spermatozoa with bound particles |

# Etiology

- Idiopathic (25%)
- Varicocele (present in 40%)
- Cryptorchidism (undescended testes)
- Functional sperm disorders: immunological infertility (sperm antibodies); head or tail defects; Kartagener's syndrome
- Erectile or ejaculatory problems
- Testicular injury: orchitis

# Cont.

Hormone excess: excess prolactin (pituitary tumor)

- Genetic disorders: Kleinfelter's syndrome (47XXY)
- Male genital tract obstruction: congenital absence of vas deferens
- Systemic disease: renal failure; liver cirrhosis; cystic fibrosis
- Drugs: chemotherapy; alcohol; marijuana; sulfasalazine; smoking
- Environmental factors: pesticides; heavy metals; hot baths

# History

- sexual and reproductive:: duration of problem; frequency and timing of intercourse; previous successful conceptions; previous birth control; erectile,or ejaculatory dysfunction, previous marrigaes, misscarraiges•

Developmental: age at puberty; history of cryptorchidism; gynecomastia

• Medical and surgical: orchitis; varicocele testicular

torsion, trauma, or tumor; sexually transmitted diseases;

Erection history.

# Cont.

- Drugs and environmental: previous chemotherapy; exposure to substances that impair spermatogenesis or erectile function; alcohol antidepressants

- Family: hypogonadism; cryptorchidism

Smoking?

Also take sexual history of the female partner

# Examination

- Perform a full assessment of all systems with attention to general appearance (evidence of secondary sexual development; signs of hypogonadism; gynecomastia).

- Urogenital examination should includeassessmentof the penis (Peyronie'splaque, phimosis, hypospadias); measurement of testicular consistency palpation of epididymis (tenderness, swelling) and spermatic cord (vas deferens present or absent, varicocele); and digital rectal examination of the prostate

# Lab investigation of male infertility and Treatment options

# Basic investigations

- ***Semen analysis***

- Obtain 2 or 3 specimens over several weeks, collected after 2–7 days of sexual abstinence. Deliver specimens to the laboratory within 1 hour.

- The mixed agglutination reaction (MAR test) is used to detect antisperm antibodies.

- The presence of leukocytes or round cells in the ejaculate (>1 x 106/mL of semen) suggests infection, and cultures should be requested

**Table 12.1** WHO semen analysis characteristics

| Semen analysis parameter | Lower reference limit (95% CI) |
|---|---|
| Serum volume | 1.5mL (1.4–1.7) |
| pH | ≥7.2 |
| Total sperm count | 39 x $10^6$ per ejaculate (33–46) |
| Sperm concentration | 15 x $10^6$ per mL (12–16) |
| Motility | 40% progressive + non-progressive (38–40)<br>32% progressive motility (31–34)<br>Forward progression >grade 2 |
| Sperm morphology | 4% normal forms (3–4) |
| Vitality | 58% live spermatozoa (55–63) |
| Time to liquefy | 5–25min |
| White blood cells (WBC) | <1 x $10^6$ WBC per mL |
| MAR-test (for antisperm antibody) | <50% motile spermatozoa with bound particles |
| Zinc | ≥2.4μmol per ejaculate |
| Semen fructose | ≥13μmol per ejaculate |

Adapted from World Health Organization (WHO) 2010 lower reference limits (5th centile and their 95% CI) for semen characteristics

**Table 12.2** Grading of sperm motility

| Grade | Type of sperm motility |
|---|---|
| 0 | No motility |
| 1 | Sluggish; no progressive movement |
| 2 | Slow, meandering forward progression |
| 3 | Moving in a straight line with moderate speed |
| 4 | Moving in a straight line at high speed |

- ***Hormone measurement***

-Obtain serum FSH, LH, testosterone and prolactin, TSH

- Elevated serum FSH levels (2 x normal) suggest irreversible testicular failure.
- In cases of isolated low testosterone level, it is recommended that morning and free testosterone levels be tested.
- Elevated prolactin is associated with sexual dysfunction and low serum testosterone levels, and usually indicates the presence of a pituitar

**Table 11.3** Clinical diagnosis on hormone assay

| FSH* | LH** | Testosterone | Diagnosis |
|---|---|---|---|
| ↑ | Normal | Normal | Seminiferous tubule damage (defective spermatogenesis) |
| Normal | Normal | Normal | Normal; or bilateral genital tract obstruction |
| ↑ | ↑ | Normal/↓ | Testicular failure |
| ↓ | ↓ | ↓ | Hypogonadotrophism |

* Follicle stimulation hormone.

** Luteinizing hormone.

# Special investigations

- **Chromosomal analysis:** karyotyping to identify Klinefelter's syndrome in patients presenting with azoospermia (5–10% of azoospermic patients have Klinefelter's syndrome), small soft testes, gynaecomastia, d FSH/LH and d testosterone.

- **Post-orgasmic urine analysis:** the presence of >10–15 sperm per high powered field confirms the diagnosis of retrograde ejaculation.

- **Fructose:** Although the fructose test is not part of a routine semen analysis, it is useful in cases of azoospermia (absence of sperm in semen). In azoospermia secondary to the **absence of vesicles** or if there is an **obstruction**, no fructose is present. In **testicular azoospermia**, fructose is present.

# Testicular biopsy

- Performed for azoospermic patients to help differentiate between obstructive and non-obstructive causes.
- Simultaneous sperm retrieval can be carried out (testicular sperm extraction, TESE) for use in intracytoplasmic sperm injection (ICSI) treatment, either at the time or at a later date (following freezing and storage).
- The degree of spermatogenesis can be histologically scored (The Johnsen score). Only mature spermatozoa (score 8 or above) can be used for fertility treatment.

# Testicular biopsy

**Table 12.4** The Johnsen Score. Histological analysis of testicular biopsy[1]

| | |
|---|---|
| 10 | Complete spermatogenesis, many spermatozoa |
| 9 | Many spermatozoa, disorganized germinal epithelium |
| 8 | Few spermatozoa (<5–10) |
| 7 | No spermatozoa but many spermatids |
| 6 | No spermatozoa and few spermatids (<5–10) |
| 5 | No spermatozoa or spermatids, but many spermatocytes |
| 4 | Few spermatocytes (<5), no spermatozoa or spermatids |
| 3 | Spermatogonia are the only germ cells |
| 2 | Sertoli cells only |
| 1 | No cells in tubules |

# Radiologic Evaluation

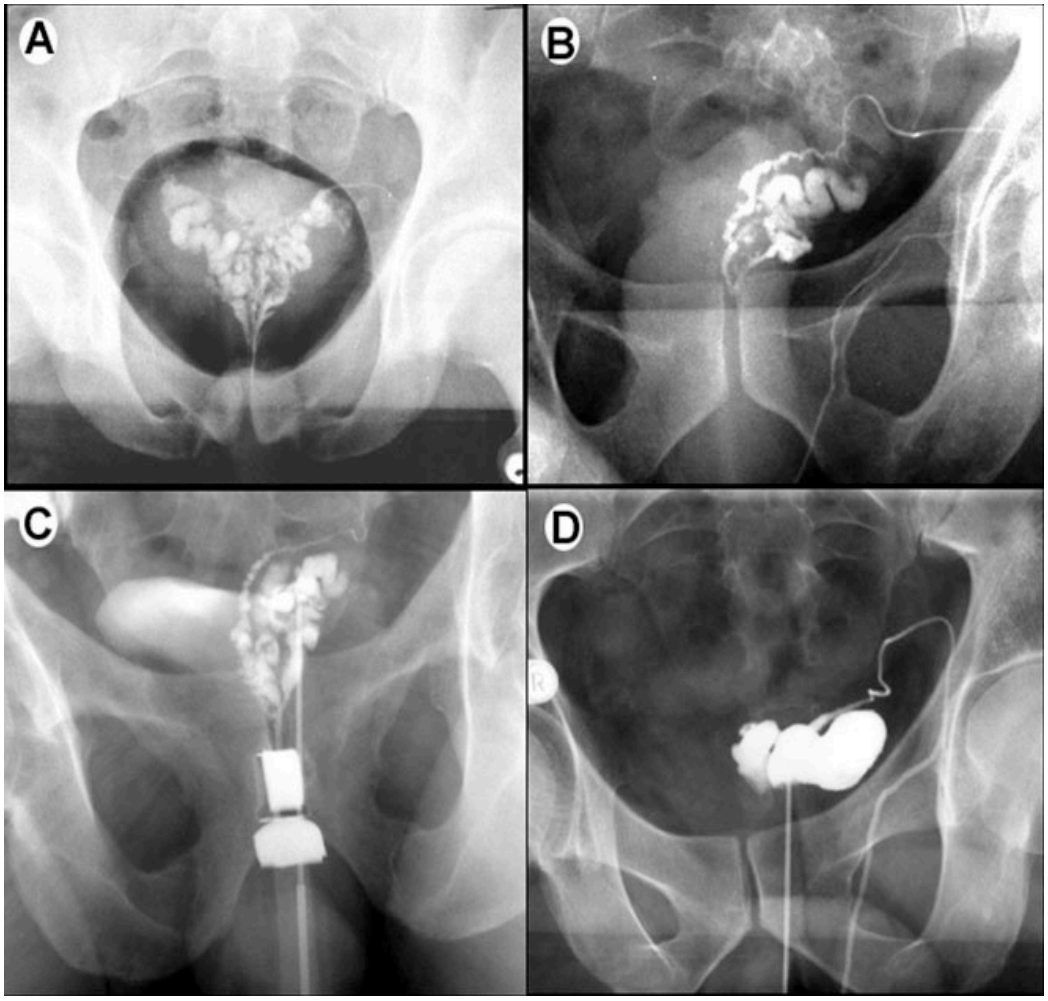
- ***Vasography***
- ***Transrectal Ultrasonography***
- ***Venography***
- ***Scrotal Ultrasonography***

# *Vasography*

- The traditional and most commonly employed radiologic imaging study employed for the evaluation of the vasal and ejaculatory duct patency is vasography.
- The 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.
- Vasography is indicated to determine the site of obstruction in azoospermic patients who have active spermatogenesis documented by testis biopsy

# *Vasography*

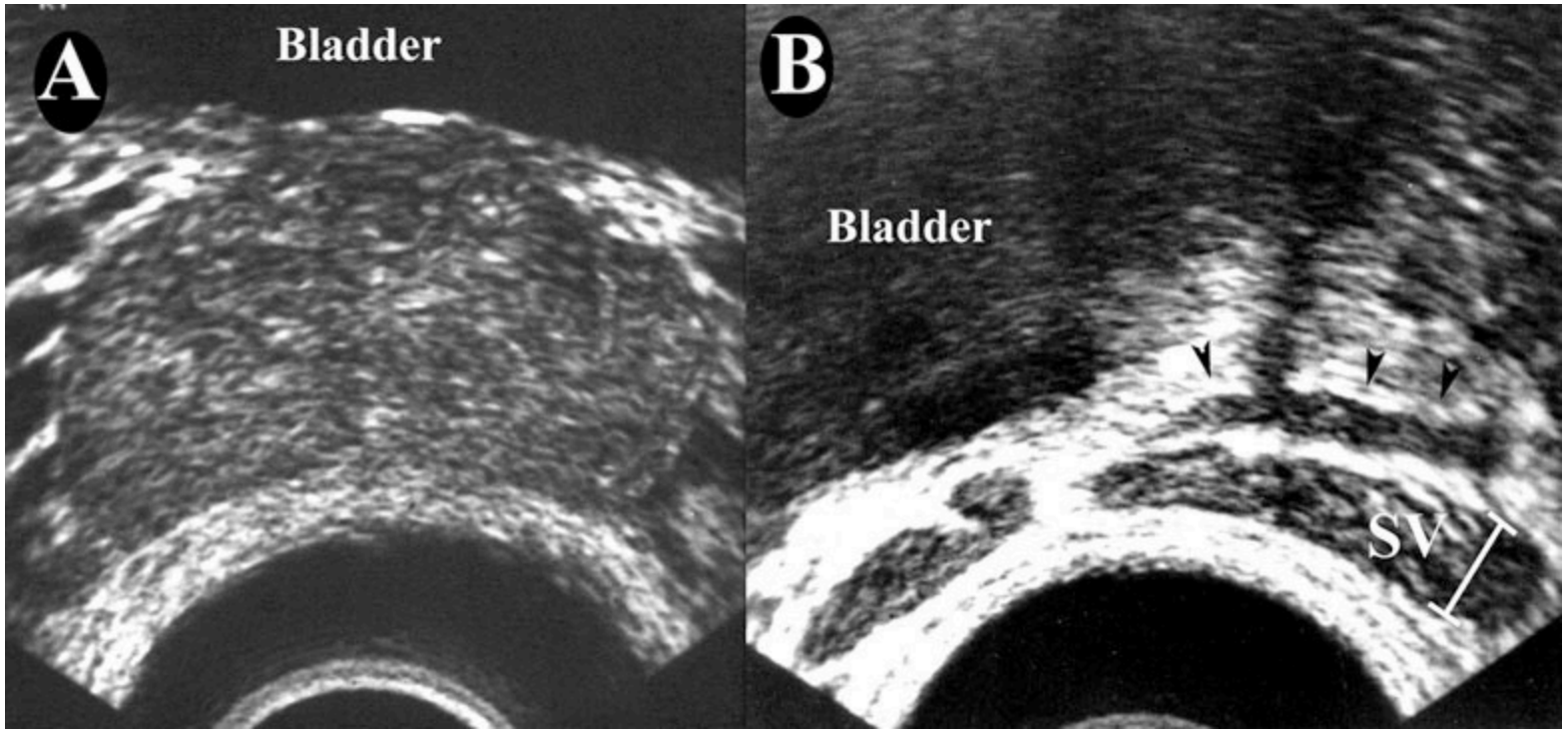
- A normal vasogram is documented when contrast agent is visualized throughout the length of the vas deferens, seminal vesicles, ejaculatory duct, and bladder



# *Transrectal Ultrasonography*

- TRUS allows for the anatomic visualization of the prostate, seminal vesicles, and ampullary portion of the vas deferens
- TRUS is indicated in azoospermic patients suspected of having ejaculatory duct obstruction .
- TRUS is indicated for low ejaculate volumes, to investigate seminal vesicle obstruction (>1.5cm width) or absence
- The normal diameter of the seminal vesicles on transverse imaging behind the bladder is up to 1.5 cm

# *Transrectal Ultrasonography*



# *Scrotal Ultrasonography*

- The main application of scrotal ultrasonography in male infertility has been for the diagnosis of varicoceles
- Color duplex scrotal ultrasonography has been applied as a noninvasive alternative to internal spermatic vein venography in an attempt to objectively diagnose varicoceles

  The initial criteria developed to diagnose a varicocele include the presence of numerous large veins (>3 mm) and reversal of blood flow with Valsalva maneuver

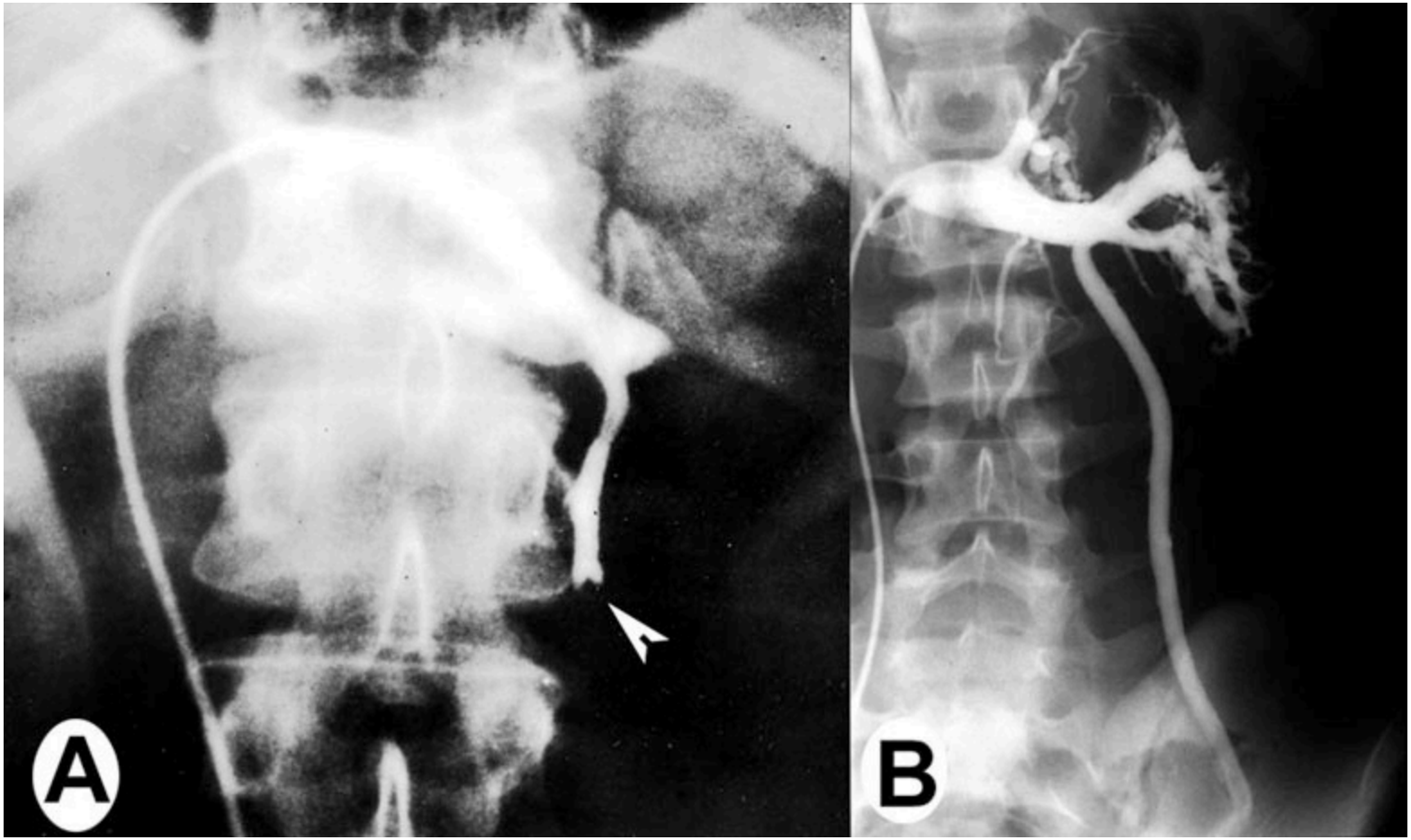
# *Scrotal Ultrasonography*

- Scrotal ultrasonography to detect testicular tumors should be restricted to patients with suggestive histories, physical examinations, or hormonal values.
- It should not be used as a routine examination to screen all infertile men.

# *Venography*

- Internal spermatic vein venography is used to both detect and potentially treat varicoceles
- The femoral vein approach is generally preferred, but the internal jugular approach is superior if embolization of bilateral varicoceles is being observed.

# *Venography*



# *Treatment options for male factor infertility*

**General:** aim to identify and treat reversible causes of subfertility and improve semen quality. Advice on modification of lifestyle factors (i.e. reduce alcohol consumption, avoid hot baths).

## Medical treatment:

- **Antibiotics:**

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

- **Hormonal:**

1. **-Secondary hypogonadism (pituitary intact):** may respond to administration of human chorionic gonadotrophin (HCG) 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 LHRHcan be administered subcutaneously via a minipump (used for treating Kallman's syndrome).
2. **-Hyperprolactinaemia**: is treated with dopamine agonists. Arrange an MRI to rule out a pituitary tumour.

- **Antioestrogens (clomiphene citrate 25mg od):**

are used empirically to increase LHRH which stimulates endogenous gonadotrophin secretion. Used for idiopathic oligospermia.

- **Antioxidants:**

Vitamin E supplements have been shown to improve sperm function and IVF success rates; zinc and folic acid may increase sperm concentrations.

## 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

1. **Epididymal obstruction:** can be overcome by microsurgical anastomosis between the epididymal tubule and vas (vasoepididymostomy).

2. **Vas deferens obstruction:** is treated by microsurgical reanastomosis of ends of the vas (vasovasotomy) and is used for vasectomy reversal. Highest success rates for fi nding viable sperm occur in the fi rst 8y postvasectomy (80–90%); overall pregnancy rates are 750%. Patency rates are better than pregnancy rates; success rates drop to 30% if >15y.

**Post-vasectomy:**

3. Ejaculatory duct obstruction: requires transurethral resection of the ejaculatory ducts (TURED).

**Varicocele:**

4. can be treated by embolization or open or laparoscopic surgical ligation.

# Assisted reproductive techniques (ART)

## *Sperm extraction*

- sperm are removed directly from the epididymis by *PESA* or *MESA*.
- If these methods fail, *TESE* by conventional biopsy or microsurgical techniques, 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, sperm* are placed directly into the uterus.

- ***In vitro fertilization (IVF)****: Controlled ovarian stimulation produces* oocytes that are then retrieved under transvaginal ultrasound guidance. Oocytes and sperm are placed in a Petri dish for fertilization to occur. Embryos are incubated and cultured for 2–3 days and then 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 spermatozoa is injected directly into the oocyte cytoplasm (through the intact zona pellucida). The advantage is that fewer sperm are needed. ICSI is always combined with IVF and the clinical pregnancy rate is 28–40% per cycle.


thankyou