MALE INFERTILITY

Infertility

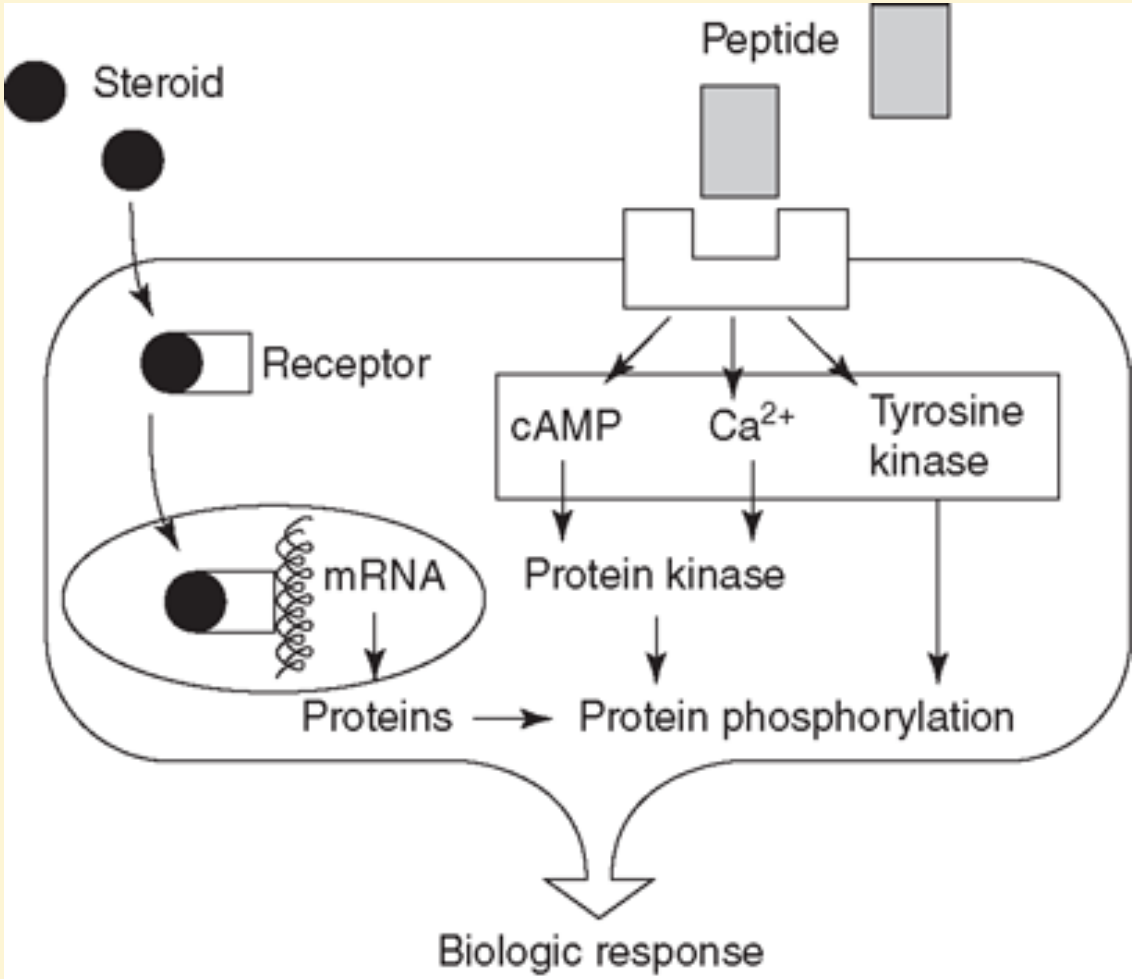
- Infertility is defined as the failure to conceive despite 1 year of regular unprotected intercourse.
- Approximately 15% of couples will experience infertility, and of these, 40% will have a male factor that is solely responsible; male factors will contribute in an additional 20% of cases.

- The causes of male infertility are widely varied and are best evaluated by a urologist.
- Some causes of male infertility can be identified and reversed (or improved) with *specific* surgery or medication while other causes can be identified but not reversed.
- Occasionally, the underlying cause of infertility or an abnormal semen analysis cannot be identified, in which case it is termed **idiopathic**. These cases may be amenable to *empiric treatment to improve the chances of conception.*

MALE REPRODUCTIVE PHYSIOLOGY

Hormone Classification

- Both **peptide** and **steroid** hormones are required for communication in the reproductive axis.
- Receptor location and binding in plasma?



Source: McAninch JW, Lue TF: *Smith & Tanagho's General Urology*, 18th Edition: www.accessmedicine.com

Peptide Hormones

- Peptide hormones are small secretory proteins that bind receptors on the cell surface membrane and induce a series of intracellular events.
- Hormone signals are transduced by second-messenger pathways whose actions culminate in the phosphorylation of various proteins that alter cell function.
- The key peptide hormones of the HPG axis are luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Steroid Hormones

- Steroid hormones are derived from cholesterol and, unlike peptide hormones, are not stored in secretory granules.
- As a result, steroid secretion is limited by the rate of production.
- Since they are lipophilic, steroid hormones are generally cell membrane permeable.
- In plasma, steroid hormones are largely bound to serum proteins, with only a small “free” component available to diffuse into the intracellular space and bind receptors.
- Once bound to an intracellular receptor, steroids are translocated to deoxyribonucleic acid (DNA) recognition sites within the nucleus where they act by regulating the transcription of target genes.
- The key steroid hormones of the HPG axis are testosterone (T) and estradiol (E2).

The Hypothalamic–Pituitary-Gonadal

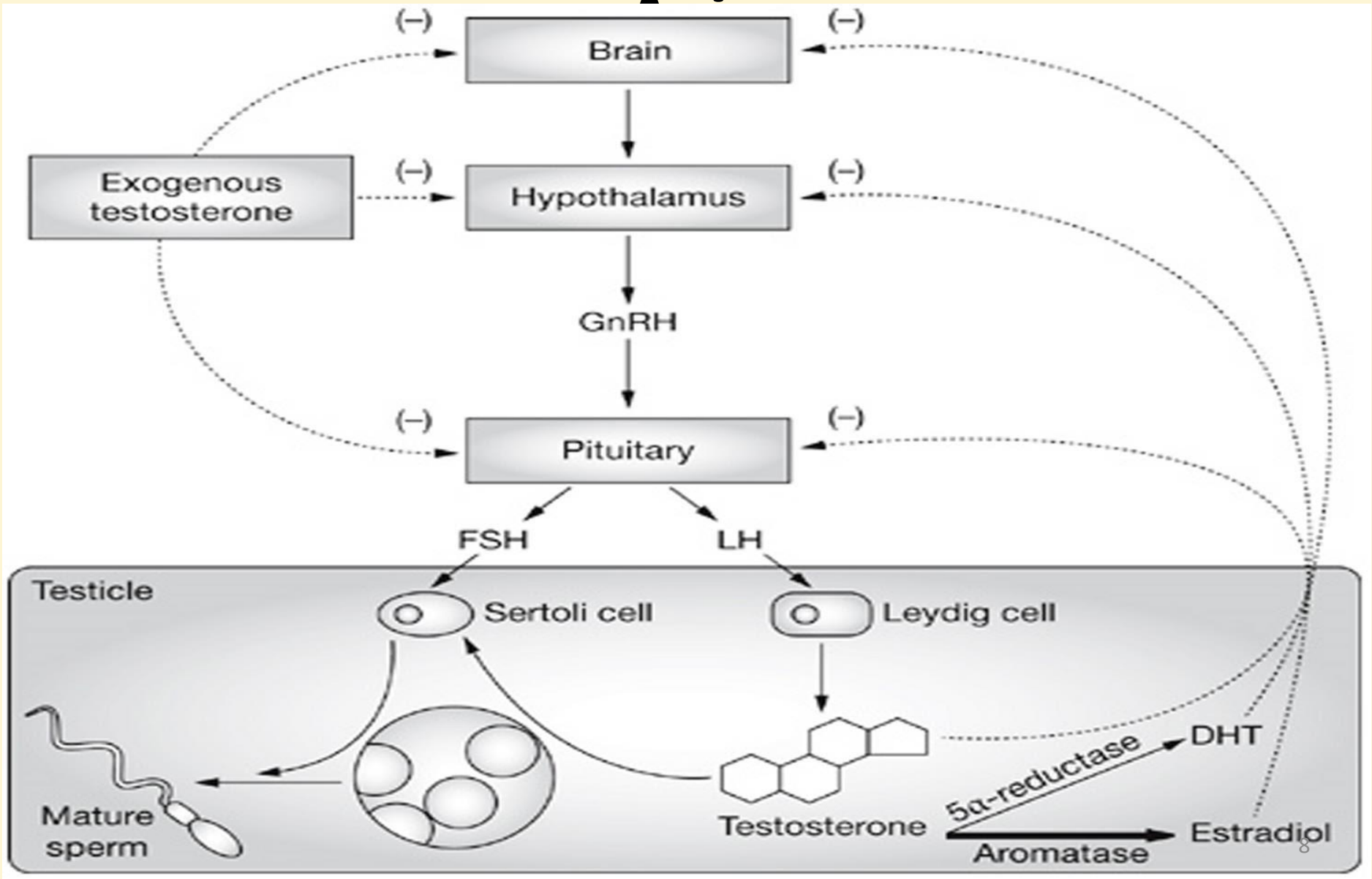


Table 44–1. Substances That Modulate GnRH Secretion.

GnRH Modulator	Type of Feedback	Examples
Opioids	Negative/inhibitory	β-endorphin
Catecholamines	Variable	Dopamine
Peptide hormones	Negative/inhibitory	FSH, LH
Sex steroids	Negative/inhibitory	Testosterone
Prostaglandins	Positive/stimulatory	PGE_2

FSH, follicle-stimulating hormone; LH, luteinizing hormone; PGE_2, prostaglandin E_2.

- Both FSH and LH are glycoprotiens hormones and bind cell surface receptors that activate adenylate cyclase and cause increases in intracellular cyclic adenosine monophosphate (cAMP).
- Prolactin is also produced and secreted by the anterior pituitary and can impact both the HPG axis and fertility.
- Normal prolactin levels may be important in the maintenance of libido.
- Elevated prolactin appears to abolish gonadotropin pulsatility by interfering with episodic GnRH release.
- Importantly, a markedly elevated prolactin may be evidence of a prolactin secreting adenoma of the pituitary (prolactinoma) that requires further evaluation.

- Normal male reproduction requires that the testes have both **endocrine (steroid production)** and **exocrine (sperm maturation and excretion)** function.
- Both of these functions are under the control of the HPG axis.
- **Steroidogenesis** occurs in the interstitial compartment, where Leydig cells reside.
- **Spermatogenesis** occurs in the seminiferous tubules with the support of Sertoli cells.

Endocrine testis

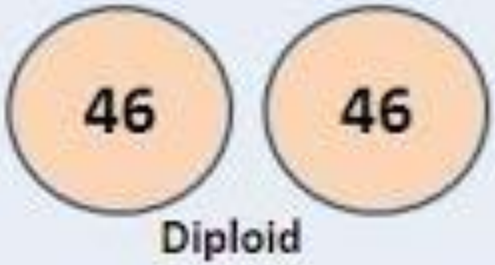
- Men normally produce approximately 5 g/day.
- Approximately 2% of testosterone circulates “free” in the serum and is considered the biologically active fraction. The remaining testosterone is bound to **sex hormone–binding globulin (SHBG)** and, to a slightly lesser extent, albumin within the blood.
- Elevated estrogens and thyroid hormone decrease plasma SHBG and increase the free testosterone fraction.
- Whereas androgens, growth hormone, and obesity increase SHBG levels and decrease the active androgen fraction.
- Further, as men age, SHBG levels rise.

Exocrine testis

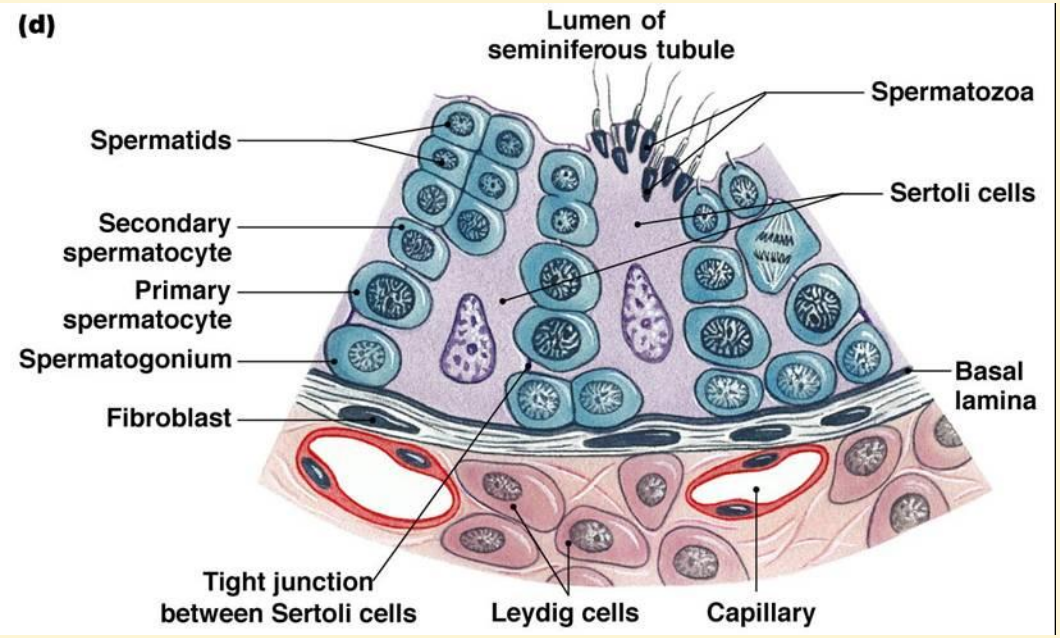
- FSH acts primarily on Sertoli cells within the seminiferous tubules to induce the production of a number of proteins necessary for spermatogenesis.
- Through these actions, seminiferous tubule growth is stimulated during development, and sperm production is initiated during puberty and maintained in adulthood.

SPERMATOGENESIS

- Spermatogenesis is a complex process during which primitive, multipotent stem cells divide to either renew themselves or produce daughter cells (**mitosis**) that further divide (**meiosis**) to become spermatozoa.
- These processes occur within the seminiferous tubules of the testis and 80–90% of testis volume is made up of the seminiferous tubules and germ cells at various developmental stages.

	Mitosis	Meiosis
Start		
End		

Seminiferous tubule: Cross section



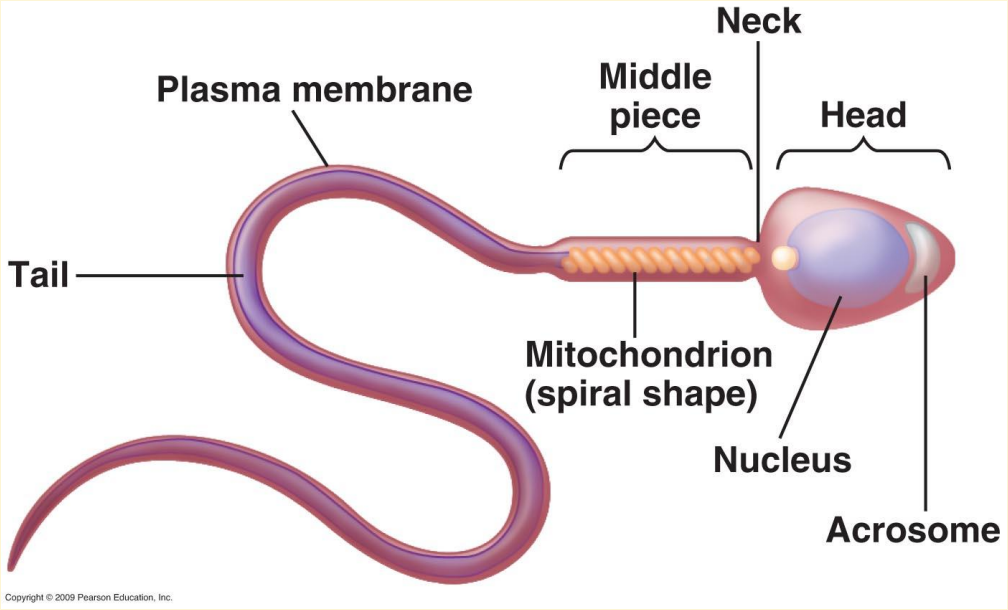
Spermiogenesis

- Spermiogenesis is the process by which spermatids mature to become elongated spermatozoa within the basilar compartment of the seminiferous tubules.

Spermiogenesis

This process requires several weeks, and requires the following:

(1) formation of the acrosome from the Golgi body
(2) formation of the flagellum from the centriole
(3) reorganization of the mitochondria around the midpiece
(4) extensive compaction of nuclear material
(5) elimination of residual cytoplasm.



DIAGNOSIS OF MALE INFERTILITY

History

- Important components of this history include
  - (1) duration of infertility, coital timing and frequency, and sexual health
  - (2) prior paternity or fertility treatments
  - (3) childhood illnesses and development
  - (4) medical illnesses, prior infections, and medications
  - (5) prior surgeries or traumas
  - (6) exposure to potential gonadal toxins, such as heat, radiation, chemical solvents, or pesticides.

PHYSICAL EXAMINATION

- A complete examination of the infertile male is important to identify general health issues associated with infertility. For example, the patient should be adequately virilized; signs of decreased body hair or gynecomastia may suggest androgen deficiency.
- The scrotal contents should be carefully palpated with the patient standing.

Testis Examination

- Two features should be noted about the testis: **size** and **consistency**.
- Size is assessed by measuring the long axis and width
  - mean testis length of 4.6 cm.
  - mean testis width of 2.6 cm.
  - Mean testis volume of 18.6 mL
- Consistency is more difficult to assess but can be described as firm (normal) or soft (abnormal).
- Both conditions (small and /or soft testis) suggest impaired spermatogenesis.

- The peritesticular area should also be examined.
- Irregularities of the epididymis,
- The presence or absence of the scrotal vas deferens is critical to observe, as 2% of infertile men may present with CAVD.
- Engorgement of the pampiniform plexus of veins in the scrotum is indicative of a varicocele. “**Bag of Worms**”. “**Valsalva Maneuver**”.

- Penile abnormalities such as hypospadias, abnormal curvature, or phimosis could result in inadequate delivery of semen to the upper vaginal vault during intercourse.
- Prostatic infection may be detected by the finding of a boggy, tender prostate on rectal examination.
- Prostate cancer, often suspected with unusual firmness or a nodule within the prostate, can occasionally be diagnosed in infertile men.
- Enlarged seminal vesicles, indicative of ejaculatory duct obstruction (EDO), may also be palpable on rectal examination.

LABORATORY TESTING

Semen Analysis

Table 2. Lower Reference Limits (WHO 2010) and Reference Value (WHO 1999) for Semen Characteristics

Parameter	Lower Reference Limits (WHO 2010)	Reference Value (WHO 1999)
Semen Volume	1.5 ml	≥ 2.0 ml
Sperm Concentration	15 million sperm/ ml	≥ 20 million sperm/ ml
Progressive Motility	32%	≥ 50%*
Total Motility	40%^	n/a
Vitality	58% live	≥ 75% live
Morphology (Strict criteria)	4% normal form	(≥ 15% normal form)#

*Grade a + b according to the WHO 1999 manual.
^Progressive motile + non-progressive motile sperm according to the WHO 2010 manual.
#No actual value given. Value was concluded from multi-centre studies.

- It is recommended that semen be collected after 48–72 hours of sexual abstinence.
- To establish a baseline of semen quality, at least two semen samples are needed.
- Because sperm motility decreases after ejaculation, the specimen should be analyzed within 1 hour of collection.
- During transit, the specimen should be kept at body temperature.

Semen Culture

- Seminal fluid that passes through the urethra is routinely contaminated with bacteria. This can make the interpretation of semen culture difficult.
- Semen cultures should only be obtained in selected situations and approximately 13% of infertile men will have positive semen cultures.

- Semen cultures should be considered when there is evidence of infection, including:
  - (1) a history of genital tract infection
  - (2) abnormal expressed prostatic secretion
  - (3) the presence of >1000 pathogenic bacteria per milliliter of semen
  - (4) the presence of >1 × 106 leukocytes/mL of semen (pyospermia).
- Gonorrhea is the most common infection found in positive semen cultures.

Hormone Assessment

- Evaluation of the pituitary–gonadal axis provides valuable information on the state of sperm production. Furthermore, abnormal function of the HPG axis can be an underlying cause of poor sperm production and infertility.

Endocrine profile in infertile men

Condition	Testosterone	FSH	LH	Prolactin
Primary testis failure	low	high	high	Nl
Hypogonadotropic hypogonadism	low	low	low	Nl
Hyperprolactinemia	low	low	low	high
Androgen resistance	high	high	high	Nl

Chromosomal Studies

- Subtle genetic abnormalities can present as male infertility.
- It is estimated that between 2% and 15% of infertile men with azoospermia (no sperm count) or severe oligospermia (low sperm counts) will harbor a chromosomal abnormality on either the sex chromosomes or autosomes.
- A blood test for cytogenetic analysis (karyotype) can determine if such a genetic anomaly is present.

Radiologic Testing

Scrotal Ultrasound

- Ultrasound of the scrotum is commonly performed for the evaluation of testicular, paratesticular, and scrotal lesions that cannot be completely evaluated on physical examination.
- Scrotal Doppler ultrasonography has been used to investigate varicoceles.
- Although diagnostic criteria that define a varicocele vary widely, a pampiniform venous diameter of >3 mm is considered abnormal.
- Retrograde blood flow through the veins with a Valsalva maneuver is a key radiologic feature of a varicocele.

Computed Tomography Scan or Magnetic Resonance Imaging of the Pelvis

- The imaging techniques of computed tomography (CT) and magnetic resonance imaging (MRI) can also be used to define reproductive tract anatomy.

Transrectal Ultrasound

- transrectal ultrasound (TRUS) can provide good anatomic detail of the prostate, seminal vesicles, and ejaculatory ducts.
- Dilation of the seminal vesicles (>1.5 cm in width) or ejaculatory ducts (>2.3 mm) in association with a cyst, calcification, or stones along the duct is highly suggestive of obstruction.
- Among infertile men, TRUS is indicated in cases of low ejaculate volume (<1.5 mL) not explained by retrograde ejaculation or abnormal hormones.

CAUSES OF MALE INFERTILITY

- The causes underlying male infertility are numerous and best categorized by effects at one or more of the following levels:
  - Pretesticular .
  - Testicular.
  - Posttesticular.

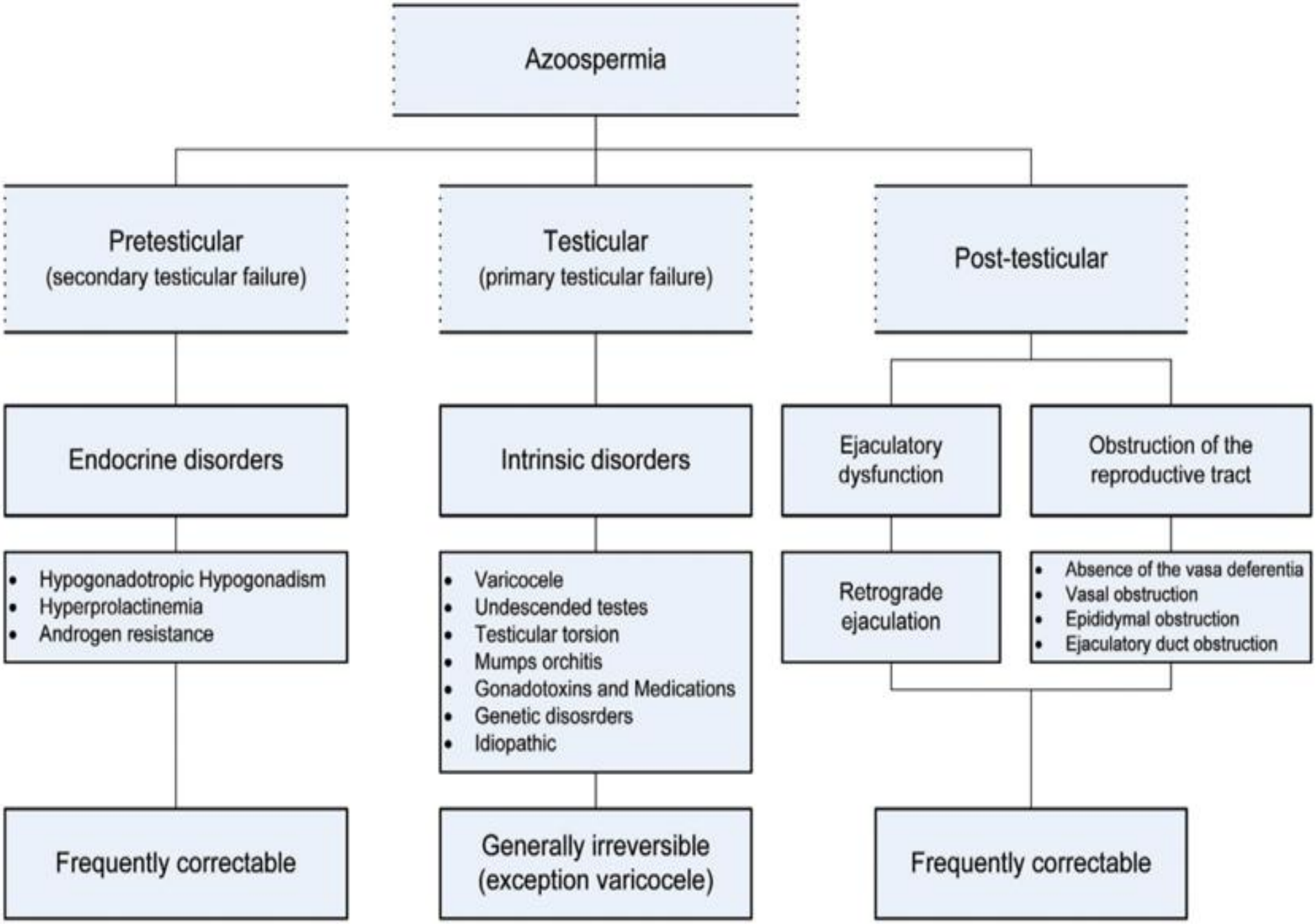


Figure 2 - Etiologies, mechanisms and prognoses of azoospermia.

PRETESTICULAR

Pretesticular causes of infertility

Hypothalamic disease
- Gonadotropin deficiency (Kallmann syndrome)
- Isolated LH deficiency ("fertile eunuch")
- Isolated FSH deficiency
- Congenital hypogonadotropic syndromes

Pituitary disease
- Pituitary insufficiency (tumors, infiltrative processes, operation, radiation, deposits)
- Hyperprolactinemia
- Exogenous hormones (estrogen-androgen excess,glucocorticoid excess, hyper- and hypothyroidism)
- Growth hormone deficiency

TESTICULAR

- Many conditions that cause infertility act at the testicular level.
- Unlike many pretesticular conditions, which are treatable with hormonal manipulation, testicular defects are mostly irreversible.

Testicular causes of infertility

- Klinefelter syndrome
- Noonan syndrome
- Myotonic dystrophy
- Vanishing testis syndrome (bilateral anorchia)
- Sertoli-cell-only syndrome (germ cell aplasia)
- Y chromosome microdeletions
- Gonadotoxins (radiation, drugs)
- Systemic disease (renal failure, liver failure, sickle cell anemia)
- Defective androgen activity
- Testis injury (orchitis, torsion, trauma)
- Cryptorchidism
- Varicocele
- Idiopathic

Klinefelter Syndrome

- Klinefelter syndrome is the most common chromosomal aneuploidy and a common genetic cause of azoospermia.
- The **classic triad** of findings is small, firm testes; gynecomastia; and azoospermia.
- Some men may present with delayed sexual maturation, increased height, decreased intelligence, varicosities, obesity, diabetes, leukemia, increased likelihood of extragonadal germ cell tumors, and breast cancer
- Among men with Klinefelter syndrome, 90% have an extra X chromosome (47,XXY) and 10% are mosaic, with a combination of XXY/XY chromosomes.
- The testes are usually <2 cm in length and always <3.5 cm;

Noonan Syndrome

- Also called male Turner syndrome, Noonan syndrome is associated with clinical features similar to Turner syndrome (45,X).
- However, the karyotype is either normal (46,XY) or mosaic (X/XY).
- Typically, patients have dysmorphic features like webbed neck, short stature, low-set ears, wide-set eyes, and cardiovascular abnormalities.
- At birth, 75% have cryptorchidism that limits fertility in adulthood.
- If testes are fully descended, then fertility is possible and likely.

Gonadotoxic Drugs

- Calcium channel blockers
- Allopurinol
- Cimetidine
- Sulfasalazine
- Nitrofurantoin
- Valproic acid
- Lithium
- Spironolactone
- Tricyclic antidepressants
- Colchicine
- Antipsychotics

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.
- Orchitis is observed in approximately 30% of postpubertal males who develop mumps parotitis.
- Testis atrophy is a significant and frequent result of viral orchitis but is less common with bacterial infections.

Torsion

- Ischemic injury to the testis secondary to twisting of the testis on the spermatic cord pedicle is common in prepubertal and early postpubertal boys.
- When diagnosed and corrected surgically within 6 hours of occurrence, the testis can usually be saved.
- Torsion may result in inoculation of the immune system with testis antigens that may predispose to later immunological infertility.
- It recognized that the “normal” contralateral mate of a torted testis could also exhibit histologic abnormalities.

Trauma

- Trauma to the testis can result in infertility.
- 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 albuginea should be surgically explored and repaired to minimize exposure of testis tissue to the body.

Cryptorchidism

- Undescended testis is a common urologic problem, observed in 0.8% of boys at 1 year of age.
- It is considered a developmental defect and places the affected testis at higher risk of developing testicular germ cell cancer.
- Although the newborn undescended testis is morphologically normal, deterioration in germ cell numbers is often seen by 2 years of age.
- The contralateral, normally descended testis is also at increased risk of harboring germ cell abnormalities.
- Thus, males with either unilaterally or bilaterally undescended testes are at risk for infertility later in life.

Varicocele

- Varicocele is defined as dilated and incompetent veins within the pampiniform plexus of spermatic cord.
- Varicocele has been described as the most common surgically correctable cause of male subfertility.
- This is a disease that develops during puberty when both endocrine and exocrine function of the testicle dramatically increases, along with testicular blood flow.

- A left-sided varicocele is found in 15% of healthy young men. In contrast, the incidence of a left varicocele in subfertile men approaches 40%.
- Bilateral varicoceles are uncommon in healthy men (<10%) but are palpated in up to 20% of subfertile men.

- Several anatomic features contribute to the predominance of left-sided varicoceles.
- The left internal spermatic vein is longer than the right and it typically joins the left renal vein at a right angle compared with the oblique insertion of the right spermatic vein into the inferior vena cava.
- As a result of these characteristics, higher venous pressures are transmitted to the left spermatic cord veins and result in retrograde reflux of blood.

- Varicoceles are associated with testicular atrophy and varicocele correction can reverse atrophy in adolescents.
- There is strong evidence that the varicocele affects semen quality.
- Varicocele can cause abnormalities in concentration, motility, viscosity and morphology; however, **deficits in motility can be the most profound**.
- The finding of semen abnormalities constitutes the most common indication for varicocele surgery in infertile men.

Idiopathic

- It has been estimated that nearly half of male infertility has no readily identifiable cause.
- The etiology of male infertility is likely multifactorial, encompassing genetic, endocrine, and environmental factors.
- In addition, modifiable lifestyle characteristics may make a significant contribution to the disease.
- The effects of physical activity, obesity, alcohol and tobacco use, psychological stress, and cell phone usage on male infertility are under study.

POSTTESTICULAR

- Reproductive tract obstruction
  - Congenital blockages
    - Congenital absence of the vas deferens (CAVD)
    - Young syndrome
    - Ejaculatory duct obstruction
  - Acquired blockages
    - Vasectomy
    - Groin surgery
- Disorders of sperm function or motility
  - Immotile cilia syndromes
  - Maturation defects
  - Infection
- Disorders of coitus
  - Impotence
  - Hypospadias
  - Timing and frequency

SURGICAL TREATMENTS

Varicocele

- The association of varicoceles with male infertility is well established.
- Several treatment modalities, both surgical and nonsurgical, are available for varicoceles. These include ligation of the veins through the inguinal or subinguinal approaches; percutaneous embolization; and laparoscopy.
- The common goal of all treatments is to stop the retrograde flow of venous blood through the internal spermatic veins.

Varicocele treatments: comparison of outcomes

Outcome parameter	Treatment		
	Incisional	Laparoscopic	Radiologic
Semen improvement	66%	50–70%	60%
Pregnancy rate	35%	12-32%	10-50%
Recurrence	0-15%	5-25%	0-10%
Technical failure	Negligible	Small	10-15%
Pain pills	9.4	11	Minimal
Days to work	5.0	5.3	1

- An overall complication rate of 1% is associated with the incisional approach, compared with a 4% complication rate for laparoscopy and 10–15% for radiologic occlusion.
- A significant problem with the radiologic approach is technical failure, meaning the inability to access and occlude the spermatic vein.

Vasectomy Reversal

- More than 500,000 men per year undergo vasectomy in the United States, and nearly 6% will eventually wish to have their vasectomy reversed.
- The most common reasons relate to changes in a man's social circumstances and include remarriage and the loss of a child.

- Several methods have been described for vasovasostomy.
- In general, either a single-layer anastomosis or a double-layer anastomosis is performed.

Epididymal Sperm Aspiration

- Epididymal sperm aspiration may be performed by two distinct techniques.
- With **microscopic epididymal sperm aspiration (MESA),** sperm are directly collected from a single, isolated epididymal tubule.
- After sperm are obtained, the epididymal tubule is closed with fine, microscopic suture, and the sperm are processed.

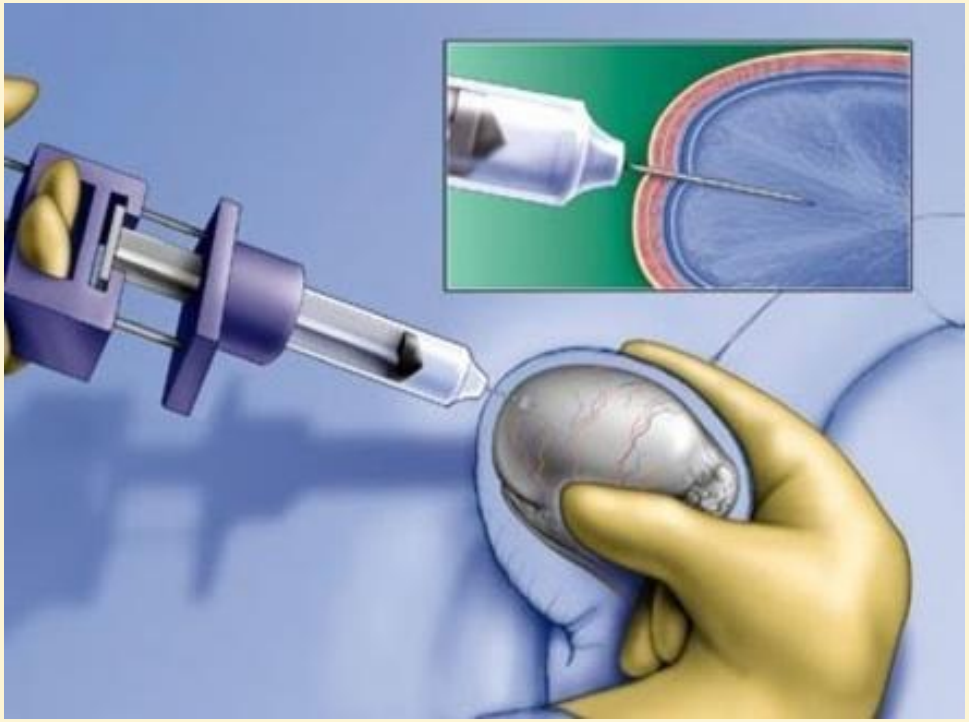
- When the epididymis is palpable, sperm may also be obtained with **percutaneous epididymal sperm aspiration (PESA)**.
- Although this technique is a less invasive, the blind insertion of a needle into the epididymis may be more likely to result in tubule injury.

Testis Sperm Extraction

- Testicular sperm retrieval procedures are highly variable.
- **Testicular sperm extraction (TESE)** is indicated for patients in whom there is an unreconstructable blockage in the epididymis, or in cases of severe testis failure, in which so few sperm are produced that they cannot reach the ejaculate.

- In traditional TESE, a small piece of testis tissue is taken in a manner similar to that of a regular testis biopsy.
- It could be achieved with the aid of a surgical microscope (micro-TESE). The testis tissue is specially treated in the laboratory to separate sperm from other cells.

- When spermatogenesis is known or suspected to be normal, or is reduced but uniformly distributed throughout the testicle, then **testicular sperm aspiration (TESA)** should be considered.



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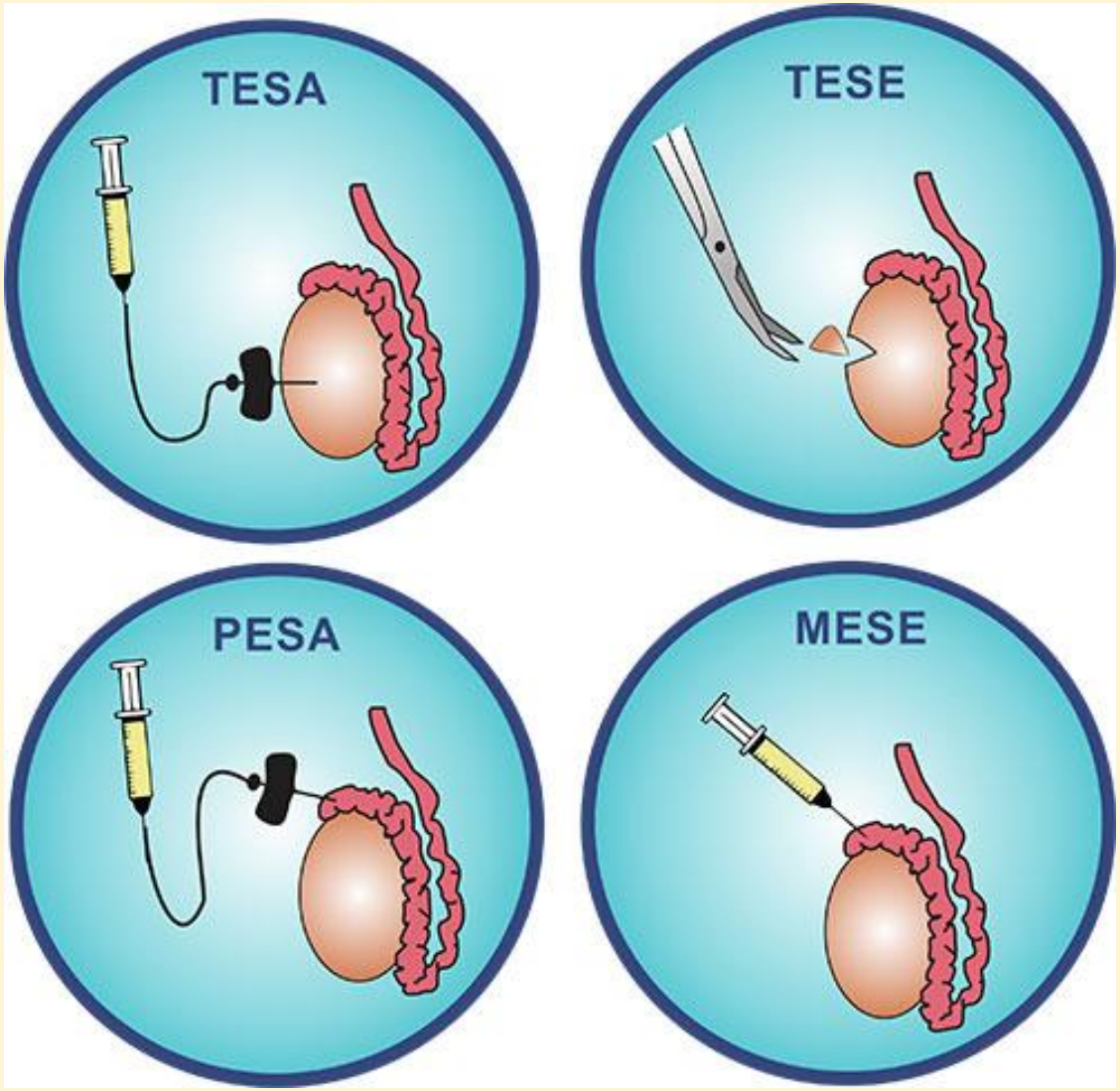

Orchidopexy

- Early orchidopexy may improve spermatogenesis later in life.
- Studies of undescended testis show that significant decreases in spermatogonial numbers occur between birth and 2 years of age.
- Orchidopexy has been recommended within 2 years of age to potentially prevent this germ cell degeneration.

Thank you