# Male infertility

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Practice Essentials

Causes of infertility in men can be explained by deficiencies in sperm formation , concentration, or transportation. This general division allows an appropriate w orkup of potential underlying causes of infertility and helps define a course of a ction for treatment.

Signs and symptoms

***The initial step in the evaluation of an infertile male is to obtain a thorough medical and urologic history. Such a history should include consideration of the following:

1. Duration of infertility
2. Previous fertility in the patient and the partner
3. Timing of puberty (early, normal, or delayed)
4. Childhood urologic disorders or surgical procedures
5. Current or recent acute or chronic medical illnesses
6. Sexual history
7. Testicular cancer and its treatment
8. Social history (eg, smoking and alcohol use)
9. Medications
10. Family history
11. Respiratory disease
12. Environmental or occupational exposure
13. Spinal cord injury

***The physical examination should include a thorough inspection of the follo wing:

1. Testicles (for presence, size, consistency, and bilateral symmetry)
2. Epididymis (for presence bilaterally, as well as any induration, cystic changes , enlargement, or tenderness)
3. Vas deferens (for presence bilaterally, as well as any defects, segmental dyspl asia, induration, nodularity, or swelling)
4. Spermatic cord (for varicocele)
5. Penis (for anatomic abnormalities, strictures, or plaques)
6. Rectum (for abnormalities of the prostate or seminal vesicles)
7. Body habitus

Depending on the findings from the history, detailed examination of other body functions may also be warranted.

Diagnosis

The semen analysis is the cornerstone of the male infertility workup and include s assessment of the following:

1.Semen volume (normal, 1.5-5 mL)
2.Semen quality
3.Sperm density (normal, >20 million sperm/mL)
4.Sperm motility (normal, >60% of sperm having normal movement)
5.Sperm morphology (>60% of sperm should be normal, and fewer than 2-3% s hould be immature)
6.Signs of infection – An increased number of white blood cells (WBCs) in the semen may be observed in patients with infectious or inflammatory processes
7.Other variables (eg, levels of zinc, citric acid, acid phosphatase, or alpha-gluc osidase)

Other laboratory tests that may be helpful include the following:

1. Antisperm antibody test
2. Hormonal analysis
3. Imaging studies employed in this setting may include the following:

Transrectal ultrasonography

Scrotal ultrasonography

Vasography

An abnormal postcoital test result is observed in 10% of infertile couples. Indica

tions for performing a postcoital test include semen hyperviscosity, increased or decreased semen volume with good sperm density, or unexplained infertility.
If the test result is normal, consider sperm function tests, such as the following:
Capacitation assay
Acrosome reaction assay
Sperm penetration assay
Hypoosmotic swelling test
Inhibin B level
Vitality stains
Testicular biopsy is indicated in azoospermic men with a normal-sized testis an d normal findings on hormonal studies to evaluate for ductal obstruction, to furt her evaluate idiopathic infertility, and to retrieve sperm.
Management
***The following causes of infertility, if identified, can often be treated by medi cal means:
1. Endocrinopathies
2. Antisperm antibodies
3. Retrograde ejaculation
4. Poor semen quality or number
5. Lifestyle issues
6. Infections
*****Surgical interventions to be considered include the following:
1. Varicocelectomy
2.Vasovasostomy or vasoepididymostomy
3. Transurethral resection of the ejaculatory ducts
4. Sperm retrieval techniques
5. Electroejaculation
6. Artificial insemination
7. Assisted reproduction techniques
8.In vitro fertilization
9. Gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIF T)

10. Intracytoplasmic sperm injectioninjection

**Background**

Infertility is defined as the inability to achieve pregnancy after one year of unpr otected intercourse.

An estimated 15% of couples meet this criterion and are considered infertile, wi th approximately 35% due to female factors alone, 30% due to male factors alon e, 20% due to a combination of female and male factors, and 15% unexplained.

Conditions of the male that affect fertility are still generally underdiagnosed and undertreated.

Causes of infertility in men can be explained by deficiencies in sperm formation , concentration (eg, oligospermia [too few sperm], azoospermia [no sperm in the ejaculate]), or transportation. This general division allows an appropriate worku p of potential underlying causes of infertility and helps define a course of action for treatment.

The initial evaluation of the male patient should be rapid, noninvasive, and cost-effective, as nearly 70% of conditions that cause infertility in men can be diagno sed with history, physical examination, and hormonal and semen analysis alone. More detailed, expensive, and invasive studies can then be ordered if necessary .

Treatment options are based on the underlying etiology and range from optimizi ng semen production and transportation with medical therapy or surgical proced ures to complex assisted reproduction techniques. Technological advancements have made conceiving a child possible with as little as one viable sperm and one egg.

Although the workup was traditionally delayed until a couple was unable to con ceive for 12 months, evaluation may be initiated at the first visit in slightly older couples.

**Pathophysiology**

Gonadal and sexual functions are mediated by the hypothalamic-pituitary-gonadal axis, a closed-loop system with feedback control from the testicles.

The hypothalamus, the primary integration center, responds to various signals from the CNS, pituitary gland, and testicles to secrete gonadotropin-releasing hormone (GnRH) in a pulsatile pattern approximately every 70-90 minutes. The half-life of GnRH is 2-5 minutes. Release of GnRH is stimulated by melatonin from the pineal gland and inhibited by testosterone, inhibin, corticotropin-releasing hormone, opiates, illness, and stress. GnRH travels down the portal system to the anterior pituitary, located on a stalk in the sella turcica, to stimulate the release of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH).

FSH and LH, (glycopeptides with a molecular weight of 10,000 daltons, are each composed of an alpha chain that is identical to that of human chorionic gonadotropin (HCG) and thyroid-stimulating hormone (TSH), but with a beta chain that is unique for each).

FSH has a lower plasma concentration and longer half-life than LH, and it has less obvious pulsatile changes. The pulsatile nature of GnRH is essential to normal gonadotropin release; a continuous stimulation inhibits their secretion.

The hypothalamus also produces thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP), both of which stimulate prolactin release from the anterior pituitary, and dopamine, which inhibits prolactin release. Men with elevated prolactin levels present with gynecomastia, diminished libido, erectile dysfunction, and occasionally galactorrhea. Prolactin inhibits the production of GnRH from the hypothalamus and LH and FSH from the pituitary. Gonadotropin release is modulated by various other signals, such as estradiol (a potent inhibitor of both LH and FSH release), and inhibin from the Sertoli cell, which causes a selective decrease in FSH release.

FSH and LH are released into system circulation and exert their effect by binding to plasma membrane receptors of the target cells. LH mainly functions to stimulate testosterone secretion from the Leydig cells of the testicle, while FSH stimulates Sertoli cells to facilitate germ cell differentiation.

Testosterone is secreted in a diurnal pattern, peaking early in the morning. In th

e body, testosterone circulates 2% in the free form, 44% bound to sex hormone–binding globulin (SHBG), and 54% bound to albumin. Testosterone is converted to dihydrotestosterone (DHT) by the action of 5-alpha reductase, both locally and in the periphery, and to estrogen in the periphery. Testosterone and estradiol function as feedback inhibitors of gonadotropin release.

The testicle contains the Leydig cells and the Sertoli cells and is covered by the tunica albuginea, which also provides septae that divide it into approximately 200-350 pyramids. These pyramids are filled with the seminiferous tubules. A normal testicle contains 600-1200 seminiferous tubules with a total length of approximately 250 meters. The interstitium between the seminiferous tubules contains the Leydig cells, fibroblasts, lymphatics, blood vessels, and macrophages. Histologically, Leydig cells are polygonal with eosinophilic cytoplasm. Occasionally, the cytoplasm contains crystalloids of Reinke after puberty.

Seminiferous tubules are made up of Sertoli cells and germ cells and are surrounded by peritubular and myoid cells.

Sertoli cells are columnar, with irregular basal nuclei that have prominent nucleoli and fine chromatin. They rest on the basement membrane and serve mainly to: 1.support, nourish, and protect the developing germ cells.

2. Provide a blood-testis barrier to provide a microenvironment that facilitates spermatogenesis and maintains the germ cells in an immunologically privileged location.

3. Sertoli cells also secrete inhibin, which provides negative feedback on the hypothalamus, and androgen-binding protein, which helps modulate androgen activity in the seminiferous tubules.

In addition to FSH, Sertoli cell function is modulated by intratesticular testosterone and signals from peritubular myoid cells.

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Germ cells (precursors to spermatozoa) are derived from the gonadal ridge and migrate as gonadocytes to the testicle before testicular descent. In response to FSH stimulation at puberty, germ cells become spermatogonia and undergo an ordered maturation to become spermatozoa. The entire process of development from spermatogonium to spermatid takes 74 days and is described in 14 steps; as t

hey mature, the developing spermatids progress closer to the lumen of the semin iferous tubule.

Spermatogonia rest on the basement membrane and contain dense nuclei and pr ominent nucleoli. Three types are described: A dark (Ad), A pale (Ap), and B ce lls. Ad cells (stem cells) divide to create more Ad cells (stem cell renewal) or di fferentiate into daughter Ap cells every 16 days. Ap cells mature into B spermat ogonia, which then undergo mitotic division to become primary spermatocytes, which are recognized by their large centrally located nuclei and beaded chromat in. The mitotic division does not result in complete separation; rather, daughter cells maintain intracellular bridges, which have functional significance in cell si gnaling and maturation.

Primary spermatocytes undergo meiosis as the cells successively pass through t he preleptotene, leptotene, zygotene, and pachytene stages to become secondary spermatocytes. During this time, the cells cross from the basal to the adluminal compartments. Secondary spermatocytes contain smaller nuclei with fine chrom atin. The secondary spermatocytes undergo a second meiosis and become sperm atids. This reduction division (ie, meiosis) results in a haploid chromosome num ber. Therefore, a total of 4 spermatids are made from each spermatocyte.

Next, the spermatids undergo the process of spermiogenesis (through stages na med Sb1, Sb2, Sc, Sd1, and Sd2), which involves the casting of excess cytoplas m away as a residual body, the formation of the acrosome and flagella, and the migration of cytoplasmic organelles to their final cellular location. The acrosom e, a derivative of the Golgi process, surrounds the nucleus anteriorly and contain s enzymes necessary to penetrate the ovum. The mature spermatid is then locate d adjacent to the tubule lumen and contains dark chromatin with an oval-shaped nucleus.

After their release from the Sertoli cells into the lumen of the seminiferous tubul es, the spermatids successively pass through the tubuli recti, rete testis, ductuli e fferentes, and, finally, the epididymis. The epididymis is a 3- to 4-cm long struc ture with a tubular length of 4-5 m. As sperm move from the head to the tail, the y mature and acquire fertilization capacity. Sperm from the head move with im mature wide arcs and are generally unable to penetrate the egg, while those fro

m the tail propel forward and have better penetration capacity. The transit time varies with age and sexual activity but is usually from 1-12 days. The epididymis additionally secretes substances for sperm nutrition and protection such as glycerophosphorylcholine, carnitine, and sialic acid.

Sperm next enter the vas deferens, a 30- to 35-cm muscular conduit of Wolffian duct origin. The vas is divided into the convoluted, scrotal, inguinal, retroperitoneal, and ampullary regions and receives its blood supply from the inferior vesicle artery. In addition to functioning as a conduit, the vas also has absorptive and secretory properties. During emission, sperm are propelled forward by peristalsis. After reaching its ampullary portion behind the bladder, the vas joins with the seminal vesicles, at the ejaculatory duct, which empties next to the verumontanum of the prostate. During ejaculation, the ejaculate is propelled forward by the rhythmic contractions of the smooth muscle that surrounds the ducts and by the bulbourethral muscles and other pelvic muscles. Bladder neck closure during ejaculation is vital to ensure antegrade ejaculation.

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**Normal ejaculation:**

1. Volume ranges from 1.5 to 5 mL

2. PH level of 7.05-7.8.

3. The seminal vesicles provide 40-80% of the semen volume, which includes:

1. Fructose for sperm nutrition,

2. Prostaglandins and other coagulating substances,

3. and bicarbonate to buffer the acidic vaginal vault. Normal seminal fructose concentration is 120-450 mg/dL, with lower levels suggesting ejaculatory duct obstruction or absence of the seminal vesicles.

4. The prostate gland contributes approximately 10-30% (0.5 mL) of the ejaculate. Products include enzymes and proteases to liquefy the seminal coagulum. This is usually occurs within 20-25 minutes. The prostate also secretes zinc, phospholipids, phosphatase, and spermine.

5. The testicular-epididymal component includes sperm and comprises about 5% of the ejaculate volume.

6. The semen is also composed of secretions from the bulbourethral (Cowper) gl

ands and the (periurethral) glands of Litre, each producing 2-5% of the ejaculate volume, serving mainly to lubricate the urethra and to buffer the acidity of the r esidual urine.

The ordered sequence of release is important for appropriate functioning.

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For conception, sperm must reach the cervix, penetrate the cervical mucus, migr ate up the uterus to the fallopian tube, and undergo capacitation and the acrosom e reaction to digest the zona pellucida of the oocyte, attach to the inner membra ne, and release its genetic contents within the egg. The cervical mucus changes consistency during the ovulatory cycle, being most hospitable and easily penetra ted at mid cycle. After fertilization, implantation may then take place in the uter us. Problems with any of these steps may lead to infertility.

History

The initial step in the evaluation of an infertile male is to obtain a thorough med ical and urologic history. Important considerations include the duration of infert ility, previous fertility in the patient and the partner, and prior evaluations. The c ouple should be asked specifically about their sexual habits, including their leve l of knowledge of the optimal timing of intercourse and the use of potentially sp ermatocytic drugs and lubricants.

Patients should be asked about a history of childhood illnesses such as testicular torsion, postpubertal mumps, developmental delay, and precocious puberty, as well as urinary tract infections, sexually transmitted diseases, and bladder neck surgery. A history of neurological diseases, diabetes, and pulmonary infections should be elicited. Anosmia (lack of smell), galactorrhea, visual-field defects, a nd sudden loss of libido could be signs of a pituitary tumor. The status of the pa rtner's workup should also be known.

Timing of puberty (early, normal, or delayed)

Precocious puberty, defined as the onset of puberty before age 9 years in males, may be the sign of a serious underlying endocrinologic disorder. Hormonally ac tive tumors from the testicle, adrenal gland, or pituitary, along with adrenal hyp erplasia, may result in early puberty.

In contrast, a delay in puberty may be caused by problems with testosterone secr

etion due to hypothalamic, pituitary, or testicular insufficiency or to end-organ a ndrogen insensitivity.

Childhood urological disorders or surgery

Both unilateral and bilateral cryptorchidism are associated with a decrease in sp erm production and semen quality, regardless of the timing of orchidopexy.

Patients with hypospadias may not place the semen at the cervical os.

Prenatal exposure to diethylstilbestrol (DES) may cause epididymal cysts and cr yptorchidism.

Prior bladder neck procedure, such as a V-Y plasty performed at the time of uret eral reimplantation, may lead to retrograde ejaculation.

The vas deferens or the testicular blood supply may be injured or ligated at the t ime of inguinal surgery, hernia repair, hydrocelectomy, or varicocelectomy.

Testicular torsion and trauma may result in testicular atrophy and the production of antisperm antibodies.

Medical history

In males, decreased general health status appears to be associated with impaired male reproductive health.Effects of specific disorders on fertility include the fol lowing:

Diabetes may cause autonomic neuropathy, neurogenic impotence, and retrogra de ejaculation

Obesity alters hormonal metabolism, leading to increased peripheral conversion of testosterone to estrogen and decreased luteinizing hormone (LH) pulse amplit ude, and has been linked with reduced sperm concentration

Sickle cell disease may lead to direct testicular ischemia and damage

Patients with sickle cell disease or thalassemia may have infertility due to hemo siderosis from multiple blood transfusions

Chronic kidney disease leads to hypogonadism and feminization

Liver disease may result in decreased male secondary sexual characteristics, test icular atrophy, and gynecomastia due to increased estrogen levels

Hemochromatosis leads to hypogonadism and signs of androgen deficiency wit hout gynecomastia and is associated with decreased estradiol levels

Postpubertal mumps may lead to testicular atrophy

Sexually transmitted diseases and tuberculosis can cause obstruction of the vas deferens or epididymis

Mycoplasma fastens itself to sperm, decreasing sperm motility

Smallpox, prostatitis, orchitis, seminal vesiculitis, and urethritis may lead to obs tructive azoospermia

Acute and chronic medical illnesses

Patients should be asked about recent acute febrile illnesses, which may tempor arily suppress gonadotropin release. The decrease in sperm production may not be realized until 1-3 months later.

Anesthesia, surgery, starvation, myocardial infarction, hepatic coma, head injur y, stroke, respiratory failure, congestive heart failure, sepsis, and burns are assoc iated with a suppression of gonadotropin release, possibly through an increase i n dopamine and opiate levels.

Chronic medical illnesses may directly suppress sex hormone production and sp erm production, leading to end-organ failure.

Sexual history

The frequency, timing, and methods of coitus and knowledge of the ovulatory c ycle should be elicited. Studies show that the optimal timing for intercourse is e very 48 hours at mid cycle.

Lubricants such as Surgilube, Keri lotion, KYJelly, and saliva are spermatotoxic , whereas egg whites, peanut oil, vegetable oil, and petroleum jelly are not know n to be spermatotoxic but still should be used in only the smallest amounts possi ble if needed for lubrication during intercourse.

Testicular cancer

Testicular cancer is associated with impaired spermatogenic function, even befo re orchiectomy, with a degree of dysfunction higher than that explained by local tumor effect.

Oligospermia is observed in more than 60% of patients at the time of diagnosis of testicular cancer.

Germ cell tumors may to share common etiological factors with testicular dysfu nction, such as testicular dysgenesis, androgen insensitivity, and cryptorchidism . Contralateral abnormalities of spermatogenesis are more common in patients

with testicular cancer. Sperm function often remains impaired, even after orchie ctomy.

Treatment for testicular cancer

Chemotherapy has a dose-dependent effect on germ cells. Alkylating agents, su ch as cyclophosphamide, mustine, and chlorambucil, severely alter the seminife rous tubules and destroy spermatogonia. (Note that chemotherapy is also mutag enic, so sperm should be donated before treatment, or attempts at conception sh ould be postponed until >1 year after treatment.)

Retroperitoneal lymph node dissection (RPLND) may impair emission (of seme n into the urethra) and/or cause retrograde ejaculation.[9]

Radiation therapy affects mainly type B spermatogonia and, possibly, spermato cytes. A dose of as little as 0.15 Gy may cause irreversible damage, although co mplete recovery may be possible if stem cell numbers are not depleted. After ex posure of less than 1 Gy, sperm production may return in 9-18 months, while 4-6 years may be necessary to recover sperm production after a dose of up to 5 Gy . Despite radiation therapy and chemotherapy, nearly two thirds of patients retai n the ability to father a child if the ejaculatory function is retained.

To potentially decrease the morbidity of adjunct therapy, select patients with gra de I germ cell tumors are now undergoing unilateral orchiectomy with surveilla nce. However, RPLND performed for salvage therapy is associated with a highe r risk of retrograde ejaculation than that performed initially.

Patients with reference range FSH levels at baseline usually observe an improve ment in semen parameters and sperm density after orchiectomy. This is thought to be unrelated to the orchiectomy, stress factors, and release of substances by t he tumor because decreased sperm counts are observed even before surgery and they do not return to baseline after surgery. Therefore, the disturbance that leads to testicular cancer is thought to be inherent and present in the primordial cell.

Patients with a testicular tumor in a solitary testicle may be offered a partial orc hiectomy in an attempt to retain fertility. Additionally, healthy testicular tissue a way from the tumor can be dissected free and cryopreserved at the time of orchi ectomy for future use in in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI).

Social history

Cigarette and marijuana smoking lead to a decrease in sperm density, motility, a nd morphology.

Abuse of anabolic steroids has been associated with hypogonadism as well as st ructural and genetic sperm damage.

Alcohol produces both an acute and a chronic decrease in testosterone secretion.

Emotional stress blunts GnRH release, leading to hypogonadism.

Excessive heat exposure from saunas, hot tubs, or the work environment may ca use a temporary decrease in sperm production.

Contrary to widely held beliefs, no evidence supports that wearing constrictive underwear, or "briefs," decreases fertility. Even with an elevation in temperature of 0.8-1° caused by wearing constrictive underwear, no changes in sperm para meters, no decrease in spermatogenesis, and no changes in sperm function are o bserved.

Medicines

Drugs that may impair male fertility include the following:

Spironolactone, cyproterone, ketoconazole, and cimetidine have antiandrogenic properties

Tetracycline lowers testosterone levels 20%

Nitrofurantoin depresses spermatogenesis

Sulfasalazine leads to a reversible decrease in sperm motility and density

ColchColchicine, methadone, methotrexate, phenytoin, thioridazine, and calciu m channel blockers have all been associated with infertility

Family history

Congenital midline defects, cryptorchidism, hypogonadotropism, and testicular atrophy in family members may be a sign of a congenital disease. A history of c ystic fibrosis (CF) or hypogonadism should be elicited.

Respiratory disease

Infertility and recurrent respiratory infections may be due to immotile cilia synd rome, which may be isolated or part of Kartagener syndrome (with situs inversu s).

CF is associated with congenital bilateral absence of the vas deferens (CBAVD)

, leading to obstructive azoospermia. While both copies of this recessive gene ar e necessary for clinical disease, the presence of only one copy may lead to CBA VD.

Young syndrome results in recurrent pulmonary infections and azoospermia due to inspissated material in the epididymis causing obstruction.

Environmental and/or occupational exposure

Many pesticides have estrogen-like effects.

Dibromochloropropane (DBCP) is a nematocide widely used in agriculture that causes azoospermia without recovery by an unknown mechanism.

Lead exposure depresses the hypothalamic-pituitary axis.

Carbon disulfide exposure from the rayon industry leads to semen, pituitary, an d hypothalamic changes.

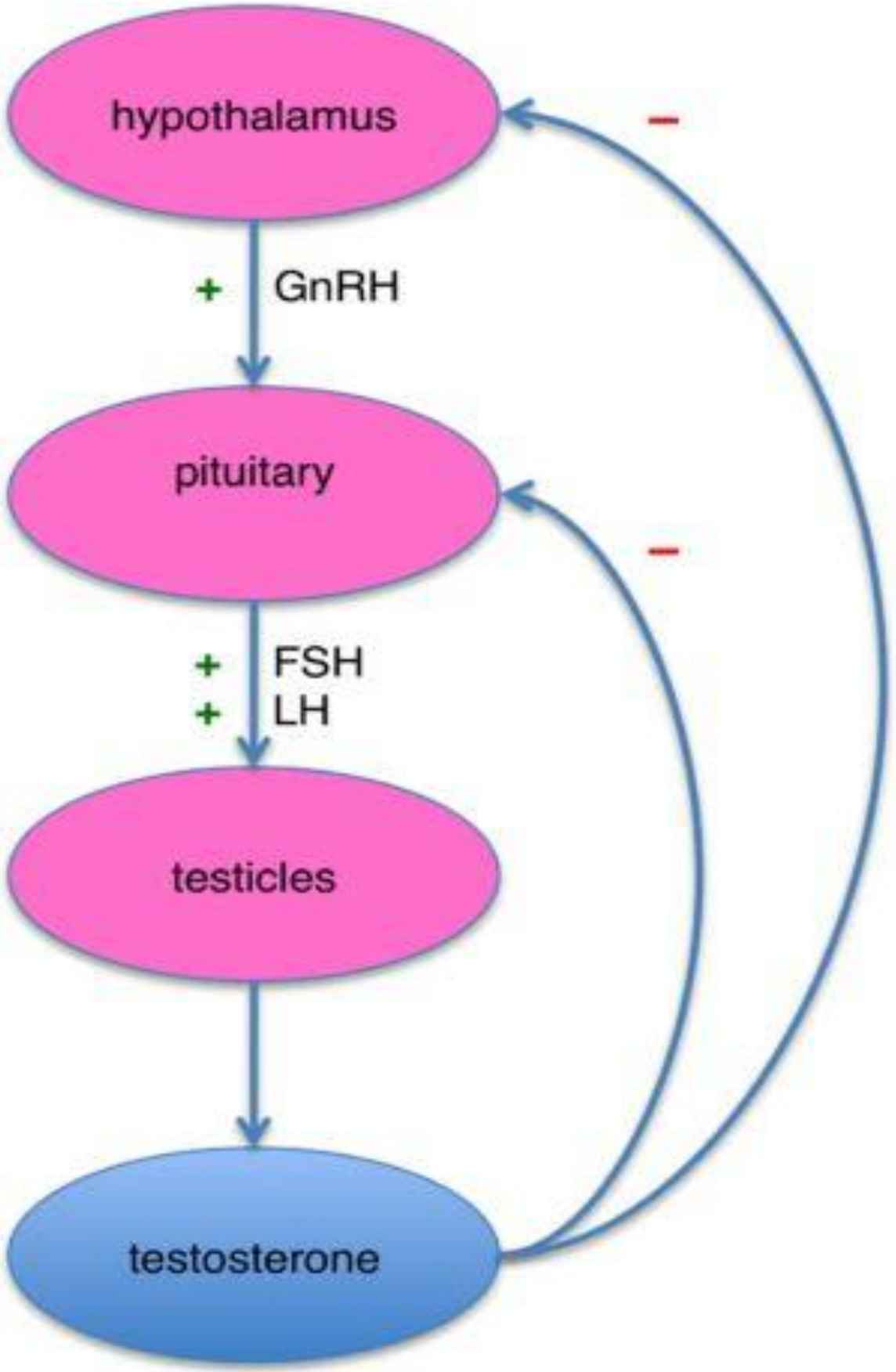
Heat exposure, as seen in workers in the steel and ceramic fields, decreases sper matocyte maturation.

Spinal cord injury

Severe spinal cord injury (SCI) may lead to anejaculation. These men may be tr eated with electroejaculation or sperm retrieval techniques.

In addition, the semen quality in patients with SCI may gradually decline. Withi n a year after injury, many of these patients have semen with dead sperm, with s igns of neutrophil infiltration on semen analysis.

In patients with SCI, sperm aspirated from the vas deferens show 54% motility and 74% viability, while only 14% motility and 26% viability is observed in eja culated sperm, which suggests an abnormality of seminal plasma.[14] Studies of seminal plasma point to functional failure of the prostate gland, likely from lac k of neurogenic stimulation, along with hyperactivation of the immune system, which is probably not triggered by microbial infection, as causal elements for in fertility related to SCI.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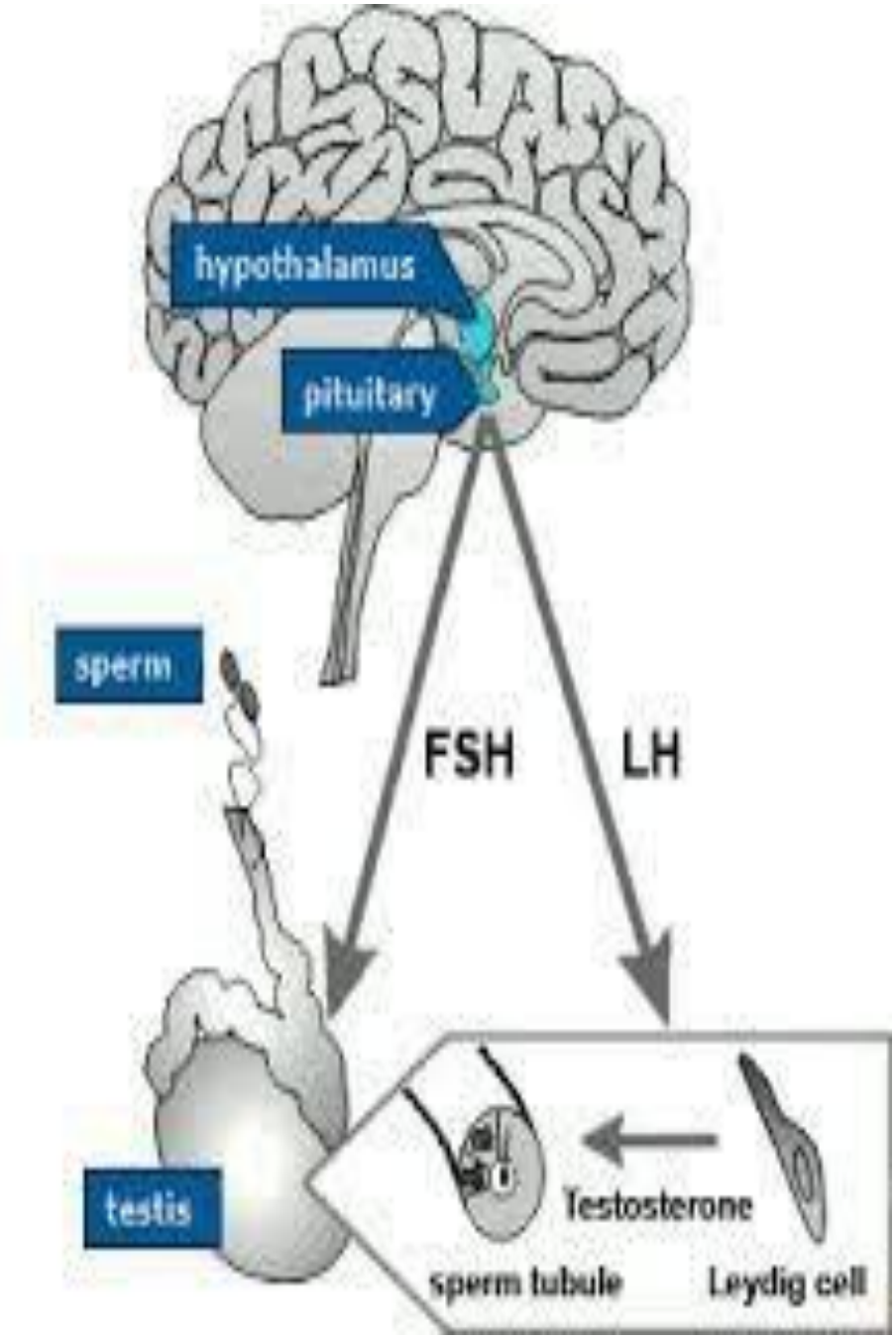
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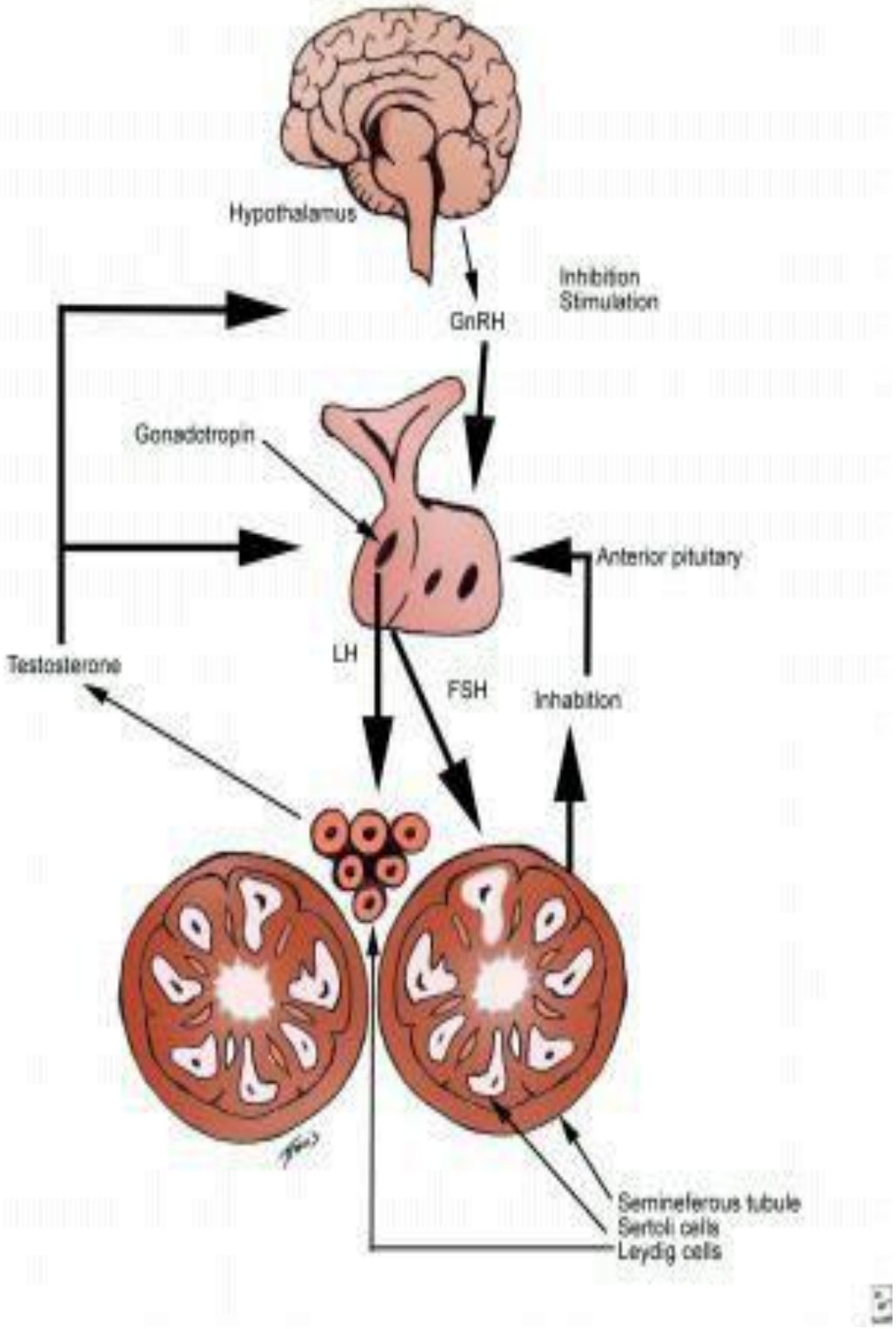
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