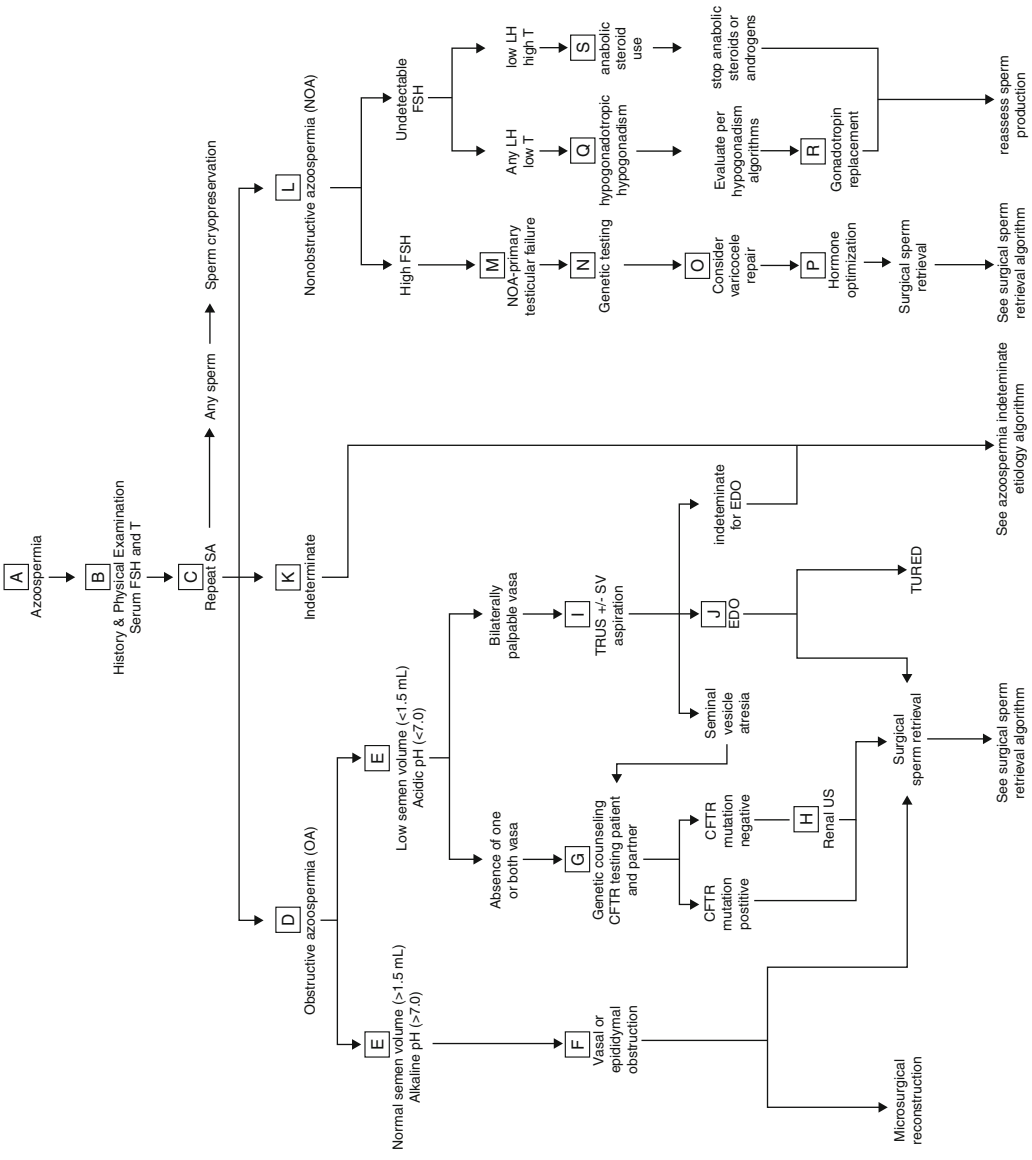
Chapter 3
Azoospermia



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Azoospermia refers to the clinical finding that sperm are not detectable in the ejaculate after centrifugation and microscopic analysis of two semen samples. This condition affects approximately 1 % of the general male population and 15 % of subfertile men. Azoospermia is generally indicative of either complete bilateral obstruction of the male excurrent ductal system (obstructive azoospermia) or severely impaired sperm production (nonobstructive azoospermia). Fertility is only possible in affected men through medical or surgical intervention. The goals of the diagnostic evaluation are to identify underlying etiologies that are of medical or prognostic significance, to identify genetic abnormalities that may affect the patient's offspring, and to guide the selection of medical or surgical therapy. The differential diagnosis of azoospermia is listed in Table 3.1.

(A)

The diagnosis of azoospermia requires the absence of sperm within the centrifuged pellets of two separate semen samples.

(B)

The initial evaluation of azoospermia should include a detailed medical history (Table 3.2), a directed physical examination (Table 3.3), and measurement of serum testosterone (T), and follicle stimulating hormone (FSH). This simple initial evaluation is usually sufficient to distinguish between suspected obstructive (OA) and nonobstructive azoospermia (NOA). Elevated serum FSH (>8 IU/L) suggests NOA due to testicular failure, which may occur with normal or low serum T. Very low serum FSH suggests NOA due to hypogonadotropic hypogonadism, and usually coexists with T deficiency.

(C)

Sperm are often intermittently present in the ejaculate of patients with severely impaired sperm production. Rare sperm detected upon repeat semen analysis in a patient who was previously azoospermic should be cryopreserved whenever possible. Ejaculated cryopreserved sperm may be used for assisted reproduction and obviate the need for surgical sperm retrieval. Intermittently azoospermic and severely oligozoospermic men (<5 million sperm/mL) should undergo the same diagnostic evaluation as azoospermic men prior to assisted conception. These men are at risk for transmissible genetic abnormalities that may affect their own health as well as that of any offspring and should undergo appropriately directed genetic testing.

(D)

OA occurs when testicular sperm production is normal but the male excurrent ductal system is blocked anywhere between the testis and urethra. OA should be suspected when testicular volume is normal (>12 mL per testis) and serum FSH within normal limits (1.5–8 IU/L), as would be expected when sperm production is not impaired.

The working diagnosis of OA is further supported by suggestive factors in the medical history, such as prior inguinal surgery or prior known fertility, and by signs on physical examination, including

epididymal fullness, induration, or non-palpable vasa deferentia. However, it is important to note that testicular volume may be normal and serum FSH may be in the upper range of normal in some cases of NOA. This is often seen in patients with histological maturation arrest, a form of NOA in which germ cell development fails to progress.

(E)

Approximately 70 % of ejaculated semen is derived from the seminal vesicles, which produce alkaline, fructose positive fluid that is delivered into the posterior urethra via the paired ejaculatory ducts along with a small volume (<5 % of total semen volume) of sperm-containing fluid from the testis. The remaining 20–30 % of the ejaculate comprises acidic fluid produced by the prostate, which does not pass through the ejaculatory ducts but rather enters the posterior urethra via many prostatic ducts. Knowledge of the fluid composition of ejaculated semen enables determination of the anatomic location of obstruction based upon the semen volume and pH. When the semen volume (<1.5 mL) and pH (>7.0) are normal, the alkaline high volume seminal vesicle component of the ejaculate must be present, and the obstruction must therefore be in the epididymis or vas deferens. Conversely, when the semen volume is low (<1.5 mL) and the pH is acidic (<7.0), fluid from the seminal vesicles is absent from the ejaculate. This implies that the seminal vesicles are either obstructed, as is the case in ejaculatory duct obstruction (EDO), or hypoplastic/absent, as is the case in congenital bilateral absence of the vas deferens (CBAVD).

(F)

For the classic OA patient with vasal or epididymal obstruction, options include bypass of the obstruction (vasoepididymostomy or vasovasostomy) and sperm extraction for intracytoplasmic sperm injection (ICSI). Treatment decisions should be individualized to each couple based upon the number of desired children, the duration of obstruction (if known), the female partner's fertility status, and access to a skilled reconstructive microsurgeon. Microsurgical reconstruction is generally favored when the couple desires multiple children, the obstructed interval is short (<15 years) and the female partner is young (<37 years old) and does not have risk factors for infertility. Sperm retrieval with ICSI is favored when the obstructed interval is long (>15 years), the female partner is older (>37 years old), or the female partner has known or suspected infertility.

(G)

Men with acidic, low semen volume semen, and absence of one or both vasa deferentia (congenital unilateral or bilateral absence of the vas deferens, CUAVD and CBAVD respectively) on physical examination should undergo genetic counseling and testing for mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which plays a central role in the embryological development of the seminal vesicles and vasa deferentia, and is critical for pulmonary and pancreatic function. More than 1,300 CFTR mutations have now been described that vary considerably in their effect on CFTR protein function. Approximately 1/25 North American Caucasians carries one mutated CFTR allele, but only patients with two mutated alleles are clinically affected. The phenotypic manifestations of disease in an individual patient depend on the severity of the paternal and maternal mutations that they have inherited, and range from overt cystic fibrosis (always associated with CBAVD) to isolated CBAVD with otherwise normal health. The prevalence of detectable CFTR

mutations in men with CBAVD is approximately 70 %, and is lower in men with CUAVD. CFTR mutation screening commonly includes testing for the 30–100 most prevalent point mutations and for a commonly encountered polymorphism known as the 5T allele that, when present, causes decreased production of functional CFTR protein. Negative CFTR mutation testing does not exclude the presence of less commonly detected mutations that are not included in standard mutational screening panels, which should be presumed to be present in all men with CBAVD who test negative for CFTR mutations. Therefore, CFTR testing should be performed in all female partners of men with CBAVD considering assisted reproduction. If the female is positive, genetic counseling and pre-implantation genetic diagnosis may be performed to select unaffected embryos for uterine transfer.

(H)

Patients with CBAVD who test negative for CFTR mutations and all men with CUAVD should undergo renal ultrasonography to evaluate for potential associated renal anomalies or agenesis. The association of vasal agenesis and renal anomalies is due to the common embryological origin of the vas deferens and kidney from the mesonephric duct. Renal agenesis is found in 26 % of men with CUAVD and 11 % of men with CBAVD.

(I)

In cases of low volume azoospermia when the vasa deferentia are palpable, EDO should be suspected. In such cases, transrectal ultrasonography (TRUS) is indicated. EDO is suggested by visualization of dilated seminal vesicles (>2 cm in anteroposterior diameter), dilated ejaculatory ducts, and/or the presence of midline prostatic cysts. Some experts advocate TRUS-guided needle aspiration of fluid from the seminal vesicles. Microscopic visualization of many sperm in the aspirated seminal fluid supports the diagnosis.

(J)

EDO may be treated by either transurethral resection of the ejaculatory ducts (TURED) or ICSI using surgically retrieved sperm. Some experts advocate transurethral laser incision of the ejaculatory ducts as an alternative to TURED. A midline prostatic cyst may cause compressive EDO and may be treatable by unroofing of the cyst alone. Treatment decisions should be individualized to each couple based upon their reproductive goals, the anatomic location of the obstruction relative to the bladder neck, the location of the obstruction within the ejaculatory ducts, and the fertility status of the female partner.

(K)

The initial evaluation may be indeterminate for the etiology of azoospermia in rare cases in which the history, physical examination, and serum FSH are discrepant. Typical patients have mildly low testicular volumes and/or serum FSH levels in the high normal to slightly elevated range. In such cases, exploratory surgery can be both diagnostic and therapeutic and is recommended. Genetic testing to exclude Karyotype abnormalities and Y chromosome microdeletions should be considered (see “N”).

(L)

NOA occurs when sperm production is either absent or so impaired that sperm fail to reach the ejaculate. NOA should be suspected when serum FSH is undetectable or elevated (>8 IU/L) and the testicles are small (<12 mL per testis) and/or soft in consistency. However, in some cases of NOA, testicular volume and FSH may be close to normal. The working diagnosis of NOA is further supported by suggestive factors in the medical history, such as a history of bilateral cryptorchidism, lifelong hypogonadism, gonadotoxin exposure, and by signs on physical examination, including flat epididymities or a gynecoid body habitus.

(M)

Primary testicular failure accounts for the vast majority of NOA and is usually characterized by an elevated serum FSH level. It is sometimes referred to as hypergonadotropic hypogonadism. This condition has many separate etiologies including Klinefelter syndrome (KS), gonadotoxin exposure, cryptorchidism, systemic illness, prior orchitis, testicular tumors, and Y chromosome microdeletions. Testosterone (T) deficiency may also be present.

(N)

Genetic testing is recommended in all men with NOA. The goals of testing are to identify genetic abnormalities that are medically important, that affect the prognosis for surgical sperm retrieval, or that may affect the health of offspring conceived by assisted reproduction. Karyotype abnormalities are found in 10–15 % of men with NOA, with Klinefelter syndrome (usually 47,XXY) being the most commonly detected abnormality. Men with KS have an excellent prognosis for surgical sperm retrieval, but are at risk for testosterone deficiency and osteoporosis, and may be at increased risk for breast cancer, diabetes, impairments in cognitive processing, and auto-immune disorders. Patients with translocations on inversions identified during Karyotyping should be sent for genetic counseling, as some of these lesions increase the risk for sperm and embryo aneuploidy. Pre-implantation genetic diagnosis should be considered.

Y chromosome microdeletions are found in approximately 10 % of men with NOA. Men with AZFa and AZFb deletions have been shown to have zero chance of sperm retrieval and are not candidates for sperm retrieval surgery and should be counseled towards use of donor sperm or adoption. On the contrary, men with AZFc deletions are excellent candidates for surgical sperm retrieval with retrieval rates of 70 % being consistently reported. Any sons conceived using sperm from a patient with a Y chromosome microdeletion will inherit the abnormal Y chromosome and the infertile phenotype.

(O)

Repair of grade II or III varicoceles may be beneficial in men with NOA. Rare sperm return to the ejaculate after varicocele repair in approximately one third of cases. This may obviate the need for surgical sperm retrieval. However, in this scenario varicocele repair is unlikely to improve sperm production sufficiently to enable reproduction by natural contraception or with intrauterine insemination.

(P)

Some experts advocate hormone optimization of men with NOA and coexistent testosterone (T) deficiency prior to surgical sperm retrieval, though this approach is controversial and has not been prospectively validated. The selective estrogen receptor modulator clomiphene citrate may be used to inhibit the negative feedback of estradiol (E) on the hypothalamus and pituitary, thereby increasing pituitary gonadotropin production and potentially driving up intratesticular Leydig and Sertoli cell function. Given its mechanism of action, clomiphene citrate is most likely to be effective when the serum LH level is low or normal. The result is increased intratesticular and peripheral T concentrations, which may be beneficial for sperm production. The typical starting dose is 25–50 mg every other day. Aromatase inhibitors provide an alternative method for hormone optimization. These drugs inhibit the peripheral conversion of T to estradiol, which similarly suppresses the central negative feedback of estradiol and stimulates pituitary production of FSH and LH. Anastrazole (1 mg daily), testalactone (100–200 mg daily), and letrazole (2.5 mg daily) are the most commonly used agents. Optimal candidates for aromatase inhibition are those with Klinefelter syndrome and patients who have serum T:E ratios <10.

(Q)

Secondary testicular failure (hypogonadotropic hypogonadism) is indicated by very low or undetectable serum FSH, LH, and T. In this condition, both sperm production and testosterone synthesis are insufficient due to inadequate stimulation of the testes by gonadotropins. This rare cause of NOA may be congenital (Kallman's syndrome), acquired (pituitary tumor, surgery or infarct), or idiopathic. Genetic tests for hypogonadotropic hypogonadism are available but are not yet part of routine clinical practice. One important caveat to note is that laboratory evidence of hypogonadotropic hypogonadism in a man who is particularly muscular and androgenized should raise suspicion for anabolic steroid use with an anabolic compound that is not detectable on standard testosterone assays (nandrolone or stanozolol).

(R)

Sperm production may be restored in hypogonadotropic men by gonadotropin replacement therapy. The first step in gonadotropin replacement therapy is typically stimulation of testicular production of testosterone with human chorionic gonadotropin (hCG) (1,000–3,000 IU 3 times per week), which has a biologically equivalent action to LH on the testis. After 6 months, FSH replacement therapy may be added by administration of recombinant human FSH (100–150 IU 3 times weekly). Sperm production is reassessed every 3 months thereafter. Optimization of sperm production may take up to 2 years.

(S)

Anabolic steroid abuse should be suspected when the serum T level is elevated with very low levels of serum LH and FSH. In such cases, the patient's sperm production should be serially assessed after cessation of exogenous androgen supplementation. In some cases, recovery may be expedited by gonadotropin replacement therapy.

Table 3.1 Differential diagnosis of azoospermia

Hypogonadotropic hypogonadism (Kallman's syndrome, idiopathic)
Pituitary pathology including tumors, infiltrative diseases, and infarction
Systemic malignancies
Anabolic steroid abuse
Klinefelter syndrome
Y chromosome microdeletions
Testicular cancer
Leydig cell or Sertoli cell tumors
Idiopathic testicular failure
Prior testicular vascular or traumatic insults
Prior orchitis
Gonadotoxin exposure (chemotherapy, radiation, medications)
Congenital bilateral absence of the vas deferens (mutations in the cystic fibrosis transmembrane receptor gene)
Congenital, iatrogenic, or post-inflammatory epididymal obstruction
Iatrogenic vasal obstruction
Ejaculatory duct obstruction

Table 3.2 Important points to elicit in the medical history of azoospermic men.

Medical history	Interpretation
Developmental history, including testicular descent	Delayed/absent puberty suggests impaired androgen synthesis or activity and NOA
	Cryptorchidism suggests NOA
Fertility history	Prior spontaneous conception suggests acquired OA
Partner's reproductive history and status	Guides treatment selection, particularly in cases of OA
Current or prior medical conditions, including sexually transmitted infections (STI)	Malignancy and hypogonadism may be associated with NOA
	STIs may cause epididymal obstruction
Current or prior gonadotoxin exposure	Suggests NOA
Prior scrotal events including epididymitis, orchitis, and testicular torsion	Prior epididymitis suggests epididymal obstruction
	Prior orchitis, torsion, or injury may be associated with NOA
Prior scrotal, inguinal, retroperitoneal, or pelvic surgery	Raises the possibility of iatrogenic OA
Medication use, including anabolic steroids	Current or prior immunosuppressive or antineoplastic therapy suggest NOA
	Anabolic steroid use is a common reversible cause of NOA
Symptoms of hypogonadism	Hypogonadism may be associated with NOA
Recurrent pulmonary infections	May be associated with inherited causes of OA including CFTR mutations, Young's syndrome, and Kartagener's syndrome
Gastrointestinal dysfunction	May be associated with or mutations in the CFTR gene and OA
Family medical and fertility history	May suggest genetic causes of azoospermia

Table 3.3 Important points to elicit in the physical examination of azoospermic men

Physical examination	Interpretation
Body habitus and hair distribution	Tall stature and long limbs suggest congenital hypogonadal states
	Decreased body and/or facial hair suggest hypogonadism and NOA
	Very large muscles may suggest anabolic steroid use
Visual fields	Visual field deficits associated with pituitary tumors
Sense of smell	Smell deficits (hyposmia, anosmia) associated with Kallman's syndrome
Gynecomastia	Gynecomastia indicates imbalance in the testosterone:estradiol ratio, may occur in Klinefelter syndrome, Leydig cell tumors, germ cell tumors, or idiopathic NOA
Lower abdominal, inguinal, or scrotal surgical scars	Indicate prior surgery and may be associated with OA
Spermatic cord examination	Absence of one or both vasa deferentia suggest OA due to CFTR mutations or aberrant embryological development of the Wolffian duct structures
	Varicoceles may be associated with NOA, but are also commonly found in men with OA
Epididymal examination	Fullness or induration of the epididymis suggest OA
	An empty, flat epididymis is consistent with NOA
Testicular examination	Very small (< 5 mL) and hard testicles suggest Klinefelter syndrome
	Small (<12 mL) and soft testicles suggest NOA
	Normal testicular size and consistency suggest OA

Suggested Reading

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