
به نام خدا

Male Infertility

Nasser Mogharabian

Assistant Professor of Andrology and Urology

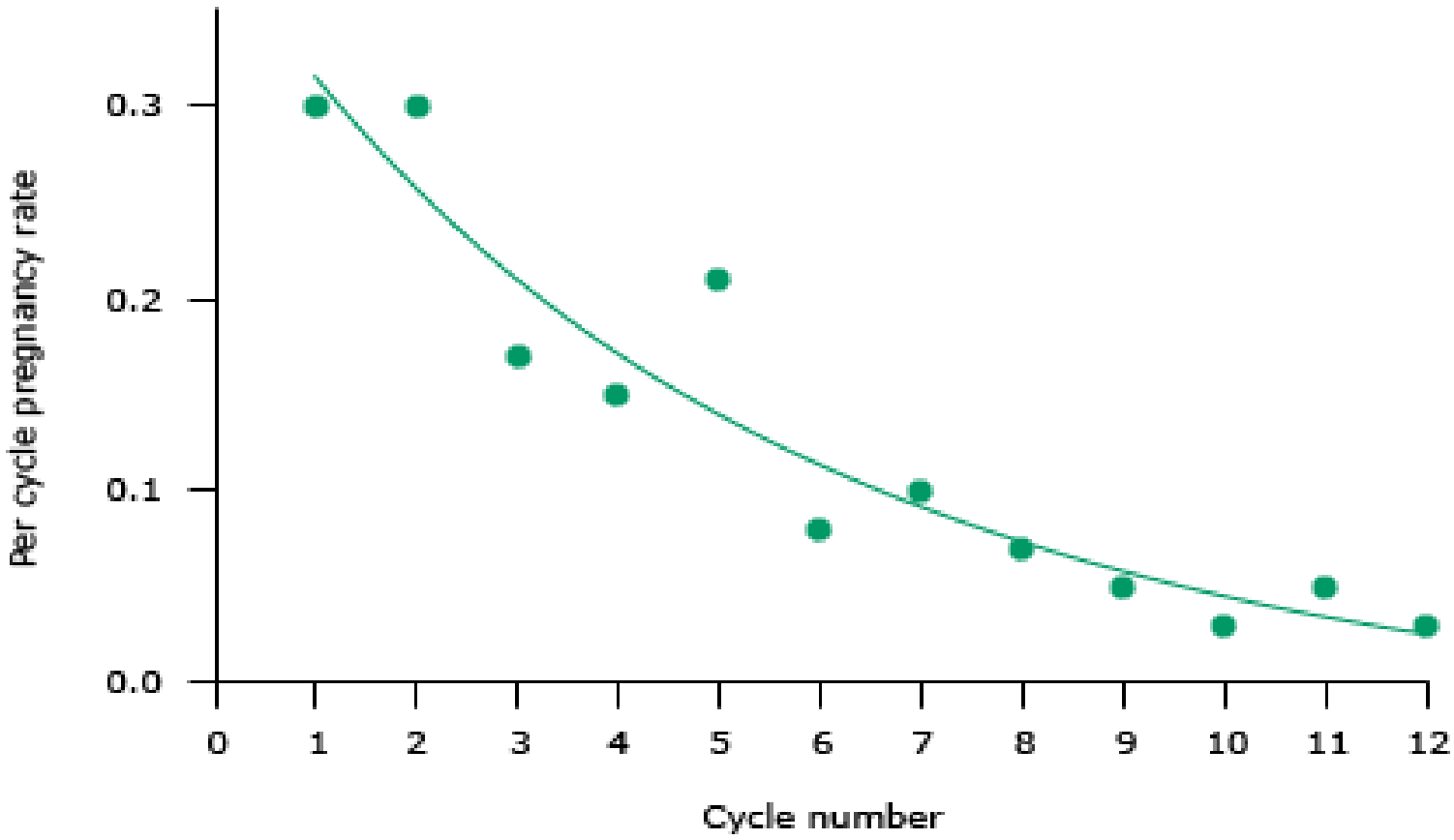
Shahrude University Of Medical Sciences

- ✓ The infertility affects approximately **15%** of couples (20% in Iran)

- ✓ **men to contribute equally to women (and even more)**

- ✓ The most important determinant of a couple's reproductive potential is **maternal age**

Fecundability



Indications and timing of the infertility evaluation

- Initiate evaluation after **12 months** of unprotected and frequent intercourse in Women under age 35 years without risk factors for infertility.

- Initiate evaluation after **six months** of unprotected and frequent intercourse in Women age 35 to 40 years.

- Initiate evaluation **upon presentation** despite less than six months of unprotected and frequent intercourse in:

  - Women over age **40** years.
  - Women with **oligomenorrhea/amenorrhea**.
  - Women with risk factors for **premature** ovarian failure such as previous extensive ovarian surgery, exposure to cytotoxic drugs or pelvic radiation therapy, autoimmune disease, smoking, strong family history of early menopause/premature ovarian failure, advanced stage endometriosis,
  - Women with known or suspected **uterine/tubal** disease.
  - Women whose **male** partner has a history of groin or testicular trauma and surgery, adult mumps, impotence or other sexual dysfunction, chemotherapy and/or radiation, or a history of subfertility with another partner.

Causes of male infertility

- **Pre-testicular** - **Endocrine and systemic disorders** (usually with hypogonadotropic hypogonadism) – **up to 5 percent**.

- **Testicular** **defects in spermatogenesis** – **60 percent**, of which the majority have **idiopathic dysspermatogenesis**, an isolated defect in spermatogenesis without an identifiable cause.

- **Post-testicular** - **Sperm transport disorders** – **5 percent**.

- **Idiopathic** **male infertility** – **30 percent**. **Idiopathic male infertility** should be distinguished from **idiopathic dysspermatogenesis**

Distribution of Final Diagnoses from a Male Infertility Clinic

Immunologic 2.6%

Idiopathic 32.6%

Varicocele 26.6%

Obstruction 15.3%

Normal female factor 10.7%

Cryptorchidism 2.7%

Ejaculatory failure 2.0%

Endocrinologic 1.5%

Drug or radiation 1.4%

Genetic 1.2%

Testicular failure 1.1%

Sexual dysfunction 0.7%

Pyospermia 0.5%

Cancer 0.4%

Systemic disease 0.3%

Infection 0.2%

Torsion 0.1%

Ultrastructural 0.1%

TOTAL 4710 100.0%

Congenital hypogonadotropic hypogonadism

congenital hypogonadotropic hypogonadism (IHH)

- Isolated GnRH deficiency
- is a family of genetic disorders
- defects in the production or action of GnRH.
- IHH with anosmia is referred to as Kallmann syndrome wich many of them have midline facial defects, color blindness, hearing difficulties, renal agenesis, and/or cryptorchidism.

Acquired hypogonadotropic hypogonadism

- **Sellar** masses, and surgical or radiation treatment of these lesions.
- **Infiltrative** diseases include sarcoidosis, histiocytosis, tuberculosis, fungal infections, iron overload syndromes
- Lymphocytic hypophysitis is an **autoimmune** condition that affects the pituitary and/orthe infundibulum
- Head **trauma**
- **Vascular** lesions include pituitary infarction and carotid aneurysm.
- **Endocrine** disorders such as hyperprolactinemia, estrogen excess , glucocorticoid excess , androgen excess, and overt hypothyroidism or hyperthyroidism.

Acquired hypogonadotropic hypogonadism

- **Drugs**, such as **opioids** or other central nervous system-activating drugs (including **cannabinoids**), and many **psychotropic** drugs

- exogenous androgenic **steroids** suppress endogenous gonadotropin secretion and thereby reduce spermatogenesis
  - low sperm counts
  - low serum LH concentrations
  - very muscular phenotype

- **GnRH** analogues (agonists and antagonists)

Systemic disorders

- **Diabetes** mellitus
- **Metabolic** syndrome
- Sleep **apnea**
- Any serious systemic **illness** or chronic **nutritional** deficiency can cause combined hypogonadotropic and primary hypogonadism
- **Obesity** in men results in hypogonadotropic hypogonadism with low total testosterone, free testosterone, and low or inappropriately normal gonadotropin concentrations.

Congenital testicular defects

- **Idiopathic dysspermatogenesis**
  - sperm number, morphology, and/or motility
  - no identifiable cause
  - The most common primary testicular defect
- **Genetic**
  - 5 to 10 percent of cases of male infertility

Congenital testicular defects

- **Y chromosome microdeletions** and substitutions
  - azoospermia and severe oligozoospermia
  - Up to 20 percent of infertile men
  - the long arm of the Y chromosome
  - Testicular biopsies show maturation arrest or Sertoli cell-only syndrome
  - not only in idiopathic severe dys-spermatogenesis but also in men with other causes of testicular dysfunction
- **Autosomal and X chromosome defects**
- **Karyotypic anomalies in somatic chromosomes**

- **Epigenetics in male infertility -** Sperm DNA methylation, histone acetylation, and noncoding RNAs may contribute to defective embryogenesis and idiopathic male infertility.

- **Klinefelter syndrome** (most common)

- **Cryptorchidism**

- **Inactivating mutation in the FSH receptor gene**

- **Myotonic dystrophy**

- **Androgen receptor or biosynthesis disorders**

- **Disorders of the estrogen receptor**

Acquired disorders of the testes

- Varicocele
- Infection especially mumps
- Drugs and radiation
- Environmental factors, smoking, and hyperthermia
- Systemic disorders such as chronic renal insufficiency or malnutrition
- Antisperm antibodies
- Cancer - even before spermatotoxic chemotherapy, especially if the cancer is of testicular origin

Environmental factors

- pesticides
- cell phones
- insecticides and fungicides
- lead, cadmium, and mercury
- others

Antisperm antibodies

- Some infertile men have antisperm antibodies in serum or semen

- Whether antibodies occur spontaneously or only after some testicular injury is not known

SPERM TRANSPORT DISORDERS

(anatomic or functional)

- **vas deferens**
- **epididymis**
- **Seminal vesicles**
- **prostate**
- **Ejaculatory duct**
- **Sexual dysfunction**

Idiopathic male infertility

repeatedly normal semen analyses

cannot achieve pregnancy

apparently normal female partner

careful assessment of all possible causal mechanisms

Evaluation of male infertility

- **Any couple** should be evaluated and consulted primarily but for more evaluation and any treatment:

Indications and timing of the infertility evaluation

- Initiate evaluation after **12** months of unprotected and frequent intercourse in Women under age 35 years without risk factors for infertility.

- Initiate evaluation after **six** months in Women age 35 to 40 years.

- Initiate evaluation **less** than six months in:

  - Women over age 40 years.
  - Women with oligomenorrhea/amenorrhea.
  - Women with risk factors for premature ovarian failure such as previous extensive ovarian surgery, exposure to cytotoxic drugs or pelvic radiation therapy, autoimmune disease, smoking, strong family history of early menopause/premature ovarian failure, advanced stage endometriosis, or known or suspected uterine/tubal disease.
  - Women with known or suspected uterine/tubal disease.
  - Women whose male partner has a history of groin or testicular trauma and surgery, adult mumps, impotence or other sexual dysfunction, chemotherapy and/or radiation, or a history of subfertility with another partner.

Important notes

Evaluate more prevalent causes firstly

Remind less prevalent causes finally

May be more than one cause

Important notes

- ✓ Primary and Full evaluation
- ✓ Team work
- ✓ Proper consults
- ✓ Follow up

Causes of male infertility

- **Pretesticular** – up to 5 percent.
- **Primary testicular** 60 percent
- **Posttesticular** - 5 percent.
- **Idiopathic** male infertility – 30 percent.

EVALUATION OF MALE INFERTILITY

- History
- Physical examination
- Semen analysis
- Additional procedures
  - Sperm function tests
  - Immunological tests
  - Semen culture
  - Hormone assays
  - Testicular biopsy
  - Chromosomal analysis
  - Vasography
  - Scrotal ultrasound
  - Transrectal ultrasound (TRU)
  - DNA integrity tests

I. STANDARD SEMEN ANALYSIS

II. SPECIALIZED SEMEN ANALYSIS

1. Sperm autoantibodies
2. Semen Fructose
3. Semen culture
4. Sperm function tests
   - ✓CASA
   - ✓SDF

III. ENDOCRINE TESTS

1. T
2. LH and FSH
3. Prolactin

IV. GENETIC TESTS

1. Karyotyping
2. Y chromosome microdeletions
3. Cystic fibrosis conductance regulator (CFTR) gene mutation

History

1. Questions regarding medical and surgical history

2. Questions specifically related to male reproduction:

   - a history form

   - a helpful mnemonic is ***TICS****:*

T*oxins*

I*nfectious disease*

C*hildhood history*

S*exual* history

Significance of partner

- If the partner of the patient is present during the history, she may relate valuable information

- The patient may also feel reluctant to divulge specific facts of reproductive significance before his partner

File Number:	Andrology Dept. MALE INFORMATION SHEET	ROYAN INSTITUTE

Ht:	Wt:	BMI:	Waist:	Hip.c:

How long from marriage?

What kind of contraception used? Time of used?

How long are you trying for child?

Had you any child or abortion?

Have you or your wife married before?

Have you or your wife had any child or abortion from previous marriage?

Past hospital admission?

Mumps	M.orchitis	U.D.T
Hypertension	Test. Pain	UTI
Venereal Dz.	Renal Dz.	Epididymorchitis
Allergy	T.B	DM.

Exposures Yes ☐ No ☐

Drug Hx Yes ☐ No ☐

Pervious HX: ART Medical

R/F06-03/01

File Number:	Andrology Dept. MALE INFORMATION SHEET	ROYAN INSTITUTE

Surgical HX Yes ☐ No ☐

	RT	LT	Bilat
Varicocelectomy			
Orchiopexy			
Hernia			
Hydrocele			
T.BX, TESE, PESA, TESA			
VEA , V.V			
Orchiectomy			
Vasectomy			
Urethral Surgery			
Others			

Cigarette Alcohol Addiction Water Pipe

Family HX Number of Brothers .....

General appearance		Ab	NL
Hair. Distrubution.		Ab	NL
Gynecomastia	Yes	Rt / Lt	No
Surgical Scar		Yes	NO
Penis		Ab	NL
Scrotum		Ab	NL

R/F06-03/01

File Number:	Andrology Dept. MALE INFORMATION SHEET	ROYAN INSTITUTE

		NL	Ab	C	Volume
Testes	Rt				
	Lt				

		NL	Ab	Agenesis
Vas	Rt			
	Lt			

		NL	Ab	Mass
Epididymis	Rt			
	Lt			

	RT	LT	G
Varicocele			
Hydrocele			
Hernia			

Libido	Normal ☐	Abnormal ☐	Duration .....
Erection	Normal ☐	Abnormal ☐	Duration .....
Premature ejaculation	Yes ☐	No ☐	Duration .....
Painful ejaculation	Yes ☐	No ☐	Duration .....

Intercourse / WK .....

Result and Order	Date

R/F06-03/01

Toxines - TICS

- *Endocrine Modulators*
- *Recreational Drugs*
- *Cytotoxic Chemotherapeutics*
- *Environmental Toxicants*
- *Thermal Toxicity*
- *Radiation and radiofrequency*

Medications

- antiandrogens : bicalutamide, flutamide, and nilutamide
- antihypertensive : spironolactone
- Antiretroviral protease inhibitors : indinavir
- nucleoside reverse transcriptase inhibitors : stavudine
- corticosteroids
- exogenous estrogen and androgrn
- 5α-reductase inhibitors: finasteride and dutasteride
- *Anti-Inflammatory Agents*
- *Antihypertensives*
- *Antipsychotics*
- *Opioids*
- *Antibiotics*
- *Phosphodiesterase V Inhibitors*

Medications

- **Antipsychotics** → loss of libido

- **SSRIs** → anorgasmia and delayed or absent ejaculation

- **Opioids** → suppress LH release
  directly by inhibition of Sertoli cell function
  discontinuation may rapid return of androgen within 1 month

- **Antiandrogens**

Recreational Drugs

- **Cannabis**
  - decreases plasma testosterone
  - dose-dependent
  - duration dependent

- **Chronic alcohol intake**
  - decreases in androgens and sperm parameters
  - increase aromatization
  - may decrease intracytoplasmic sperm injection (ICSI) outcomes

- **cigarette smoking**
  - deterioration of seminal parameters
  - dose-dependent manner
  - increased seminal oxidative stress parameters
  - Decreased sperm DNA quality

- **maternal cigarette smoking** (≥10 cigarettes per day while pregnant)
  - smaller testes
  - lower sperm counts
  - alterations in sex hormones
  - higher risk of having oligozoospermia

Chemotherapy

- dose and time dependent
- lower doses and shorter durations leading to reversible dysfunction
- higher doses and longer durations resulting in permanently impaired fertility

Cyclophosphamide , chlorambucil ,doxorubicin,Vincristine , prednisone

Cisplatin, Etoposide, Bleomycin

local instillation of bacille Calmette-Guérin into the bladder for superficial transitional cell carcinoma resulted in a significant decrease in sperm concentration and motility

sperm DNA integrity and mutagenicity → **cryopreserve sperm before induction**

Radiation

- Doses as low as 0.015 Gy (15 rads) → **transiently** suppress spermatogenesis
- Doses above 6 Gy (600 rads) → **irreversible** azoospermia

- In one survey of boys with acute lymphoblastic leukemia who underwent testicular irradiation at 12, 15, and 24 Gray (Gy), all became azoospermic, but those receiving less than 24 Gy had normal testosterone production

- In a survey of childhood cancer survivors, chances of having future offspring were lessened by radiation doses to the testes of 7.5 Gy and above

- The testis need not be directly irradiated for spermatogenic impairment to occur

Radiofrequency devices

- Negative effects after **electromagnetic** radiation generated by 850- and 900- MHz **cell phone** transmission systems in vitro
  - Sperm count, motility, viability, and normal morphology
  - reactive oxygen species (ROS) generation
  - decreasing ratio of boys to girls
- linear decrease in sperm parameters based on cell phone talking time

Thermal Toxicity

- Scrotal temperature in humans is maintained to be 2° C to 4° C below core body temperature.
- small increases in testicular temperature accelerate germ cell **apoptosis**

  - spinal cord injuries
  - Varicocele
  - chronic sauna or hot tub exposure
  - febrile illness
  - prolonged sitting during work
  - truck driving, welding, baking
  - tight fitting underwear
  - laptop use

- **laptop** computer resting on the lap for 1 hour raised the scrotal temperature an average 2.6° C on the left and 2.8° C on the right side

- Simply **sitting** without a laptop raised the scrotal temperature an average of 2.1° C

Infections and Inflammation- TICS

- Infections of the testis, epididymis, prostate, and urethra may lead to male infertility through anatomic (stricture) and functional (impairing sperm) means

- **Mumps**
- **Mycobacterium tuberculosis**
- **Human papillomavirus**

- direct toxic effects of the infectious organism on sperm or through induction of immunologic responses

- incubating sperm with increasing concentrations of ***C. trachomatis*** *elementary* bodies was associated with degradation of sperm DNA in a time dependent manner

- ~~hepatitis C and human immunodeficiency virus~~

Infections and Inflammation

Evidence suggests that noninfectious or infectious inflammatory processes of the prostate may lead to sperm alterations and male infertility by several mechanisms:

- pyospermia and the release of ROSs resulting in sperm damage
- generation of antisperm antibodies
- biochemical alterations in prostatic ions such as zinc, magnesium, calcium, or selenium
- Prostatitis may itself damage sperm by inducing ROSs without leukocytosis

Childhood Diseases- TI**C**S

- *Pediatric Surgery* (Hydroceles and hernias)
- *Testis Torsion*
- *Cryptorchidism*
- *Testicular Dysgenesis*
- *Genetics*

Sexual History- TICS

- Optimum timing for intercourse appears to be daily around the time of ovulation :
  - Because ovulation is detectable by basal body temperature or home hormonal kits after it has occurred, a couple should be encouraged if possible to record the day of ovulation for two or three menstrual cycles, and begin daily intercourse several days before the earliest recorded day.

- Frequency of intercourse
- Saliva
- Lubricants

PHYSICAL EXAMINATION

Alterations in secondary sexual characteristics

- Loss of facial, truncal, axillary, and pubic hair
- female facial characteristics
- high-pitched voice
- Gynecomastia
- tall height for age
- arm span 5 cm longer than the patient's height
- lower body segment more than 5 cm longer than the upper

Obesity

- Serum **testosterone** is also well known to be lower in obese men
- elevated **estradiol** as a result of peripheral conversion
- decreased serum **inhibin** B concentrations
- decreased **Sertoli** cell number
- obesity may primarily interfere with **epididymal** function that imparts **motility** to sperm
- adverse effects of obesity on male reproduction may be also **independent of the endocrine system**
- obesity may degrade sperm **DNA integrity** and **mitochondrial** activity

- **High estradiol**

- **Low LH**

- **Low testosterone**

Scrotum

- syncope during palpation of the scrotum
- scrotum may be hypoplastic, indicating an absence of the scrotal contents since birth
- Hydrocele
- Tumor
- varicocele
- proximity to the thighs

Epididymis

- If it is easily palpated, it is likely **engorged**, which suggests obstruction.

- If the portion near the upper pole is easy to discern but the lower pole is not, wolffian ductal development may have been **incomplete**

Testis

Testis size is well established to correlate with sperm production

1. Testis long axis more than 4.6 cm

   – Caliper (Seager) orchidometer

1. Testis volume more than of 20 mL

   – Prader orchidometer

   – ultrasonography

Spermatic Cord

- whether the vas deferens is palpable
- whether a varicocele is present

Vas deferens

- Search for the vas and bringing it to the surface of the skin

- If what is presumed to be the vas disappears from the examiner's fingers three times, the clinician can be confident that the vas is absent

Varicocele

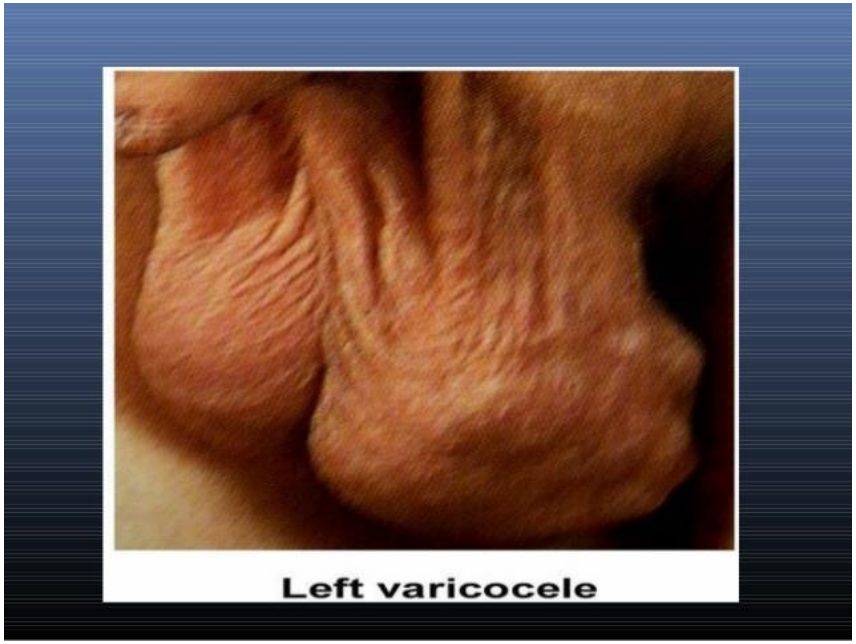
- **Incidence:**
  - one fifth to one sixth in the general population
  - one third to one half in infertile
- **Not all** men with varicocele are infertile

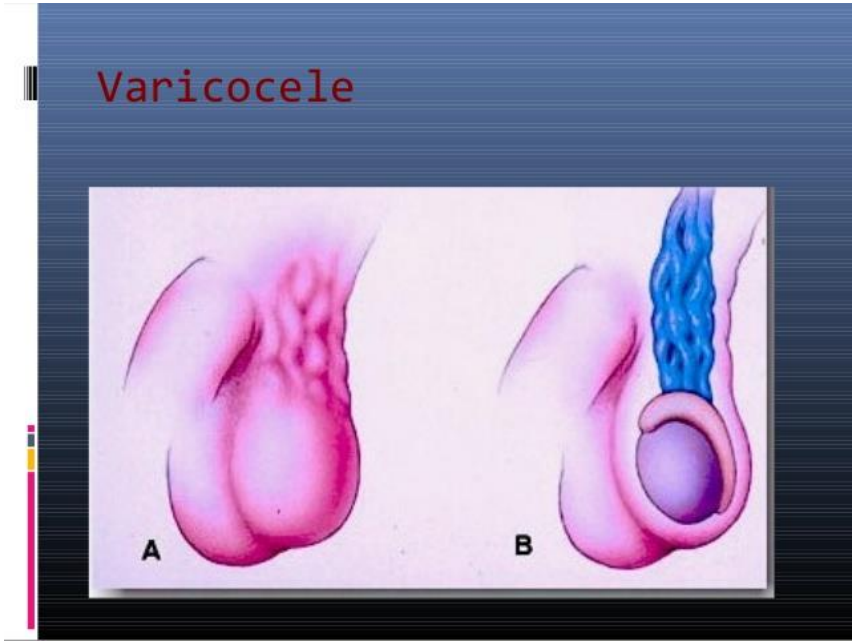
Varicocele

- examine the upper scrotum for
  - plexus of varicose veins may be visible
  - plexus of varicose veins may be palpable

- Grade I → only be detected by radiographic evaluation
- Grade II → palpable but not visible
- Grade III → visible

Varicocele





Phallus

- In the typical setting of intercourse, semen must be deposited proximal to the cervical os for optimal chance of reproduction

- Phimosis
- hypospadias
- Epispadias
- penile curvature

Examining the Prostate and Seminal Vesicles

- it may be prudently omitted
- size of the prostate (may be aplastic or hypoplastic)
- If seminal vesicles are palpable, it is suggesting ejaculatory ductal obstruction

LABORATORY EVALUATION OF MALE INFERTILITY

Endocrine Evaluation

1. Testosterone (total – free)
2. LH
3. FSH
4. Estradiol
5. SHBG – Albumin
6. Others if there is any symptoms or clue

- spermatogenesis is highly dependent on **intratesticular** testosterone Synthesis

- either **280** ng/dL or 300 ng/dL as a threshold for adequate androgenization in a man

- A **ratio** of total testosterone to estradiol below 10 : 1 is suggested to indicate reproductive dysfunction

Circadian rhythm

In the early morning:

Total T is the highest

SHBG is the lowest

bioavailable testosterone is the highest

Accurate laboratory assessment of testosterone

- determining bioavailable testosterone is to **calculate** it from total testosterone, SHBG, and albumin

- assays are typically performed in the **morning**, although the necessity of such timing is more important in younger men

- 3 serum **samples** with 20 min intervals

- **In the case of hypoandrogenism, a pituitary or testicular source is identified by assessing LH :**
  - Leydig cell dysfunction → LH is elevated
  - pituitary dysfunction → LH is decreased

- **Because testosterone and LH are released in a pulsatile fashion:**
  - both assays may be performed **simultaneously**
  - borderline results may be investigated further by obtaining **three** morning samples at 20-minute intervals
    - pooled these samples for a **single** measure
    - Three **separate** assay results may be determined and arithmetically averaged

Azoospermia

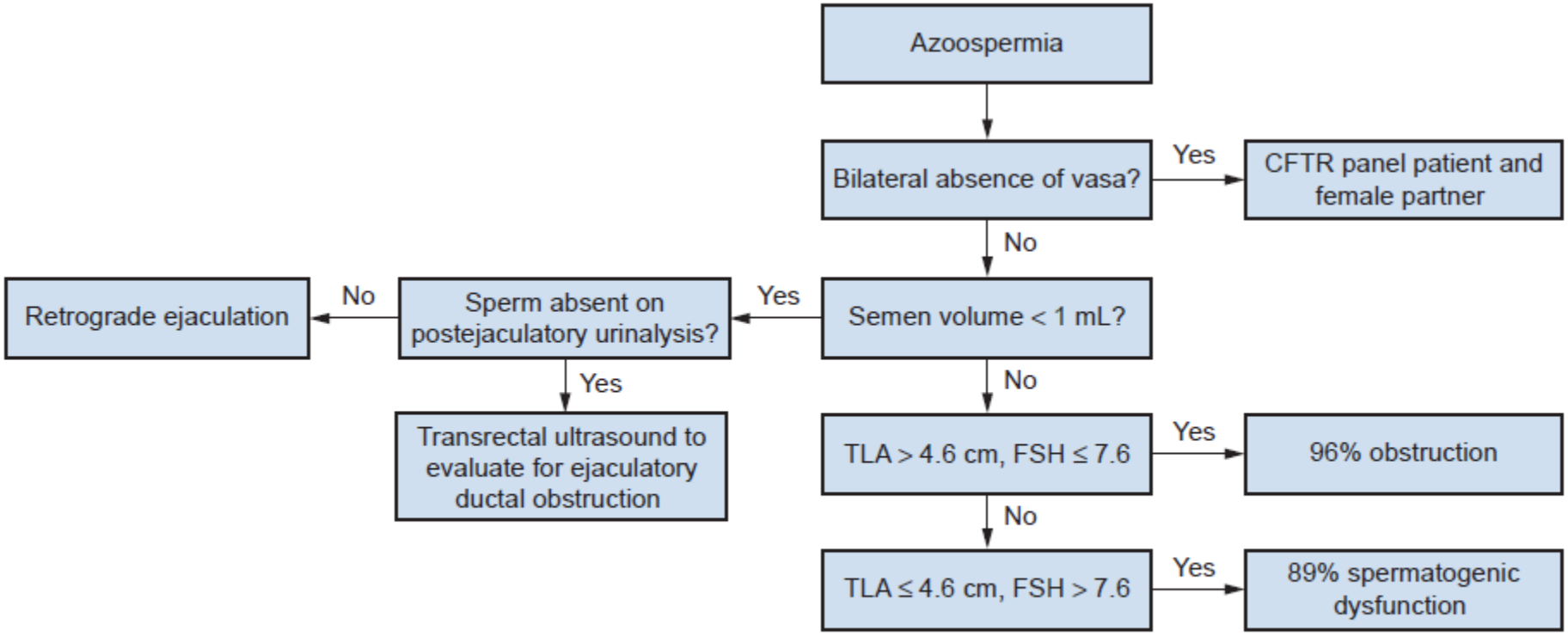


Figure 24-11. **Algorithm for evaluation of azoospermia. CFTR, cystic fibrosis transmembrane conductance regulator; FSH, follicle-stimulating hormone; TLA, testis longitudinal axis measured by caliper orchidometer.**

LABORATORY EVALUATION OF MALE INFERTILITY

Semen Evaluation

Notes

- 2 – 3 samples
- Standard evaluation
- Variations
- Interpretation

John MacLeod study

- **Comparing** semen analysis from fertile and infertile men:

  - shape
  - movement
  - Concentration

- The histograms for sperm parameters from fertile and infertile men are largely overlapping, meaning that a substantial range of values for any parameter do not discriminate between male fertility and infertility

John MacLeod study

The **first** problem:

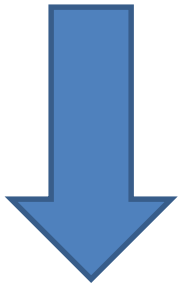
The parameters be lower than the threshold

The man is **likely** to be infertile

The parameters be higher the threshold

???????

- The **second** problem:



- Fertile men may be found below the thresholds and infertile men above.

Two thresholds for semen analysis?

- **As an example for sperm concentration:**

- Less than **13.5** million/mL → likely infertile
- Greater than **48.0** million/mL → likely fertile
- Between 13.5 million/mL and 48.0 million/mL → **????????**

Semen sampling

A single day of abstinence is optimal(2-7 for WHO)

- linear decline in seminal parameters with increasing days of abstinence

- **variability in abstinence** may be responsible for variability in semen analysis results

❖ semen analysis parameters are highly variable during the time

❖ Two analyses separated by 2 to 3 weeks should be done

Collection of semen

A nontoxic wide-mouthed glass or plastic cup

Special nontoxic condom may be used

- **Sterile** collection for assisted reproduction or microbiological analysis
- **Clean** collection for diagnostic or research purposes

Note in the report if the sample is incomplete

- The specimen container should be kept at 20 to 37 °C temperature

- The specimen container is placed on the bench or in an incubator (37 °C) while the semen liquefies

Confirming the compatibility of semen collection vessels

Select several semen samples with high sperm concentration and good sperm motility

Place half of each specimen in a container known to be non-toxic (control) and the other half in the container being tested

Assess sperm motility at hourly intervals in replicate at room temperature or at 37 °C for 4 hours

If there are **no differences** at each time point between control and test assessments, *the test containers can be considered to be* non-toxic

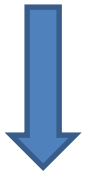
The physical and chemical characteristics

The sample is allowed to liquefy for 30 minutes before evaluation

- assessed before ~~**microscopic**~~ examination
- **Sperm odor (new)**
- Viscosity is no longer than 2 cm
- normal ejaculate is white or light gray
- semen ~~**pH**~~ is no longer recommended because environmental conditions may alter it
- semen volume is of significant clinical importance and should not be less than **1.0 mL**

Aspermia or seminal hypovolemia

- **Aspermia =** No fluid is discharged from the urethra during male orgasm
- **Seminal hypovolemia** = less than 1 cc



1. Postejaculatory urinalysis is performed to identify retrograde ejaculation

2. Transrectal ultrasonography (TRUS) is conducted to evaluate ejaculatory ductal obstruction

Postejaculatory urinalysis

1. Void before ejaculation for a semen analysis
2. Collect the semen sample
3. Urinate after into separate container
4. The urine is reconstituted by centrifugation and the number of sperm in the pellet is counted

5. If the number of sperm in the **urine** nears or exceeds that in the antegrade **specimen**, retrograde ejaculation is considered clinically significant

Semen parameter	WHO 1980	WHO 1987	WHO 1992	WHO 1999	WHO 2010[1]	WHO 2021
Volume (mL)	ND	≥2	≥2	≥2	1.5	1.4
Sperm concentration ($x10^6$/mL)	20-200	≥20	≥20	≥20	15	16
Total sperm number ($x10^6$)	ND	≥40	≥40	≥40	39	39
Total motility (%)	≥60	≥50	≥50	≥50	40	42
Progressive motility (%)[2]	≥2[3]	≥25	≥25 (grade a)	≥25 (grade a)	32 (a+b)	30
Vitality (%)	ND	≥50	≥75	≥75	58	54
Normal morphology (%)	80.5	≥50	≥30	(14)	4	4

Comparing 2010 and 2020 WHO manual semen analysis

Semen parameters	WHO 2010	WHO 2020
semen volume	1.5 ml	1.4 ml
sperm concentration	15 million /ml	16 million/ ml
total motility	40%	42%
progressive motility	32%	30%
viability	58%	54%
morphology (normal forms)	4%	4%

Sperm Density

- **Oligospermia** = low sperm density
- **Cryptozoospermia** = so few as to be difficult to reliably measure
- A large CART analysis revealed 13.5 million/mL to be a lower parameter for sperm density and 48.0 million/mL to be an upper parameter
- The 5th percentile for sperm density according to the fifth edition of the WHO laboratory manual is 15 million/mL and the 50th percentile is 73 million/mL

Total sperm count

- Total sperm count = semen volume * sperm density
  - The 5th percentile = 39 millions
  - The 50th percentile = 255 million
- Total sperm count and the sperm concentration are related to:
  - time to pregnancy
  - pregnancy rates
  - predictors of conception

Sperm Motility

- Assessed optimally within 30 minutes of liquefaction

- Low motility = asthenospermia

- Classification:

1. **Progressive(32%)** = moving actively, either linearly or in a large circle, **regardless of speed**
2. **Nonprogressive** = all other patterns of motility with an absence of progression — 40%
3. **Immotility(60%)**

Sperm Morphology

- **Teratozoospermia**

- **Kruger** → several aspects of sperm are assessed, and if any one was out of range, the sperm was counted as abnormal

- Threshold is **5%**

- **Strict morphology** is unassociated with sperm ~~nuclear integrity~~ and does not predict natural conception or ~~IVF outcomes~~

Sperm Vitality

- Metabolically active living cells

- Near or total asthenospermia → discriminate **cell death** and **dysfunction**:

1. Purely **diagnostic** → staining with **eosin** Y and with or without nigrosin dead sperms absorb the pigment

2. Subsequent use in **IVF** → the hypo-osmotic swelling (**HOS**) test → the tails of live sperm swell within 5 minutes

Secondary Semen Assays

Pyospermia Assays

- May be harmful to sperm with production of **ROSs**

- Moderate levels of leukocytes in semen may be physiologic, and may even be beneficial for sperm function

- An abundance of cells resembling leukocytes observed with phase contrast microscopy:
  - the evaluating physician cannot accurately diagnose ~~**pyospermia**~~
  - The **Papanicolaou** stain may be used to differentiate leukocytes from immature germ cells based on nuclear morphology

- The threshold for leukocytes = **1 million/mL**

- Should pyospermia be excluded, the patient can be reassured

Antisperm antibody

"blood-testis **barrier**" be disrupted → sperm exposed to the immune system → humoral immunoglobulins → affecting surface of the sperm cell

orchitis

Varicocele

vasectomy

testis cancer

testis trauma

Cryptorchidism

Antisperm antibody

1. agglutination of sperm
2. sperm motility is decreased and conditions associated with antisperm antibodies exist

- **Two types of assays:**
  - test for *antibodies* on the **surface** of sperm = ***direct tests (more exact)***
  - test for *antibodies* in **fluid** such as seminal plasma or serum = *indirect assays*

Tertiary and Investigational Sperm Assays

1- Sperm DNA Integrity Assays

- Sperm DNA is **six times more compact** than in somatic cells

- Sperm DNA is arranged with protamines to form tightly linear side-by-side sheets

- Fragmentation or disturbances in DNA arrangement lead to **aberrations** in:

  - sperm function
  - fertilization
  - Implantation
  - pregnancy

Methods to assess DNA structural integrity

- **Direct**
  - more effectively correlate with clinical outcomes
  1. *TUNEL Assay* ⟶ the highest associated risk ratio for miscarriage rates
  2. *Comet Assay*

- **Indirect** (denatured)
  1. SCSA

2- Reactive Oxygen Species (ROSs)

- Free radicals from **oxidative** reactions → **ROSs**
- *involved in multiple* physiologic processes important to sperm function
- if present in excess may cause reproductive dysfunction

3- Other Tertiary Sperm Assays

1. Acrosome Reaction
2. Sperm Mucous Interaction
3. Sperm Ovum Interaction
4. Sperm Ultrastructural Assessment

Genomic Assessment

- Significant role in male reproductive dysfunction

- Passed from parent to male offspring

1- Karyotype

- The American Urological Association recommends that **genetic testing** including **karyotype** be performed in all males with

1. azoospermia caused by **spermatogenic dysfunction**

2. severe oligospermia (less than 5 million sperm/mL)

2- Y Chromosome Microdeletion Testing

- a region in the long arm of the Y chromosome is critical to the formation of sperm in man ⟶ AZF (azoospermia factor)

- recommend Y chromosomal microdeletion assessment to azoospermic men before surgical sperm extraction to counsel them on the likelihood of retrieval

- it is also reasonable to omit testing based on the relative rarity of ~~**AZFa**~~ and ~~**AZFb**~~ microdeletions in clinical practice

The chance of finding ejaculated or testis sperm in men with AZF microdeletions

Tupe of mocrodeletion	The chance	Histology of testes
complete AZFa	highly unlikely	germ cell aplasia or Sertoli cell–only
complete AZFb	highly unlikely	maturation arrest at the primary spermatocyte (early) or spermatid (late) stages
AZFc	have been detected in ejaculates	hypospermatogenesis or a Sertoli cell–only pattern with foci of spermatogenesis
Partial AZFa and AZFb	have been detected in ejaculates	
AZFa + AZFb (presumably partial)	has been reported	
AZFb + AZFc (presumably partial)	Has been reported	
AZFa + AZFc	highly unlikely	no sperm on testis biopsy

~~Genomic Sequence Assessment~~

Cystic Fibrosis Transmembrane Conductance Regulator Mutation Assessment

- More than **1600 CFTR mutations** have been identified
- A high incidence of patients harbor more than one mutation; approximately **46% have two**
- they may be mild or severe, defined by whether the full cystic fibrosis disease phenotype results from the mutation
- A severe mutation such as ΔF508 on each allele will result in a child with cystic fibrosis, making screening imperative for both the prospective father and mother for those suspected of harboring genetic alterations in CFTR.

- Testing is commercially available for all known mutations but is expectedly more **expensive**.

- Currently available CFTR screening panels typically include 25 to 40 of the most common mutations. Because a subset of known mutations is screened for, a negative result still carries a defined risk.

- **Genetic screening** of the CFTR in men with CBAVD and their partners identifies the presence of severe mutations such as ΔF508 that may result in clinically overt cystic fibrosis in offspring.

IMAGING IN THE EVALUATION OF MALE INFERTILITY

- Radiographic or ultrasonographic imaging is infrequently needed in the diagnosis of male reproductive dysfunction.

- Should be ordered cautiously. Likely benign conditions such as testicular microlithiasis may be detected, resulting in patient distress and often unnecessary additional testing

Scrotal Ultrasonography

- Ultrasonography of the spermatic cord may be indicated if the evaluating physician is uncertain whether a varicocele is present on palpation

- However, the varicoceles so identified are often so small as to be of questionable ~~clinical significance~~

- Varicoceles become **palpable** at approximately **2.7 to 3.6 mm** in diameter

- Surgical treatment of varicoceles smaller than 3.5 mm that are ~~not palpable on physical examination~~ does not result in improved seminal outcomes

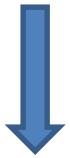
Vasography

- It is currently rarely performed because image modalities such as **TRUS** and magnetic resonance imaging (**MRI**)

- It is invasive and may result in scar tissue formation in the vasal lumen and obstruction

- Injection of saline into the vasal lumen during intended vasal reconstructive procedures with the manual feedback of whether fluid flows easily or backflow occurs offers similar information.

in the direction of the **epididymis**



rupture the delicate epididymal tubules.

Backflow

a monofilament suture such as 4-0 polypropylene may be inserted into the vasal Lumen

the location of the obstruction.

Transrectal Imaging

azoospermia + low seminal volume

ejaculatory ductal obstruction is considered

TRUS imaging evidence of ejaculatory duct obstruction:

anteroposterior seminal vesicle diameter > 1.5 cm

with or without a midline prostatic cyst

Other assessments for ejaculatory ductal obstruction

Vesiculography:

- radiographic imaging after injection of contrast directly into the seminal vesicles

Aspiration:

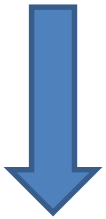
- of the seminal vesicles to determine whether sperm is present

***Chromotubation**:*

- injection of diluted indigo carmine or methylene blue dye into the seminal vesicles and observation by cystoscopy of whether the colored dye flows from the ductal orifices at the verumontanum

Cranial Imaging

assessment of whether hyperprolactinemia



distinguish between microadenomas and macroadenomas

judging whether medical or surgical therapy is indicated