



APPROACH TO THE INFERTILE COUPLE

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INFERTILITY FELLOWSHIP

Infertile couple

- Infertility :A failure to conceive after 12 months of unprotected intercourse
- It affects one in seven couples
- After one year of 85%–90% of couples will successfully conceive
- Among the remaining couples, half of them will conceive during the second year.

Starting infertility investigations

- After 12 months of unprotected intercourse
- Earlier investigation six months women over the age of 35 years
- Earlier an infertility factor is known or when it is highly suspected in the female (such as oligo/amenorrhea, tubal or uterine disease, or endometriosis) or in the male (such as undescended testes)

GENERAL ASSESSMENT OF THE COUPLE

- ❖ The main objective of the fertility workup is to find a cause for infertility, for amenable to treatment.
- ❖ Another objectives:
 - 1- Identification of infertility-associated medical conditions such as various hormonal or genetic disorders.
 - 2- Serious conditions including testicular cancer might also be encountered.
- ❖ Evaluation of the prognostic value of potential ART treatment.

etiologies of infertility

ovulatory disorders (25%)

tubal damage (20%)

male factors causing infertility (30%)

uterine or peritoneal disorders (10%)

An anatomical illustration of the male reproductive system, including the testes, vas deferens, and associated structures, rendered in a soft, pinkish-red color palette. The illustration serves as a background for the text overlay.

main common causes of male infertility

genital tract

testicular failure

Varicocele

Genetic

ejaculatory disorders

About 25% of cases of infertility remain unexplained

In about 40% of cases disorders are found in both the male and female

History-taking

Sexual history:

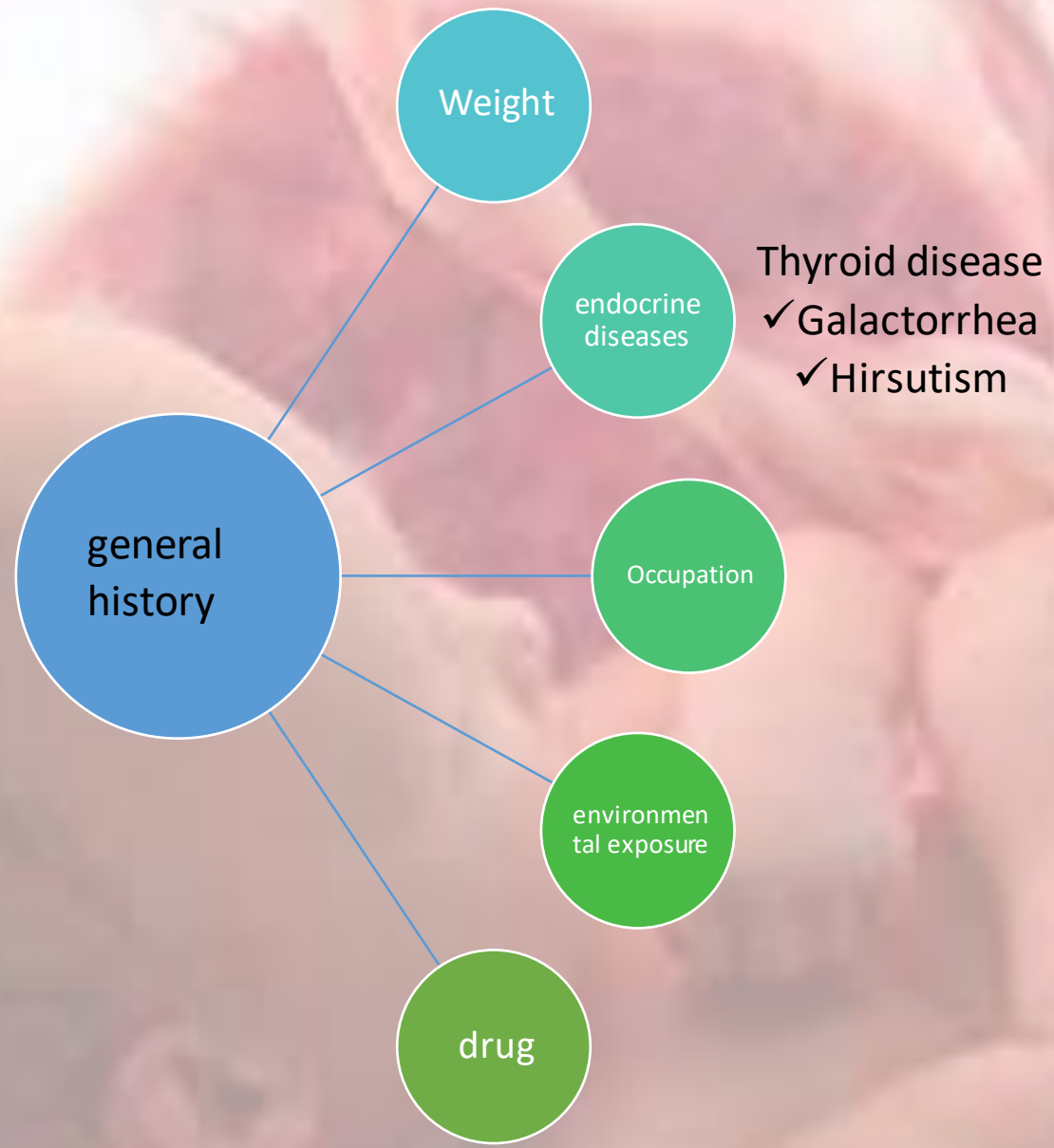
- Frequency and timing of sexual intercourse
- possibility of sexual dysfunction
- preconception care
- lifestyle changes (avoidance of smoking and toxic exposure)
- History of genetic diseases or consanguinity
- Cessation of smoking (general health and improve fertility)
- Investigations of women should consist of :
 - Rubella status
 - Diabetes screening
 - Polycystic ovarian syndrome (PCOS)
 - Obesity
 - HIV
 - Hepatitis B and C

FEMALE INVESTIGATION

History

□ Gynecological history

- Menstrual history
- previous pregnancy
- History of sexually transmitted disease
- previous methods of contraception and fertility treatments
- Pelvic surgeries
- Impair tubal and ovarian function should be noted
- Signs of endometriosis
 - Dysmenorrhea
 - Dyspareunia
 - chronic pelvic pain
- Cervical cytology



Physical investigation



Baseline investigations

☐ Ovulatory function

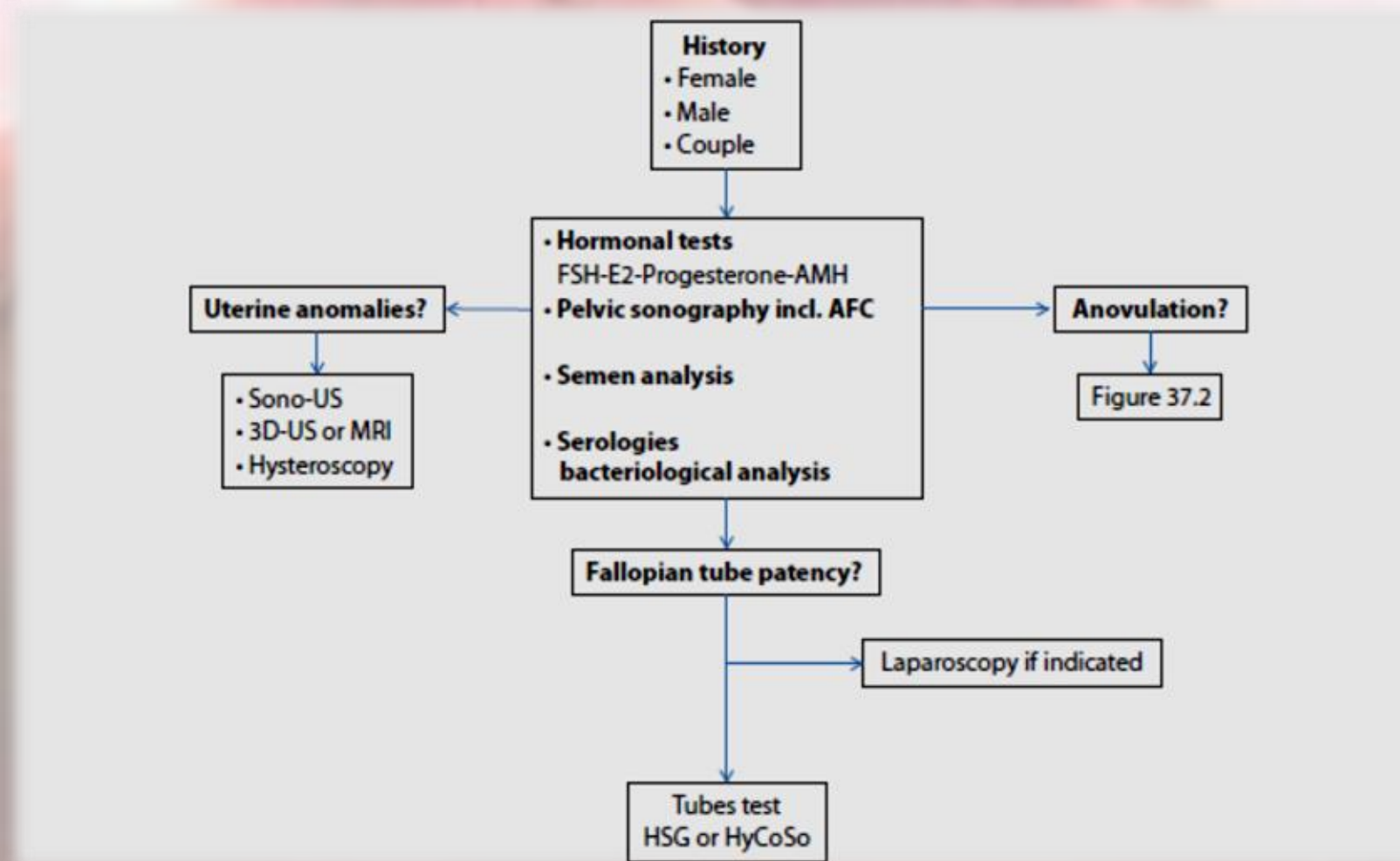
- Regular menstrual cycle(Intervals of 21–35 days)
- woman's age

☐ ovarian reserve

☐ uterine cavity

☐ Tubal patency

Initial infertility tests



(BBT) measurement.

- Provides presumptive evidence of ovulation
 - Monophasic or uninterpretable BBTs are also common in ovulatory patients
- BBT cannot accurately predict timing of ovulation
- Not recommended for assessing ovulation function
- Check of urinary LH
 - Determine the fertile period
 - Do not improve the chance of natural conception
 - Useful for couples not having regular sexual intercourse but fertile
 - Expensive and frustrating
 - Reliability and ease of use may also vary among different products
 - False-positive : 7%

❖ Endometrial biopsy and histological dating:

The results are not clearly related to fertility status. They are not routine tests

❖ Mid-luteal serum progesterone :

1-Easy method

2-The most commonly used test

3- on day 21 of a 28-day cycle or seven days before the commencement of menses

❖ US plays a role in confirming ovulation:

- Time consuming and costly
- Follicular growth
- Corpus luteum
- luteal-appearing changes

❖ Menstrual history may be all that is required in women with regular cycles in order to confirm ovulation. Still, NICE guidelines do recommend measuring mid-luteal progesterone in women undergoing infertility investigation even in the presence of regular cycles

Other hormonal tests

☐ oligo-ovulation or anovulation

- PCOS
- ovarian failure
- Thyroid disorders or hyperprolactinemia

☐ Hormonal tests

- ovarian reserve
- prolactin measurement
- thyroid function

Hormonal Diseases

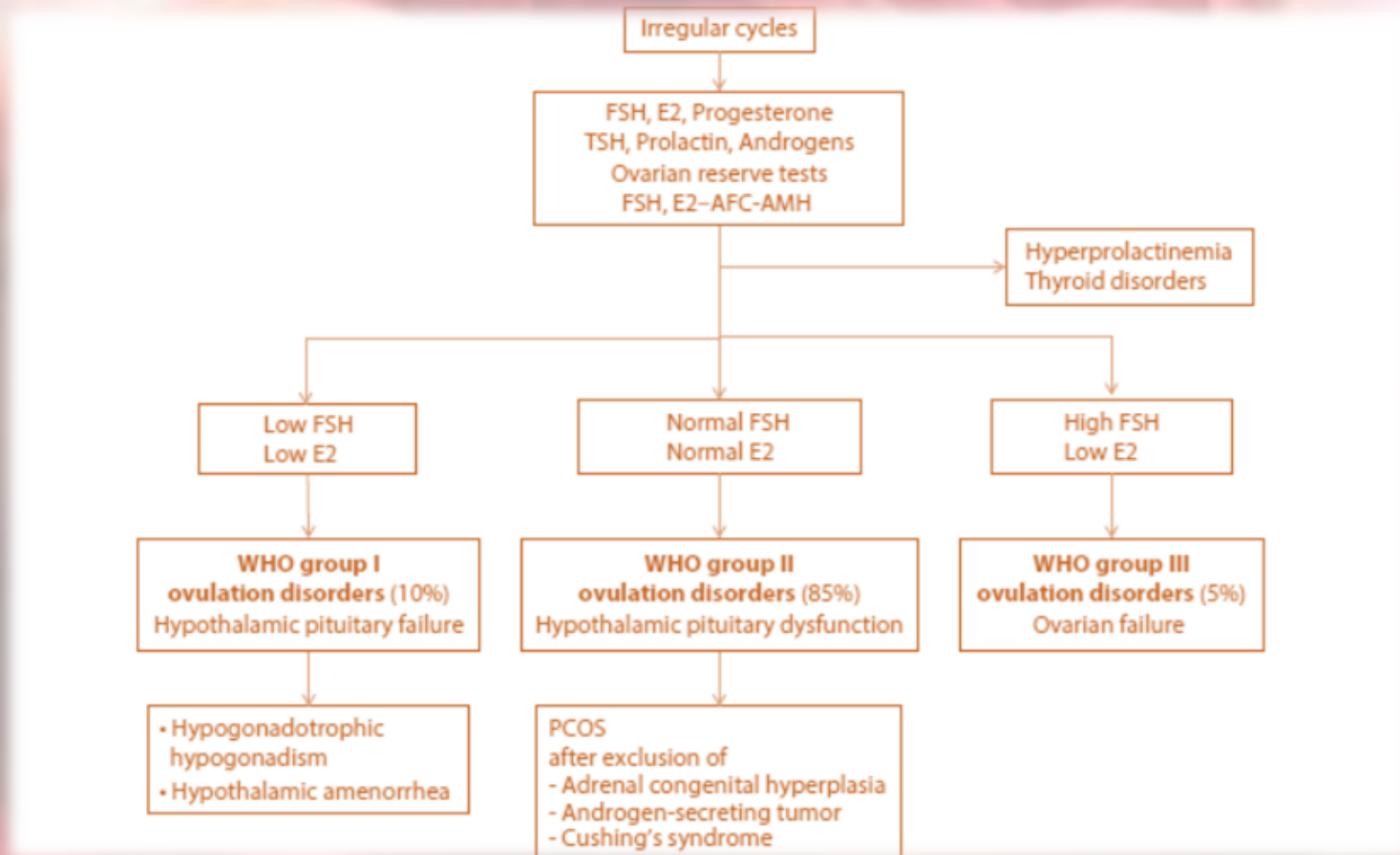
❖ Thyroid diseases:

- Although the prevalence of thyroid disease is not higher among infertile women
- Those with abnormal TSH values usually have ovulatory dysfunction.
- Screening and treatment of subclinical thyroid dysfunction seem to improve pregnancy outcomes(contraversial)

❖ Hperandrogenism:

- serum testosterone
- δ 4-androstenedione
- DeHydro epi androsterone-Sulfate
- 17-hydroxy-progesterone

Tests for ovulation function



Ovarian reserve

- ❑ Controlled ovarian stimulation
- ❑ optimal stimulation strategy
- ❑ Avoid iatrogenic complications
- ❑ Facilitates appropriate patient counseling
- ❖ Quantitative rather than a qualitative tests
- ❖ The prediction of ongoing pregnancy (for spontaneous conceptions or those achieved by ART)
- ❖ Age remains the best predictor of pregnancy following *in* IVF

Main tests for ovarian reserve

- Day-3 serum FSH and estradiol (E2)
- AMH and AFC
- ❖ Other ovarian tests
 - ✓ Serum inhibin B or isolated E2
 - ✓ ovarian volume
 - ✓ ovarian flow measurement

Day-3 serum FSH and E2

- FSH is downregulated by E2, and these hormonal markers should be considered together
- Indeed, elevated E2 could otherwise falsely normalize FSH
- An indirect marker
- High intra- and inter-cycle variability
- Sensitivity of FSH to predict poor ovarian response is better at very high threshold levels
- Repeatation in the same PT. has the highest value
- The upper threshold of FSH varies between 8.9 and 25 IU/L.

Antral follicle count

- All follicles 2–10 mm in the largest diameter measured by TV Us in early follicular phase of the cycle
 - Direct marker of ovarian reserve
- AFC has good intra- and inter-cycle reliability
- One of the three criteria of PCOS in the Rotterdam criteria :
presence of 12 or more antral follicles of 2–9 mm per ovary
- According to NICE:
- AFC greater than 16 :High response
- AFC lower than 4: low response

Anti-Mullerian hormone

- AMH is a dimeric glycoprotein member of the TGF- β superfamily
- Absent in primordial follicles
- Appears in the granulosa cells of primary follicles
- Observed in pre-antral and small antral follicles
- In growing follicles until they become dominant
- A direct ovarian reserve marker
- Since cyclic variation of AMH is minimal
- Less intra- and inter cycle variability than AFC
- NICE: AMH levels greater than 3.5 ng/mL : High ovarian response, under 0.75 ng/mL: Low response
- (controversial) AMH as a diagnostic criterion for PCOS
- Day-3 FSH and E2 are the most commonly used screening tests
- But AFC and AMH appear to be more sensitive and specific in the prediction of poor ovarian response
- AFC and AMH are highly correlated
- The Bologna criteria for poor ovarian reserve include at least one abnormal ovarian test:

AFC <5–7 follicles or AMH <0.5–1.1 ng/mL

Cervix

- PCT : poor predictor of conception and has a limited influence on treatment strategy
- This test is not routine
- Uterus
 - ☐ Endometrial polyps
 - ☐ Submucosal myoma
 - ☐ Adhesions, or a uterine septum

first-line diagnostic tool

☐Two-D US

1-Inexpensive, easy to perform, and well tolerated by patients

2-Sensitivity in detecting intrauterine lesions ranges from 56% to 89%

3- US has less diagnostic value in differentiating submucosal fibroids in the presence of multiple fibroids, endometrial polyps within a thick endometrium, and synechiae or uterine malformations

☐HSG :has a lower sensitivity and specificity and high rates of false-positive and false-negative results(poor test for uterine cavity evaluation)compromising to Hysteroscopy

☐Hysterosonography (sonohysterography)

It is more precise for diagnosing polyps or submucosal fibroids than endometrial hyperplasia or structural abnormalities

☐Three-dimensional hystero sonography

Seems to be comparable with hysteroscopy for diagnosing intrauterine lesions

☐Hysteroscopy :Gold standard for evaluate the uterine cavity (ASRM)

Hysterosalpingography

- Contraindications:
- Allergy
- Pregnancy
- active pelvic infection
- ✓ It should be performed in the early follicular phase to ensure the absence of pregnancy and to facilitate maximum uterine visibility.
- ✓ Post-HSG infection can occur in 0.3%–3.1% of cases, particularly in the presence of abnormal tubes.

HSG findings of “proximal tubal occlusion”

- Tubal spasm
- collection of debris
- Mucusplug
- ✓ HSG sensitivity and specificity rates are 65% and 83%, respectively
HSG is more specific for detecting distal as opposed to proximal occlusion, and has a high correlation (94%) with laparoscopic findings
- *Chlamydia trachomatis* serology
- ✓ Negative serology and a normal HSG indicate a low probability of tubal disease on laparoscopy examination (<5%). On the other hand, patients with positive serology have a higher risk for tubal pathology

Hysterosalpingo-contrast sonography

- HyCoSy shows intratubal flow of contrast media.
- The presence of fluid in the cul-de-sac after uterine instillation implies patency of at least one tube.
- Pain induced by HyCoSy and its complications are comparable to HSG.
- HyCoSy might have been considered inferior to HSG
- As reliable as HSG in low-risk patients

HSG and HyCoSy are the first-line tests

- well tolerated
 - Inexpensive
 - rates as high as 80%
- ❑ The choice between these two techniques depends on
- Availability
 - operator experience
 - the patient is allergic to contrast media or iodine.

Laparoscopy

- Laparoscopy with chromo pertubation is the “gold standard” for evaluating tubal patency
- Advantages :
 - Feasibility to diagnose and treat conditions that decrease fertility, including endometriosis or peri adnexal adhesions
 - Disadvantages:
 - Invasive procedure that requires general anesthesia.
 - The risk of major complications is <1%
 - Indications:
 - Evidence or strong suspicion of endometriosis, pelvic/adnexal adhesions, or significant tubal disease requiring treatment.
- ❖ In the era of ART, today laparoscopy is rarely performed in the workup of infertility.

MALE INVESTIGATION

- Detailed history
- physical examination
- ☐ The first-line laboratory investigations
 - Semen analysis
 - Serum hormonal profile
- ☐ Reveal serious associated conditions
 - ✓ Testis cancer
 - ✓ Osteoporosis/osteopenia
 - ✓ Genetic
 - ✓ Hormone disorders

History

developmental history

congenital malformation
of the genitalia

cryptorchidism

delayed onset of puberty

history of mumps orchitis

sexually transmitted infections

genitourinary surgeries

instrumentation

Trauma

lower urinary tract

Erectile

ejaculatory functions

A systematic review of related organ system function

- pulmonary disease
- upper respiratory infections
 - ✓ Young's syndrome
 - ✓ Kartagener's syndrome
 - ✓ cystic fibrosis (CF)
- ☐ A history of a metabolic or neurological condition
 - Impaired erectile
 - Ejaculatory function
- ☐ History of gonadotoxic treatment
 - Medication
 - Alcohol
 - Drugs
 - Occupational
 - Environmental exposure

Physical examination

- secondary sex characteristics

- ✓ Hair distribution
- ✓ Absence of Gynecomastia
- ✓ Skeletal muscle development

□ Genital examination

- ❖ Penile urethral meatus
- ❖ palpation of the testes
 - ✓ Presence
 - ✓ Size
 - ✓ Consistency

- Testicular cancer risk is increased significantly among men with infertility
- Testicular size :The normal range is 12–30 mL .
- Small testes :Testicular dysfunction or hypogonadism
- carefully examined:
 - Size
 - Texture
 - Position
 - Orientation of the epididymis
 - The bilateral presence of the vasa
- ✓ Congenital bilateral absence of vas deferens (CBAVD) suggests the presence of mutation of the CF transmembrane conductance regular gene (*CFTR*). Cysts or nodularity of the epididymis suggest congenital or inflammatory changes that can lead to obstruction.

Varicocele is classified into three grades

- Palpable only with Valsalva maneuver
- palpable even without Valsalva maneuver
- Detectable by visual inspection.

☐ Semen analysis

- Bacteriological semen analysis is usually done at the same time in *C. trachomatis*
- It should be collected by masturbation after two to five days of abstinence
- Aspermia : Absence of semen (retrograde ejaculation or anejaculation due to psychological or neurological causes)
- In the case of retrograde ejaculation, a post-orgasm urine analysis may be performed, with specific preparation (such as alkalization of urine) to evaluate sperm quality

Semen analysis assesses parameters

- Volume
- pH
- sperm concentration
- Vitality
- Motility
- Morphology
- ❑ Low semen volume
 - ❖ In men with CBAVD(poor development of the seminal vesicles)
 - Collection problem
 - Androgen deficiency
 - Obstruction to the ejaculatory duct
 - Partial retrograde ejaculation

Reference values of semen analysis according to the World Health Organization

Criteria	Reference value
Volume	≥ 1.5 mL
pH	≥ 7.2
Total sperm number	≥ 39 million/ejaculate
Sperm concentration	≥ 15 million/mL
Total motility	$\geq 40\%$
Progressive motility	$\geq 32\%$
Normal morphology	$\geq 4\%$
Vitality	$> 58\%$

- PH of semen :

Reflects the balance of pH from various accessory gland secretions

- Seminal vesicle secretions : alkaline

- Prostatic secretions :acidic

- A pH of less than 7 in a sample with low volume and azoospermia strongly suggests ejaculatory duct obstruction or CBAVD

- ❑ Low spermatozoa concentration

- ❖ Completeness of semen collection

- ❖ Accidental spillage of the sample

The total number of spermatozoa per ejaculate and the sperm concentration have been shown to correlate to both time to pregnancy

(TTP) and pregnancy rate

- Severe oligo zoospermia: The limit of 5 million/mL is generally accepted
- Azoospermia :Absence of spermatozoa identified in the sample
- Crypto zoospermia : Spermatozoa only in the sediment of the semen post-centrifugation
- Azoospermia :Obstructive azoospermia (OA) or non-obstructive azoospermia (NOA).

Sperm motility

- progressive motility
- non-progressive motility
- Immotile

Sperm vitality

- An important variable
- Especially for samples with less than 40% progressively motile spermatozoa
- The percentage of dead spermatozoa cannot exceed the percentage of immotile spermatozoa
- Sperm viability is assessed using a dye test or a hypo-osmotic swelling (HOS) test

Morphological anomalies

- Head
- Neck
- mid-piece
- Tail

❑ Increased percentage of abnormal morphology of spermatozoa

- ❖ Defective spermatogenesis
- ❖ some epididymal pathologies
- ❖ Lower fertilizing potential, depending on the types of anomalies, and may also have abnormal DNA.

Antisperm autoantibodies

- Isolated astheno spermia on initial semen analysis
- Agglutination of sperm
- ❑ ASAs can be found in
 - ✓ The serum
 - ✓ The seminal plasma
 - ✓ Bound directly to sperm
- ❑ ASAs are more frequent among infertile males and may decrease the likelihood for conception by impairing sperm penetration of:
 - Cervical mucus,
 - Zona pellucida interaction
 - Oocyte fusion
- ❖ As the clinical utility of ASAs is uncertain, ASA tests should not be part of the routine male fertility evaluation

Sperm DNA fragmentation

- poor semen parameters
- Infertile men
- DNA damage is also found in men with normal semen parameters
- Damage sperm DNA
 - ✓ Gonadotoxin
 - ✓ Heat exposure
 - ✓ Radiation
 - ✓ Varicoceles

Evaluating sperm DNA integrity

- Sperm chromatin structure assay (SCSA)
- Terminal deoxynucleotide transferase-mediated dUTP nick-end labeling (TUNEL) assay
- Single-cell gelelectrophoresis assay (Comet)
- ❖ Abnormal test for SCSA (25%–27%) and TUNEL assay (>36%)
- ❖ Low DNA fragmentation is significantly associated with increased likelihood of pregnancy *in vivo* and after intrauterine insemination

Ultrasound

Evaluate scrotal and inguinal pathologies (e.g., varicoceles and testicular mass) or transrectally(prostate, ejaculatory ducts, and seminal vesicles for cystic lesions or obstruction).

- US is not done routinely in male fertility
- Confirm a pathology that was suspected during physical examination or was suggested based on semen and hormonal analysis

Endocrine tests

The main tests are:

- Serum FSH
- Total testosterone
- Indications:
 - SEXUAL DYSFUNCTION
 - Azo spermia
 - low number Concentration of sperm

☐ This test helps:

- ✓ Distinguish between pituitary–hypothalamic axis dysfunction
- ✓ Testicular dysfunction
- ✓ Reproductive tract obstruction
- ✓ Additional hormonal evaluation
 - LH
 - Prolactin
 - TSH

- Low levels of FSH, LH, and testosterone in the context of low sperm concentrations suggest hypogonadotropic hypogonadism.
- It is not a common cause of male infertility(Kallmann's syndrome or acquired causes as hyperprolactinemia and hemochromatosis).
- In testicular failure testosterone, FSH, and LH levels may be within normal limits.
- In the case of complete testicular failure, FSH and LH will be elevated whereas testosterone will be normal or low.

Genetic testing

- *NOA and severe oligozoospermia*

- ✓ Abnormal spermatogenesis such as in NOA or severe oligozoospermia (<5 million/mL)
- ✓ Genetic testing including karyotype analysis
- ✓ Y-chromosome microdeletion

- *Obstructive azoospermia*

- CBAVD is a common cause of primary OA in healthy men with no prior history of genitourinary disorders
- There is a strong association between CBAVD and mutations of the *CFTR* gene
- CF is a serious autosomal recessive condition. Almost all men with CF exhibit CBAVD. The *CFTR* mutation is also linked to congenital, unilateral agenesis of the vas deferens (CUAVD) and with congenital epididymal obstruction
- In case of agenesis of the vas deferens related to *CFTR* mutation, a history of non-severe pulmonary diseases or asthma may or may not be present.

- ❖ *CFTR* mutations should be tested in all OA patients.
- ❖ *CFTR* screening of the female partner is also essential, but even then a negative result leaves a small residual risk of a CF-affected offspring
- ❖ Where *CFTR* mutations are found in both partners, preimplantation genetic diagnosis may be proposed to the couple to prevent the birth of a child with CF

CONCLUSION

Basic infertility investigations

- uterine cavity
- Fallopian tubes
- ovarian function
- Ovarian Reserve
- semen analysis

□ Our goal

- ✓ provide education
- ✓ Counseling
- ✓ Assistance
- ✓ Emotional support

Thank you for your Attention

