Infertility

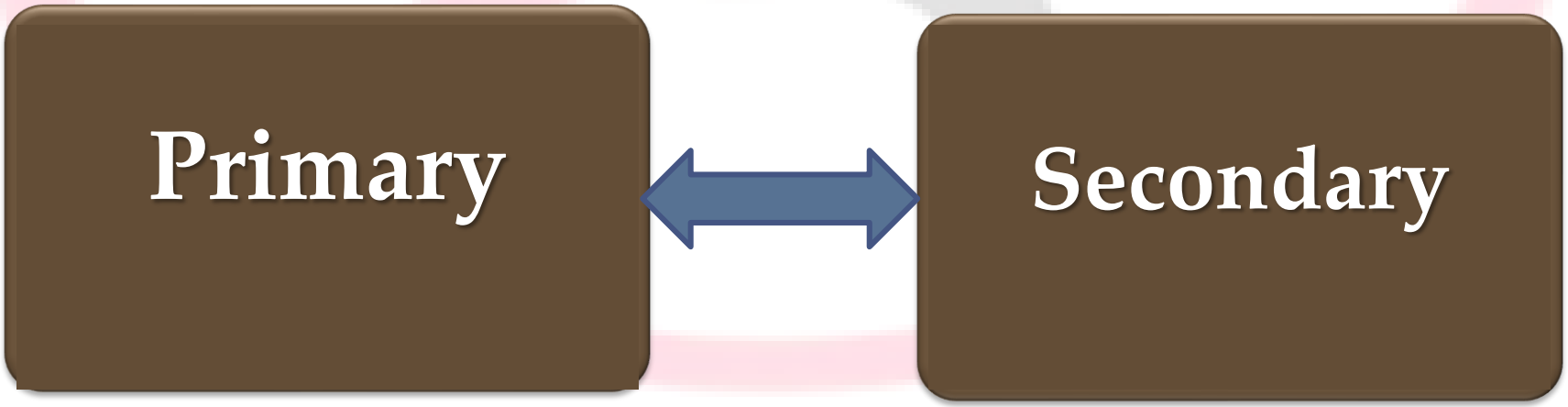
DR.GHAZI AL EDWAN
ASSOCIATE PROFESSOR.

European Association of Urology

Introduction

- Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year.
- About 15% of couples do not achieve pregnancy.
- In 30-40% of cases, no male-infertility-associated factor is found (idiopathic male infertility).
- Prognostic factors for male infertility are:
  1. • duration of infertility;
  2. • primary or secondary infertility;
  3. • results of semen analysis;
  4. • age and fertility status of female partner.

Types of infertility



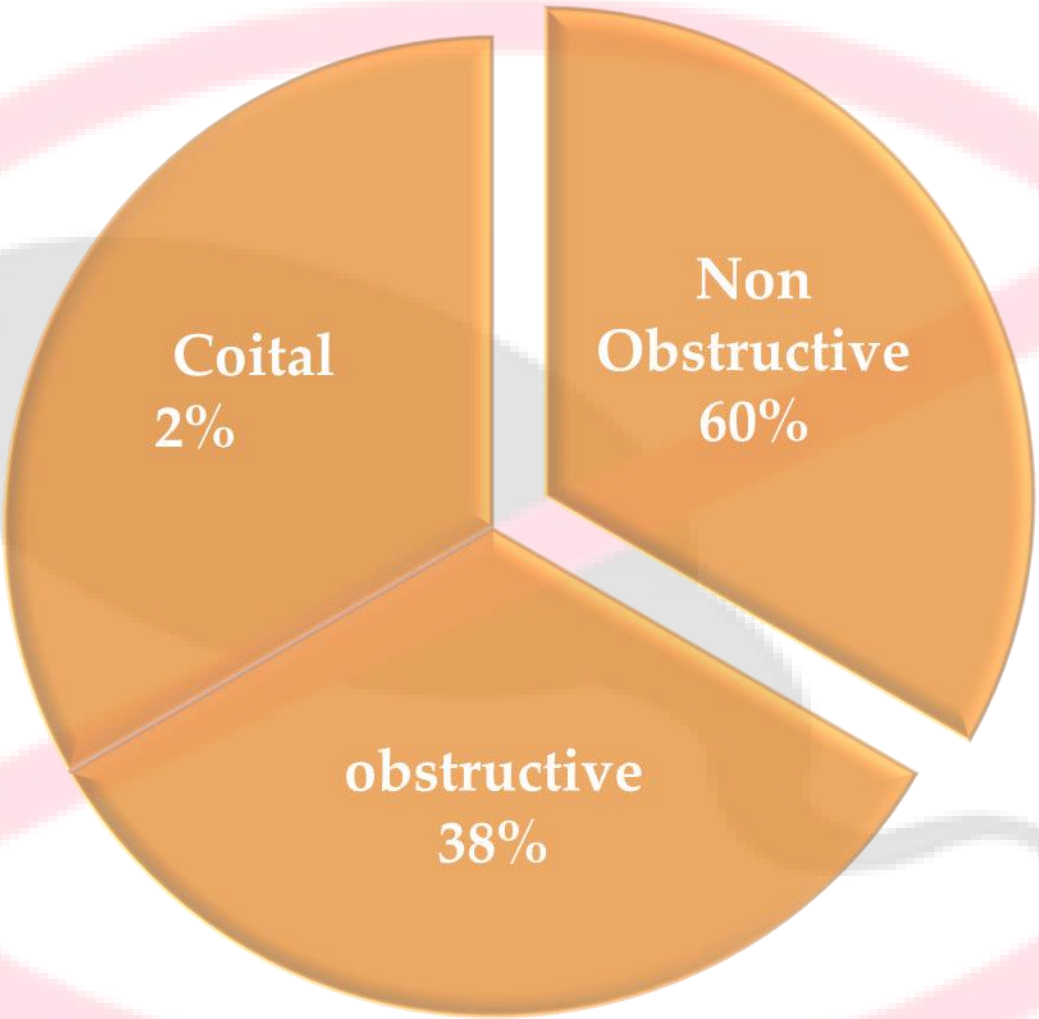
Etiology of infertility

Pre Testicular

Hypothalamic **Pituitary**

Testicular

post Testicular


Coital
2%
Non
Obstructive
60%
obstructive
38%

Etiology of Infertility

Non- obstructive infertility

- Hormonal abnormalities
- Genetic causes
- Varicocele
- Undescended testes
- Exposure to gonadotoxins
- Iatrogenic causes
- Orchitis
- Testicular torsion
- Testicular trauma
- Testicular tumours
- Autoimmune infertility

Obstructive infertility

- Congenital absence of the vas deferens
- Vasectomy
- Vasal obstruction
- Epididymal obstruction
- Ejaculatory duct obstruction

Coital infertility

- Erectile dysfunction
- Premature ejaculation
- Penile deformities
- Anejaculation
- Retrograde ejaculation

Non obstructive infertility

- **Hormonal Abnormality**

- Idiopathic hypogonadotrophic hypogonadism is caused by a deficiency of follicle-stimulating hormone (FSH) and luteinising hormone (LH).
- Brain tumours, head injuries and radiotherapy may also cause hormone abnormalities, leading to infertility. Other hormonal abnormali`ties such as thyroid gland disorders, elevated levels of prolactin and low testosterone levels will also impair sperm production

Non obstructive infertility

➢ Genetic causes

- Structural and numerical chromosomal abnormalities are found in approximately 5 per cent of infertile males and the prevalence may increase in men with complete absence of sperm.

- Genomic assessment
  - Karyotyping ;should be performed in all males with azoospermia caused by spermatogenic dysfunction and in those with severe oligospermia defined as less than 5 million sperm/mL.
  - Y Chromosome microdeletion testing
  - A region in the long arm of the Y chromosome was critical to the formation of sperm in man , which became known as AZF (azoospermia factor)
  - Microdeletions of three regions on the Y chromosome to be commonly associated with azoospermia or oligospermia , which were termed AZFa, AZFb, and AZFc

Klinefelter's syndrome and variants

(47 ,xxy ; 46,xy/47 , xxy mosaicisim)

- 24 , xy sperm : 0.9% and 7.0% with klinefelters mosaicism 1.36 – 25 % with somatic karyotype 47 , XXY
- Azoospermia : TESE (42%) or micro-TESE (57%) can be proposed
- There is growing evidence that TESE or micro- TESE yields higher sperm recovery rates when done at younger age
- ART : the conception of only one 47 ,XXY fetus has been reported

Non obstructive infertility

- **Varicocele**
- The theory is that impaired venous drainage leads to disruption of the counter-current exchange of heat mechanism from the spermatic cord, which elevates scrotal temperature and impairs spermatogenesis. Other postulated mechanisms include impaired drainage of gonadotoxins from the testes and hypoxia.

Non obstructive infertility

Cryptorchidisim :

- **Most common congenital abnormality of the male genitalia - % of all full-term infants**
- **Early surgical treatment may have a positive effect on subsequent fertility (see pediatric guidelines)**
- **Unilateral cryptorchidism : paternity is almost euqal (89.7%) to that in men without cryptorchidism (93.7%)**
- **Bilateral cryptorchism : rate of paternity is only 35-53%**

- **Germ cell tumer (GCT) IS 3.6-7.4 times higher than in general population**
- **2-6 % of men with a history of cryptorchidism will develop a testicular tumour !**
- **Orchedopexy in adulthood : testicular biopsy for detection of ITGCNU is recommended**

Non obstructive infertility

- **Iatrogenic causes:**
- Anti-androgens : biclutamide , flutamide and nilutamide;
- Corticosteroids , especially in adolescence; exogenous estrogen
- Exogenous testosterone acts to decrease intratesticular testosterone synthesis and reduce spermatogenesis

Non obstructive infertility

- **Other causes :**
  - Orchitis

    Inflammation and oedema of the testicular tissue with a surrounding tunica albuginea leads to increase of intratesticular pressure with damage and fibrosis of the germinal epithelium
  - Testicular torsion

    It leads to permanent damage and shrinking of the affected testis as a result of ischaemic necrosis. Moreover, this may be followed by production of antisperm antibodies, which affect the other healthy testis
  - Exposure to gonadotoxins:

Gonadotoxins include chemicals, recreational drugs, tobacco, alcohol, insecticides, pesticides and heavy metals

- Testicular trauma

  leads to intratesticular haematoma or even rupture of the testis; this causes damage of the testicular tissue and breach of the blood–germinal epithelium barrier, causing production of antisperm antibodies

- Testicular tumours

  lead to infertility by destroying and compressing the healthy testicular tissue.

- Autoimmune infertility

  Antisperm antibodies are produced in autoimmune infertility. Germ cells are normally sequestrated from the immune system by the blood–testis barrier formed by Sertoli cells. Conditions that cause disruption of this barrier, such as trauma, testicular surgery, varicocele and orchitis, lead to exposure of the germ cells to the immune system and production of antisperm antibodies

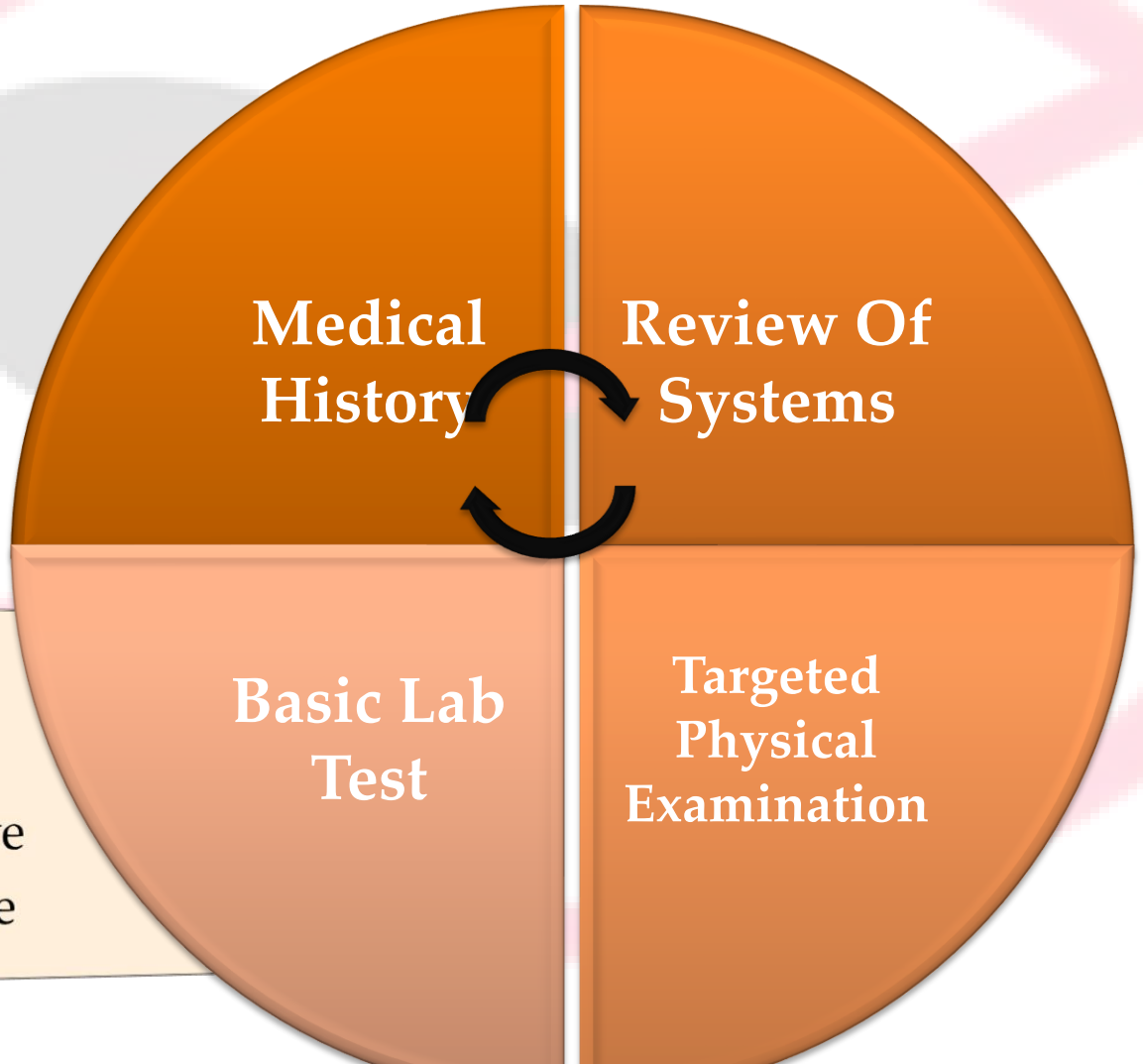
Coital infertility

- **Erectile dysfunction**
- **Premature ejaculation**
- **Penile deformities**
- **Anejaculation**
- **Retrograde ejaculation**

Obstructive infertility

- **Congenital absence of the vas deferens**
- **Vasectomy**
- **Vasal obstruction**
- **Epididymal obstruction**
- **Ejaculatory duct obstruction**

Infertility Approach



- Rapid
- Cost effective
- Noninvasive

History & Review of Systems

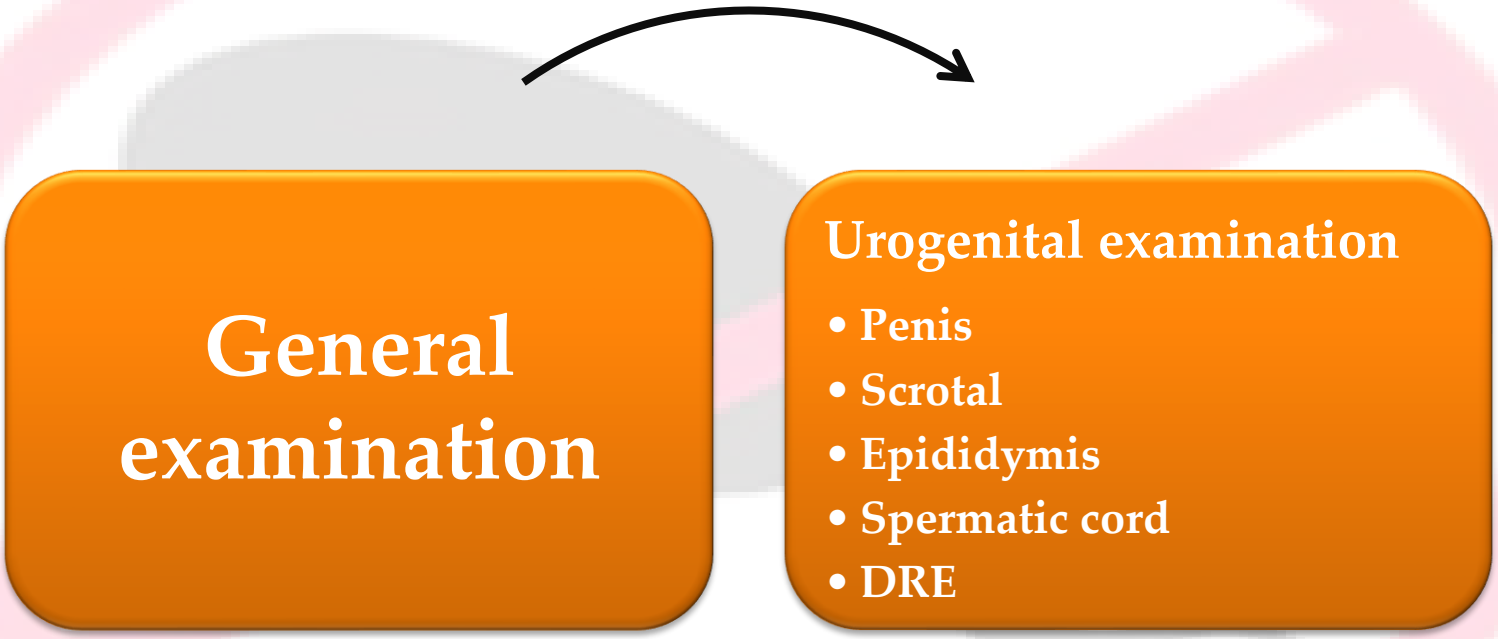
- **Primary Vs Secondary**
  - Privious conception
  - Durations of infertility
  - Method of previous conception

- **Intercourse**
  - Timing and frequency
  - Intercourse that too frequent doesn't allowed replenishment of adequate numbers of spermatozoa within Epididymis whereas infrequent intercourse may miss potential window for fertilization

- **Lubricants**
  - A number of commercially agents have been shown to adversely affect sperm motility
- **Pediatric conditions**
  - Cryptocrchidism
  - Onset of puberty
  - Testicular torsion or trauma
- **Past Surgery**
  - Scrotal , inguinal , or retroperitoneal surgeries
  - Bladder Neck or TURP

- **Systemic disease**
  - DM , Spinal cord Injuries or MS
  - Thyroid gland function
- **Infection**
  - UTI , STD or Epididymo-orchitis
- **Others**
  - Medication
  - Environments
  - Occupation
- **Family hx**

Physical examination



Investigation

- Basic investigation
  - Semen analysis
- Hormonal measurement
- Special investigation
- Imaging
- Testicular biopsy

Semen analysis

- Collecting and timing
  - Suboptimal sperm collection remain a frequent cause of error in semen analysis
  - Abstinence (More recent studies suggest that a single day of abstinence is optimal for assessing bulk seminal parameters)
  - Method of collection (masturbation)
  - Lubricants (should be avoided)
  - Should be placed in room temp. for 30 min and should examined within 1 hour

Cut-off reference values for semen characteristics

Semen analysis WHO 2010

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6/ejaculate)	39 (33-46)
Sperm concentration (10^6/mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (106/mL)	< 1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (µmol/ejaculate)	> 2.4
Seminal fructose (µmol/ejaculate)	> 13
Seminal neutral glucosidase (mU/ejaculate)	< 20

www.uroweb.org/guidelines

Changes in spermiogram parameters

WHO	2 1987 normal	3 1992 normal	4 1999 Ref.	5 2010 threshold range (%) 5	 50	 95
Ejaculate volume (ml)	2.0	2.0	2.0	1.5	3.7	6.8
Total sperm number	40	40	40	39	255	802
Concentration (M/ml)	20	20	20	15	73	213
Progr. Motility (%)	50	50	50	32	55	72
Vitality (%)	50	75	75	58	79	91
Sperm Morphology (%)	50	30	(15)	4	11	21

Macroscopic assessment

- Ph
- Coagulation
- Color
- Viscosity
- Volume

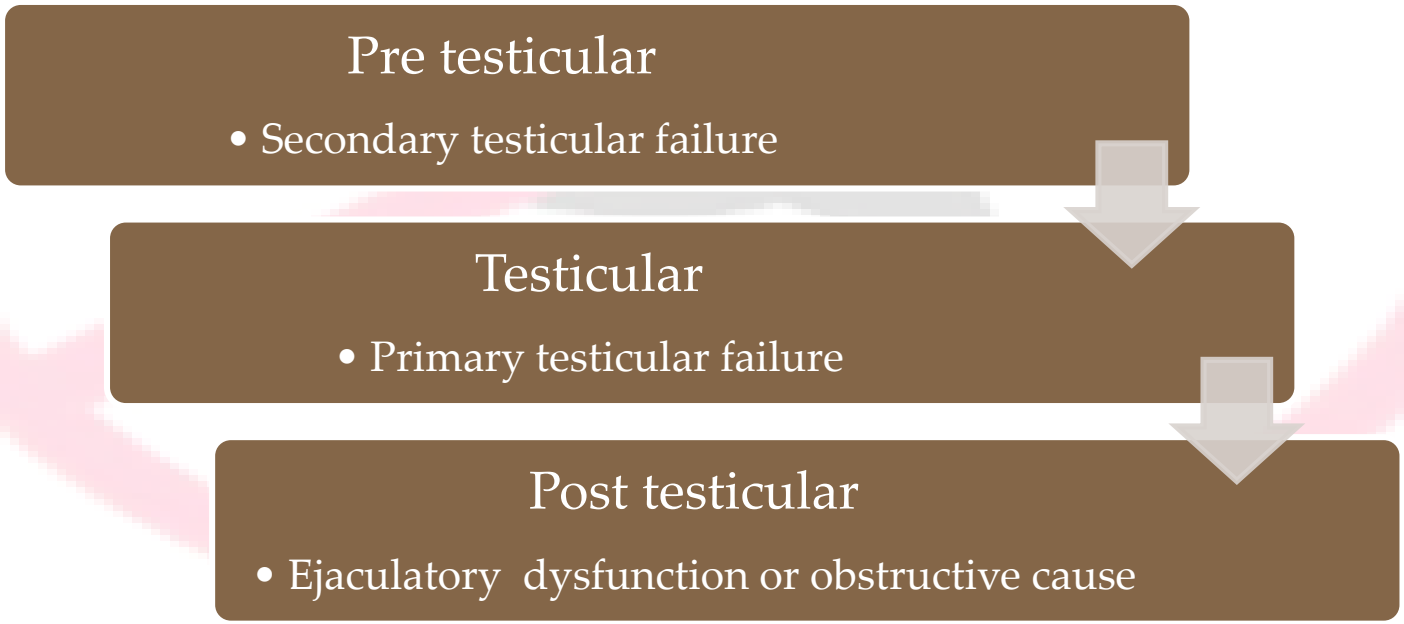
PARAMETERS	NORMAL VALUES	ABNORMALITIES	CLINICAL SIGNIFICANCE
Ph	7.8	Acidic <6.5-7	With low volume and noncoagulation: congenital bilateral absence of vas deferens Ejaculatory duct obstruction Partial retrograde ejaculation
Coagulation / liquefaction	**Within 20 min at room temp**	**No coagulation Prolonged liquefaction**	**Congenital absence of the seminal vesicles Poor prostatic secretions**
Color	**Whitish gray**	**Yellowish color Reddish brown**	**Jaundice, drugs, Haemato-spermia secondary to urethral bleeding or inflammation of the seminal vesicles, exclude genitourinary tumors**
Viscosity	**4mm**	**>6 mm No threading**	**Important when associated with low motility**
Volume	**2-4 ml**	**0 (azoospermia) <2 mL (hypospermia) >4 mL**	**Retrograde ejaculation Incomplete collection Partial retrograde ejaculation Short duration of sexual abstinence**

Microscopic assessment

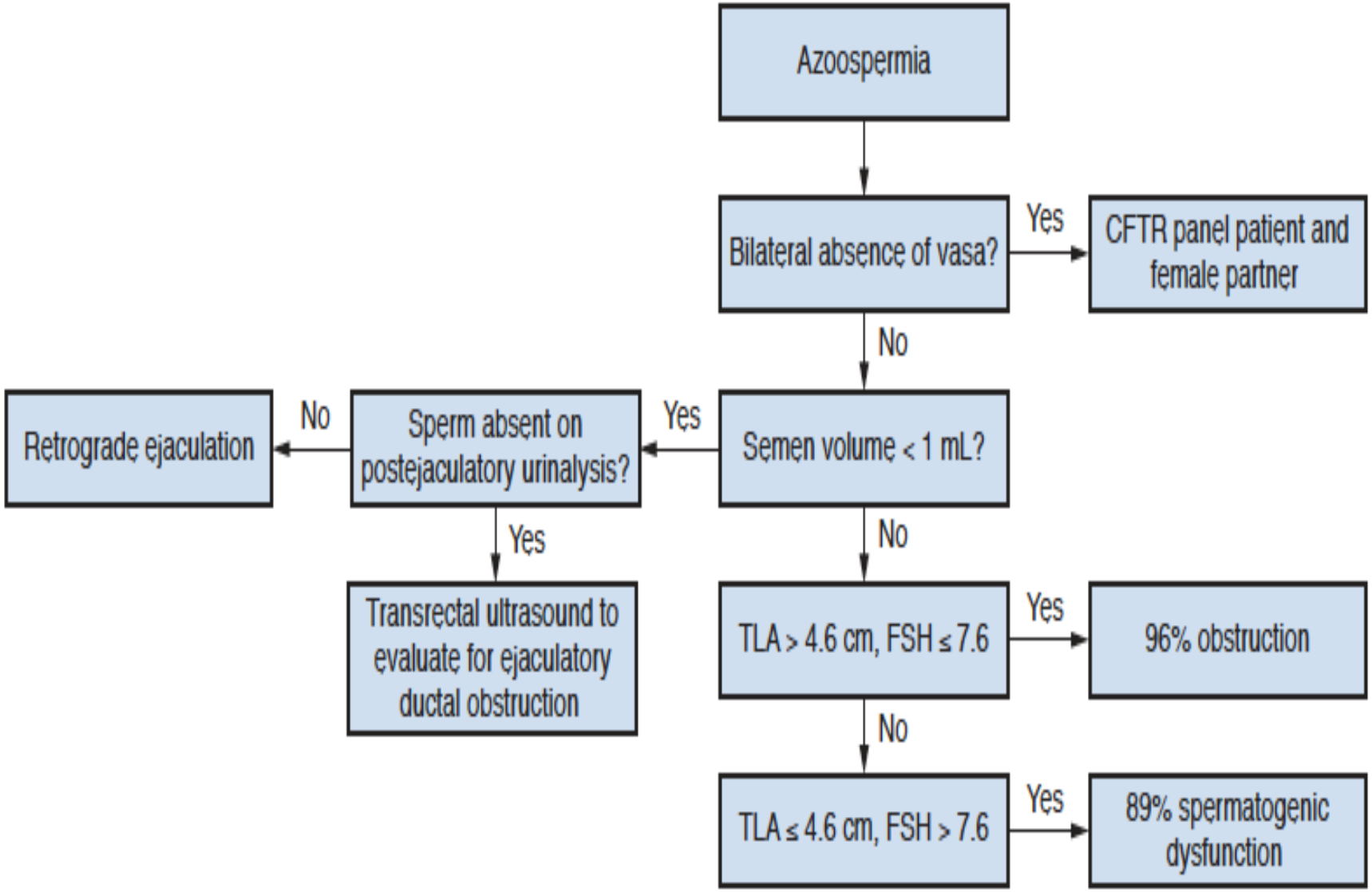
- Count & concentration
- Motility
- Morphology
- Viability
- Nonsperm cells

Azoospermia

- Absence of sperm in ejaculated
- 10-15 % of infertile males
- Should be confirmed by two SFA before further diagnostic test



Azoospermia



Oligospermia

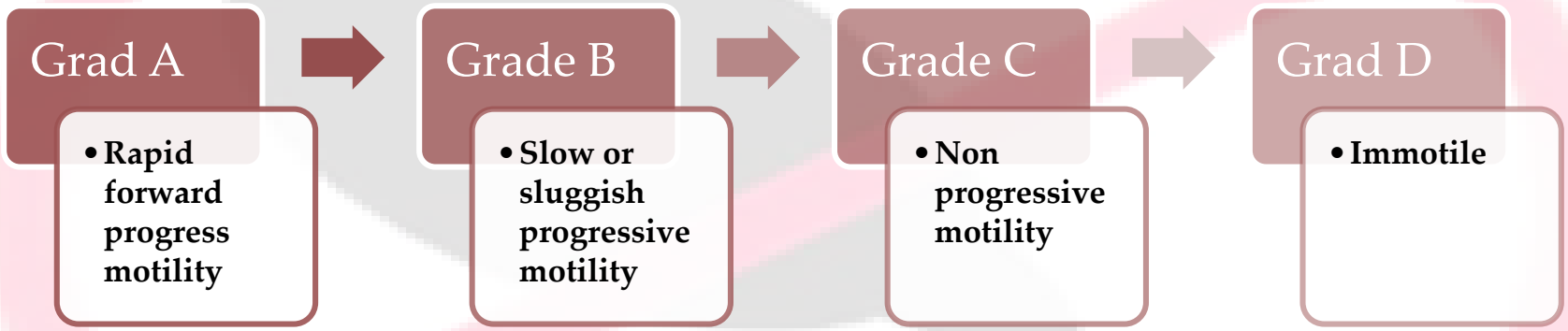
- Sperm density less 1.5 million .
- Rarely found as isolated seminal abnormality.
- If number > 10 Endocrinopathies rarely observed .
- Testosterone & FSH if < 10 million
- Testicular biopsy indicated if < 1 million

Microscopic Assessment

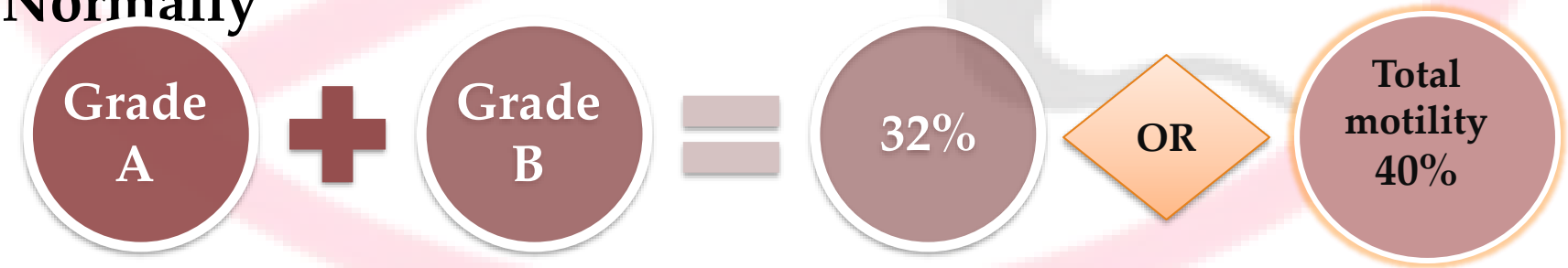
- **Motility**

The most important predictor of the functional aspect of spermatozoa.

WHO grading



Normally



Microscopic Assessment

- **Motility**

Asthenospermia

- Sperm motility less than WHO cutoff level caused by :
  - ✓ prolonged abstinence period
  - ✓ genital tract infection
  - ✓ partial duct obstruction
  - ✓ Varicocele
  - ✓ Anti-Sperm Antibodies are known to reduce sperm motility

Microscopic Assessment

- **Morphology**

Is expressed as percentage of abnormal forms present in the semen.

Teratozoospermia

- ❑ < 15 % normal morphology WHO method caused by :
  - ✓ Fever
  - ✓ Varicocele
  - ✓ stress

- **Viability**

When the motility is reported as less than 5 – 10 % viability testing is recommended because profoundly low motility may indicate dead sperm Necrospermia

This test will differentiate Necrospermia from immotile sperm secondary to ultrastructural defect such a Primary Cilia Dyskinesia

Microscopic Assessment

Non sperm Cells

Immature germ cells

Epithelial cells

High numbers indicate poor collection

Leukocytes

- Leukocyospermia > 1 * (10^6/mL)
  If +ve semen culture should be obtained

RBCs

May indicate inflammation infections or ductal obstruction

Endocrine

- When to suspect endocrainopathy?
  - Low sperm concentration
  - Impaired sexual function
  - Clinical finding suggest endocrainopathy such as marked reduction in testicular size or gynecomastia

- endocrine evaluation include
  - FSH LH Prolactin TSH and testosterone

Genetic testing

- These include Karyotype and Y-link micodeletion assessment used for evaluation of non-obstructive azoospermia and sever Oligospermia as well as CFTR which assesses in men with obstructive azoospermia

Imaging studies

- Transrectal Ultrasonography

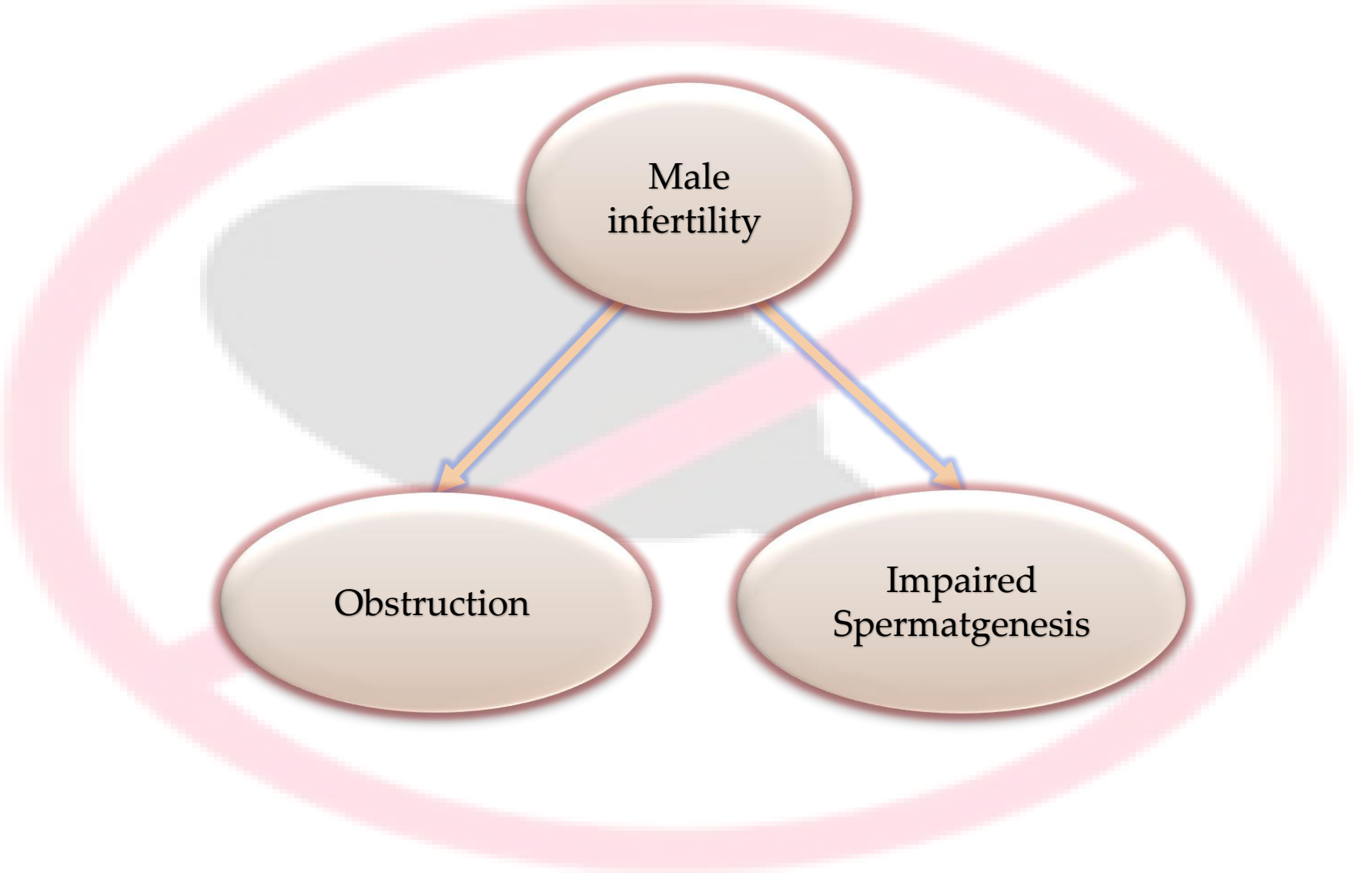
low volume azoospermia with acidic pH

- Scrotal Ultrasonography
- Vasography

Testicular Biopsy

- Diagnostic testicular biopsy is primary indicated for evaluation of the azoospemic patient presenting with clinical picture suggestive of obstruction.
- On occasion it may performed in patient with clinical evidence of primary testicular failure.

Treatment

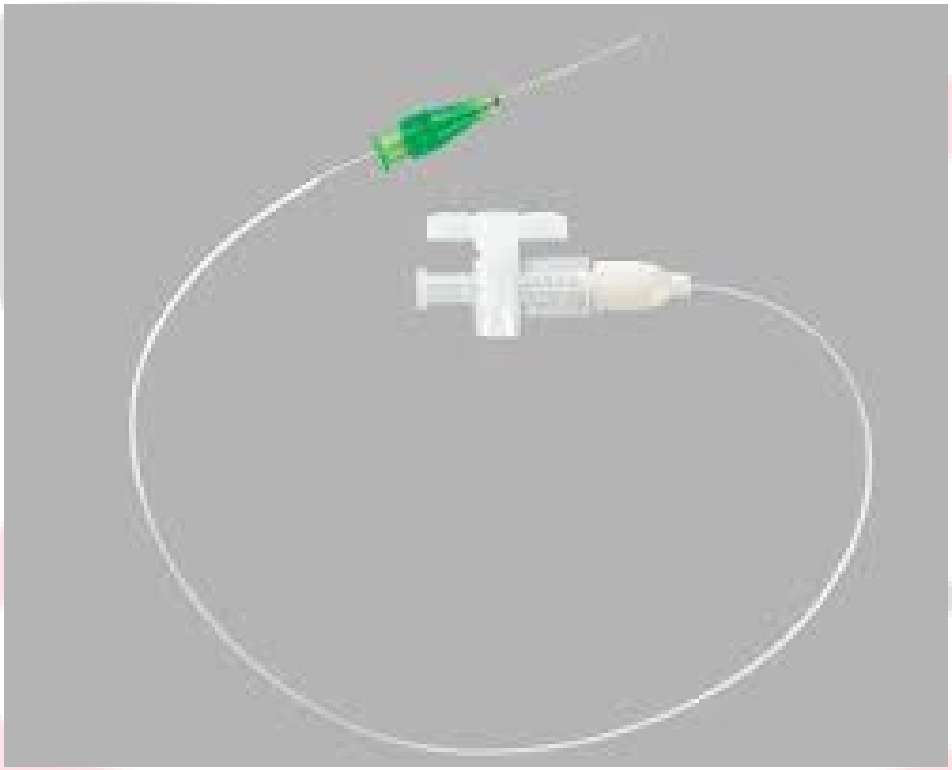


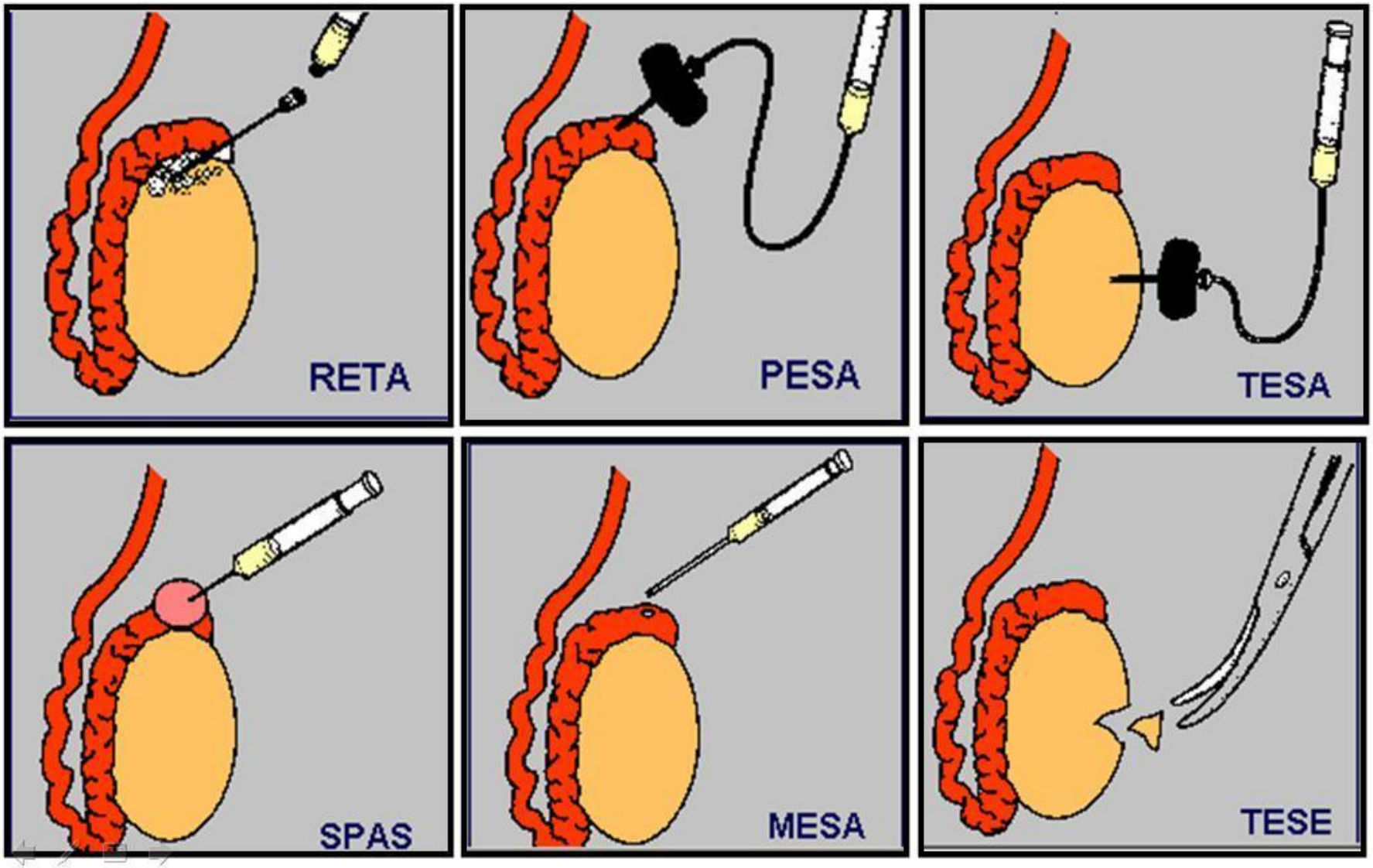
Testicular Sperm Extraction (TESE)

indications :

- Non obstructive azoospermia
- Failure to find sperm in the epididymis in the presence of the spermatogenesis or complete absence of the epididymis
- Testicular sperm has been retrieved via one of three techniques:
- Open TESE, preferably with an operating microscope (micro-TESE)
- Percutaneous core Biopsy using 14-gauge biopsy gun
- Percutaneous aspiration (testicular sperm aspiration [TESA])

TESTICULAR SPERM ASPIRATION NEEDLE




RETA
PESA
TESA
SPAS
MESA
TESE

Varicocele

- 11.7% of adult men and in 25.4% of men of abnormal semen analysis.
- Meta-analysis: semen improvement after surgical correction.
- Varicocelectomy in azoospermic men before TESE?
- Varicocelectomy can reverse sperm DNA damage.
- Treatment of clinical Varicocele favored treatment with combined odds ratio (OR) of 2.39 (95% Cl 1.56 to 3.66).
- Meta-analysis: varicocelectomy may improve outcomes followings ART in oligozoospermic men.

Varicocele

child

adult

Recommendations	Strength rating
Treat varicoceles in adolescents with ipsilateral reduction in testicular volume and evidence of progressive testicular dysfunction.	Weak
Do not treat varicoceles in infertile men who have normal semen analysis and in men with a subclinical varicocele.	Strong
Treat men with a clinical varicocele, oligozoospermia and otherwise unexplained infertility in the couple.	Weak

Techniques

TECHNIQUE	ARTERY PRESERVED	HYDROCELE (%)	FAILURE (%)	POTENTIAL FOR SERIOUS MORBIDITY
Retroperitoneal	No	7	15-25	No
Conventional inguinal	No	3-30	5-15	No
Laparoscopic	Yes	12	3-15	Yes
Radiographic	Yes	0	15-25	Yes
Microscopic inguinal or subinguinal	Yes	0	0.5-1.0	No

Treatment of Palpable Varicocele in Infertile Men: A Meta-analysis to Define the Best Technique

Review

SELAHITTIN ÇAYAN,* SHAVKAT SHAVAKHABOV,† AND ATEŞ KADIOĞLU†

*From the *Department of Urology, University of Mersin School of Medicine, Mersin, Turkey; and the †Section of Andrology, Department of Urology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey.*

- open surgery

- microsurgery

- laparoscopy

- sclerotherapy

(CAYAN, J.Androl, 2009)

Germ cell malignancy and male infertility

- Men with TGCT have decreased semen quality, even before cancer is diagnosed with azoospermia in about 5-8%.
- Semen cryopreservation before orchidectomy is recommended.
- **In case of azoospermia, testicular sperm may be recovered to safeguard the patient's fertility (Onco-TESE).**
- Men with TGCT and low normal androgen levels, long-term follow-up concerning hypogonadism is recommended (highest risk with > three cycles of chemotherapy or irradiation).

Idiopathic hypogonadotropic hypogonadism

- Isolated condition.
- Or associated with anosmia/hyposmia (Kallmann syndrome).
- Stimulation of sperm production: treatment with human chorionic gonadotropin (hCG) combined with recombinant FSH, urinary FSH or human menopausal gonadotropins (HMGs).
- *Alternatively pulsatile GnRH pump (revival).*
- Patients with androgen replacement only may need gonadotropins or GnRH for one to two years to achieve sperm production.

Idiopathic male infertility

- In at least 44% of infertile men.

Treatment options:

- Lifestyle modification.
- Clomiphene citrate and tamoxifen: meta-analysis improvement in sperm quality and spontaneous pregnancy rates.
- Androgens, bromocriptine, ◎-blockers, systemic corticosteroids and magnesium supplementation are not effective in the treatment of OAT.

- Gonadotrophins (HMG/rFSH/hpFSH) might be beneficial in regards to pregnancy rates and live birth in idiopathic male factor sub-fertility,
- Oral antioxidants: significant increase in sperm parameters and in live birth rates in IVF patients (Cochrane analysis).
- Antioxidants and natural conception: further investigations needed.

thank you
danke
謝謝
ngiyabonga
شكراً جزيلاً
teşekkür ederim
gracias
merci
obrigado
bedankt
dziękuję
go raibh maith agat
mochchakkeram
sukriya
kop khun krap
terima kasih
감사합니다
ありがとう
спасибо
Баярлалаа
рахмат
mersi
barka
welalin
tack
spas
kia ora
faafetai lava
vinaka
спасибі
blagodaram
dank je
misaotra
matondo
paldies
grazzi
mahalo
tapadh leat
хвала
asante
manana
obrigada
tenki
murakoze
kiitos
dankie
nanni
nandri
dhanyavad
hvala
mauruuru
köszönöm
bayarlalaa
gràçie
enkosi
aciu
dankon
akun
djiere dieuf
tau
дякую
mamnun
chokrane
chnorakaloutioun
gratias ago
gràcies
sulpáy
taiku
sobodi
děkuji
sagolun
arigatô
takk
dakujem
trugarez
mèsi
didi madloba
najis tuke
kam sah hamnida
rahmat
tanemirt
grazie
rahmet
diolch
dhanyavadagalu
shukriya
merce
мерси
xièxie
ευχαριστώ
তোমাকে ধন্যবাদ