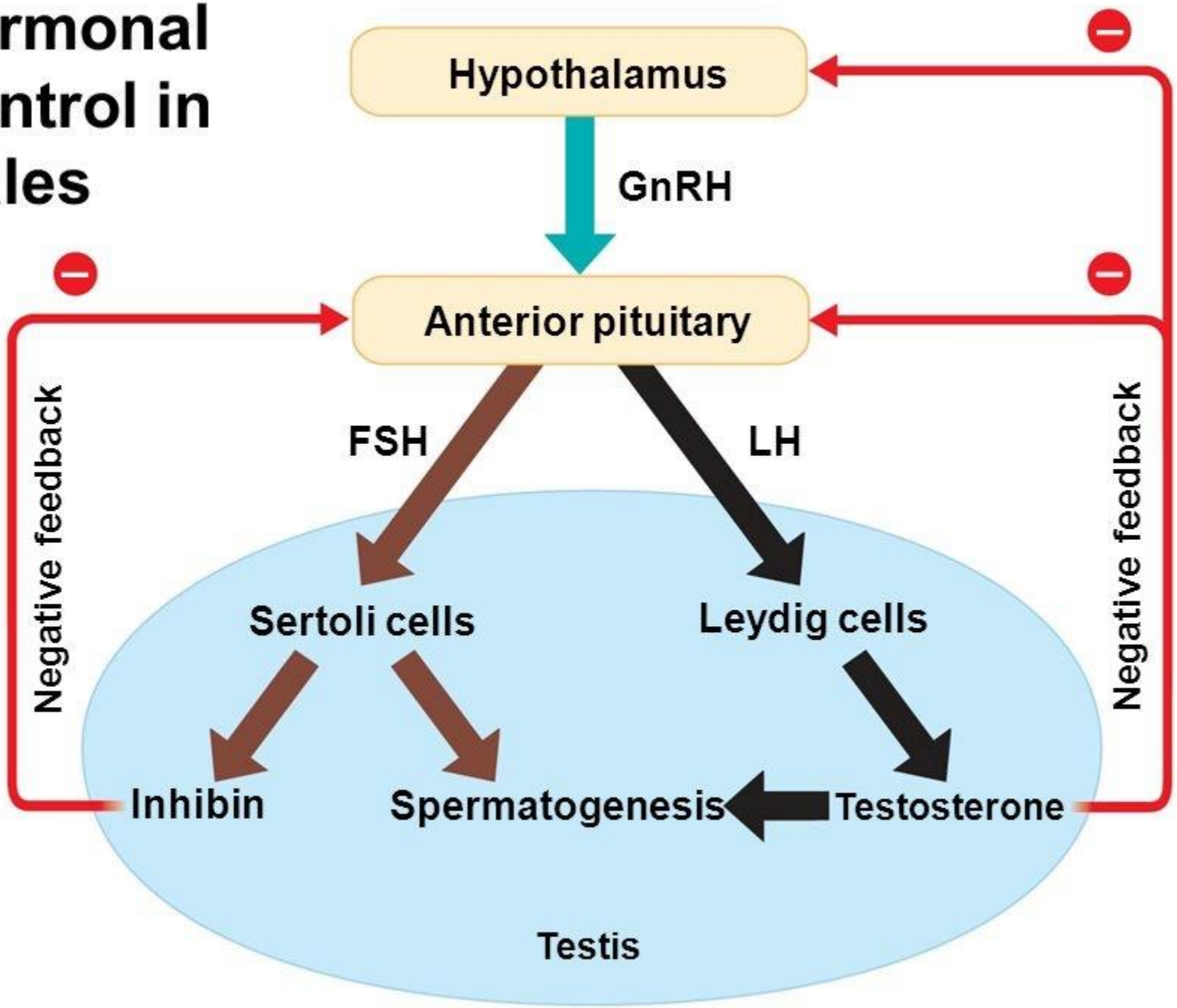
Male reproductive anatomy, physiology and infertility

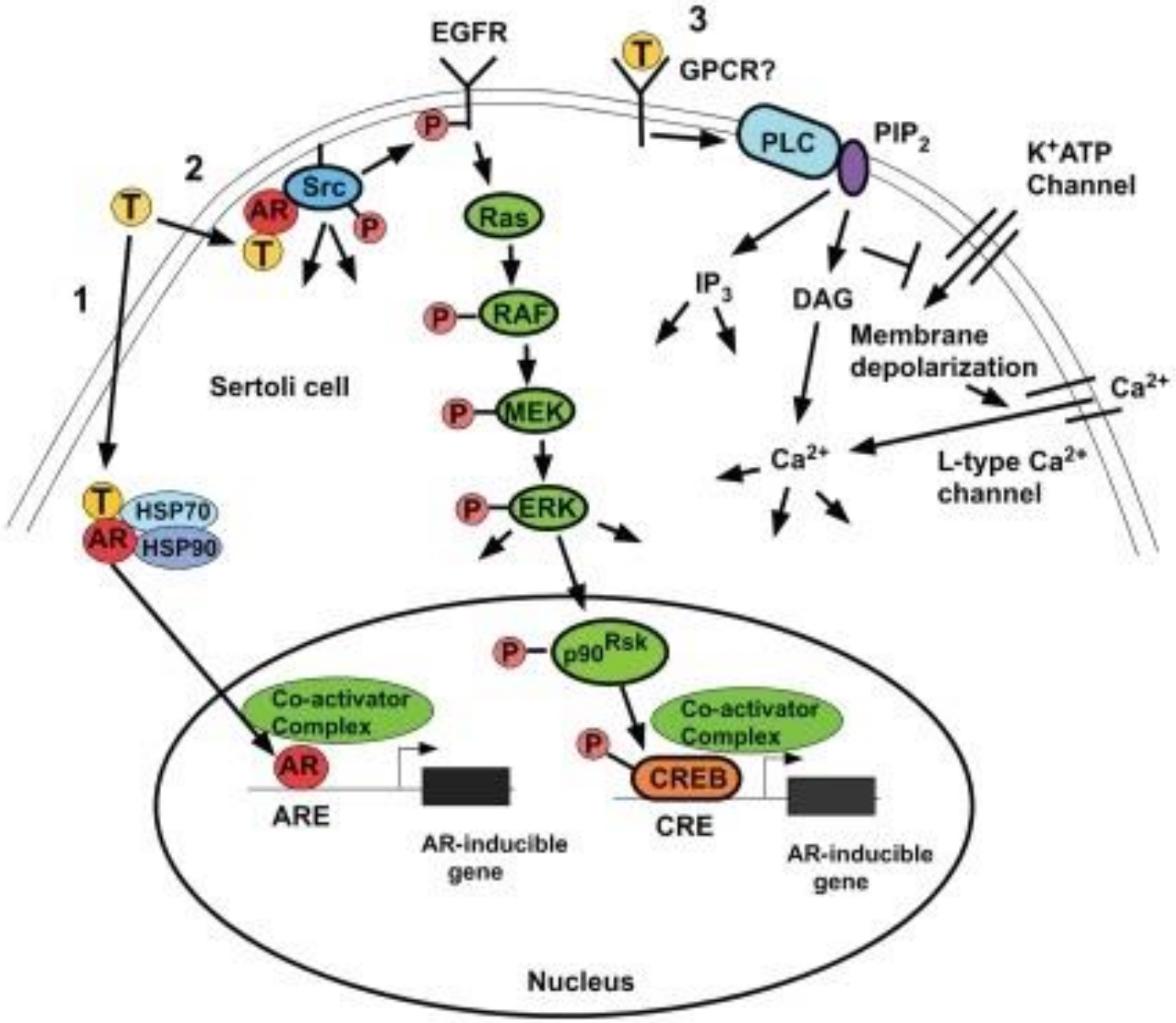
- 以胚胎學來看, 睪丸於第七週開始形成
- 第八週時,睪丸製造兩種荷爾蒙: (1) Testosterone (T) (2) Mullerian-inhibition protein (MIP)
- T 從 Leydig cell分泌, 促使同側Wolffian duct 分化成epididymis and vas deferens 並開始成形
- MIP 從Sertoli cell, 抑制Mullerian duct使其退化成 testicular appendix.
- 第八到第十六週形成外生殖器. 由testosterone 經5a reducatase 成 dihydrotestosteron (DHT), 誘發外生殖器產生
- 正常男性一天製造約5-7g testosterone.
- 在血液中與 albumin (38%), SHBG (60%)結合. 2% free form bioactive.
- 代謝物 DHT 與 estradiol

Testosterone signalling and spermatogenesis regulation

- Absence of testosterone or the androgen receptor, spermatogenesis does not proceed beyond the meiosis stage.
- The major cellular target and translator of testosterone signals to developing germ cells is the Sertoli cell.
- In the Sertoli cell, testosterone signals can be translated directly to changes in gene expression (the classical pathway) or testosterone can activate kinases that may regulate processes required to maintain spermatogenesis (the non-classical pathway).

Hormonal Control in Males




EGFR
3
GPCR?
T
PLC
PIP2
K+ATP
Channel
2
Src
AR
P
T
Ras
1
P
RAF
IP3
DAG
Membrane
depolarization
Ca2+
Sertoli cell
P
MEK
Ca2+
L-type Ca2+
channel
T
HSP70
AR
HSP90
P
ERK
P
p90Rsk
Co-activator
Complex
Co-activator
Complex
AR
P
CREB
ARE
CRE
AR-inducible
gene
AR-inducible
gene
Nucleus

Spermatogensis

- in vivo kinetic study revealed duration of spermatogenesis ranges from 42 to 76 days.
  - spermatocytogensis (proliferative phase)
    - spermatogonia self-renewal or
    - differentiation (spermatocytes)
  - meiotic phase
    - reduction division, resulting in haploid spermatids
  - spermiogensis phase
    - mature spermatozoa

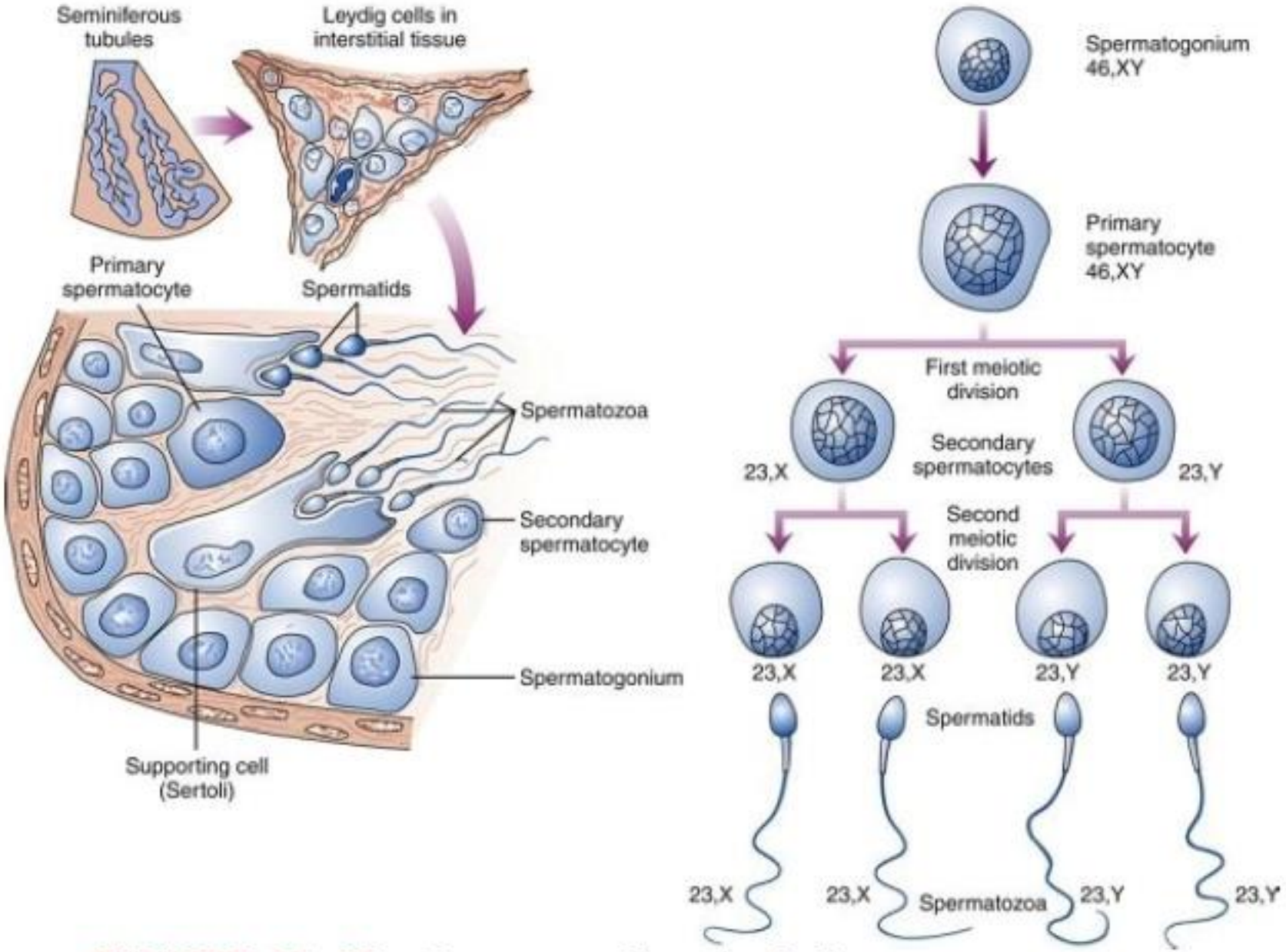
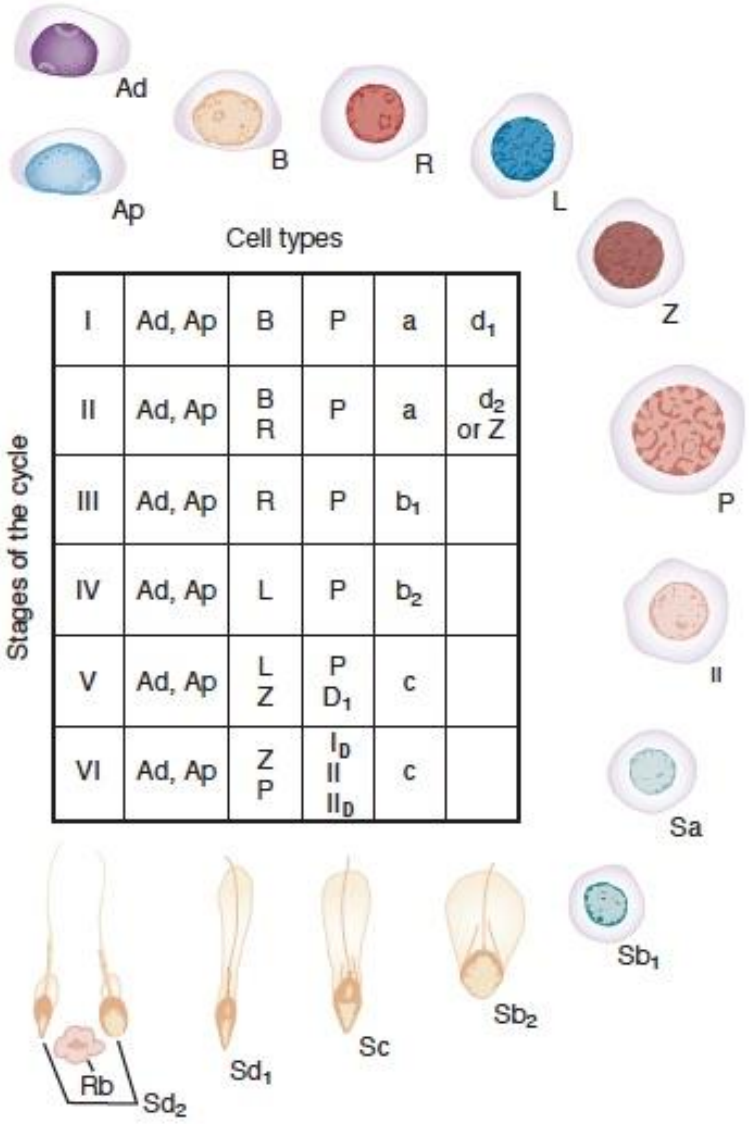


FIGURE 30-15 **Process of meiosis in spermatogenesis.**

6 steps of spermatogenesis



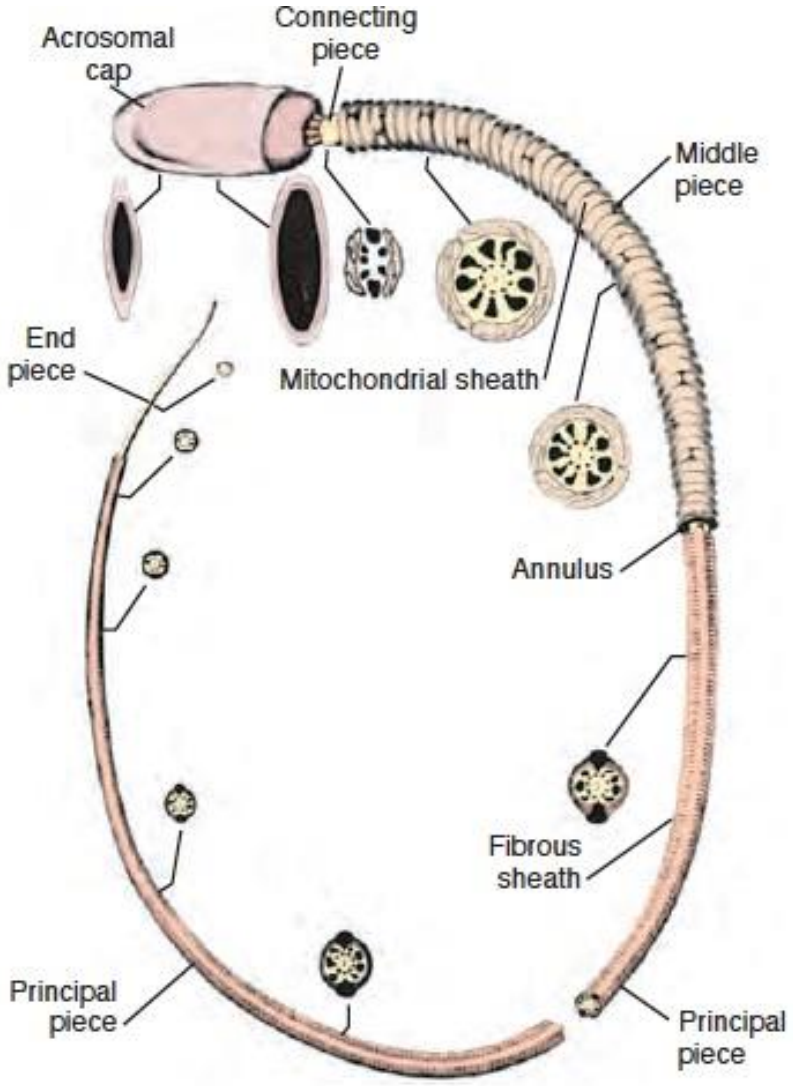
Cell types

Stages of the cycle

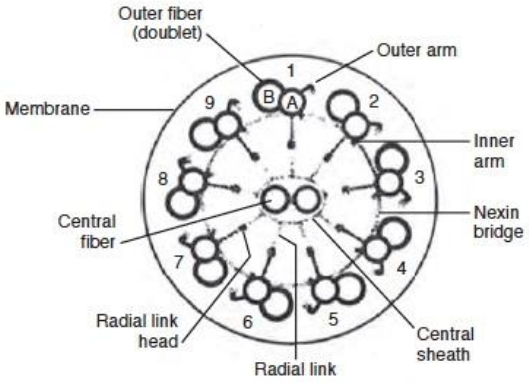
I	Ad, Ap	B	P	a	d_1
II	Ad, Ap	B R	P	a	d_2 or Z
III	Ad, Ap	R	P	b_1	
IV	Ad, Ap	L	P	b_2	
V	Ad, Ap	L Z	P D_1	c	
VI	Ad, Ap	Z P	I_D II II_D	c	

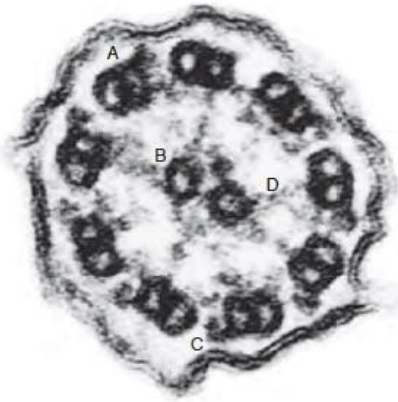
Ad, dark type A spermatogonium
Ap, pale type A spermatogonium
B, type B spermatogonium;
II, secondary spermatocyte;
L, leptotene spermatocyte;
P, pachytene spermatocyte;
R, resting or preleptotene primary spermatocyte;
Rb, residual body;
Sa(a), Sb1 (b1), Sb2 (b2), Sc (c), Sd1 (d1), Sd2 (d2), spermatids;
Z, zygotene spermatocyte.

Anatomy of spermatozoa



- approx 60 um
- acrosome contains enzymes for penetration
- Tail: middle, principle and end
- Axoneme (9+2) provides movement

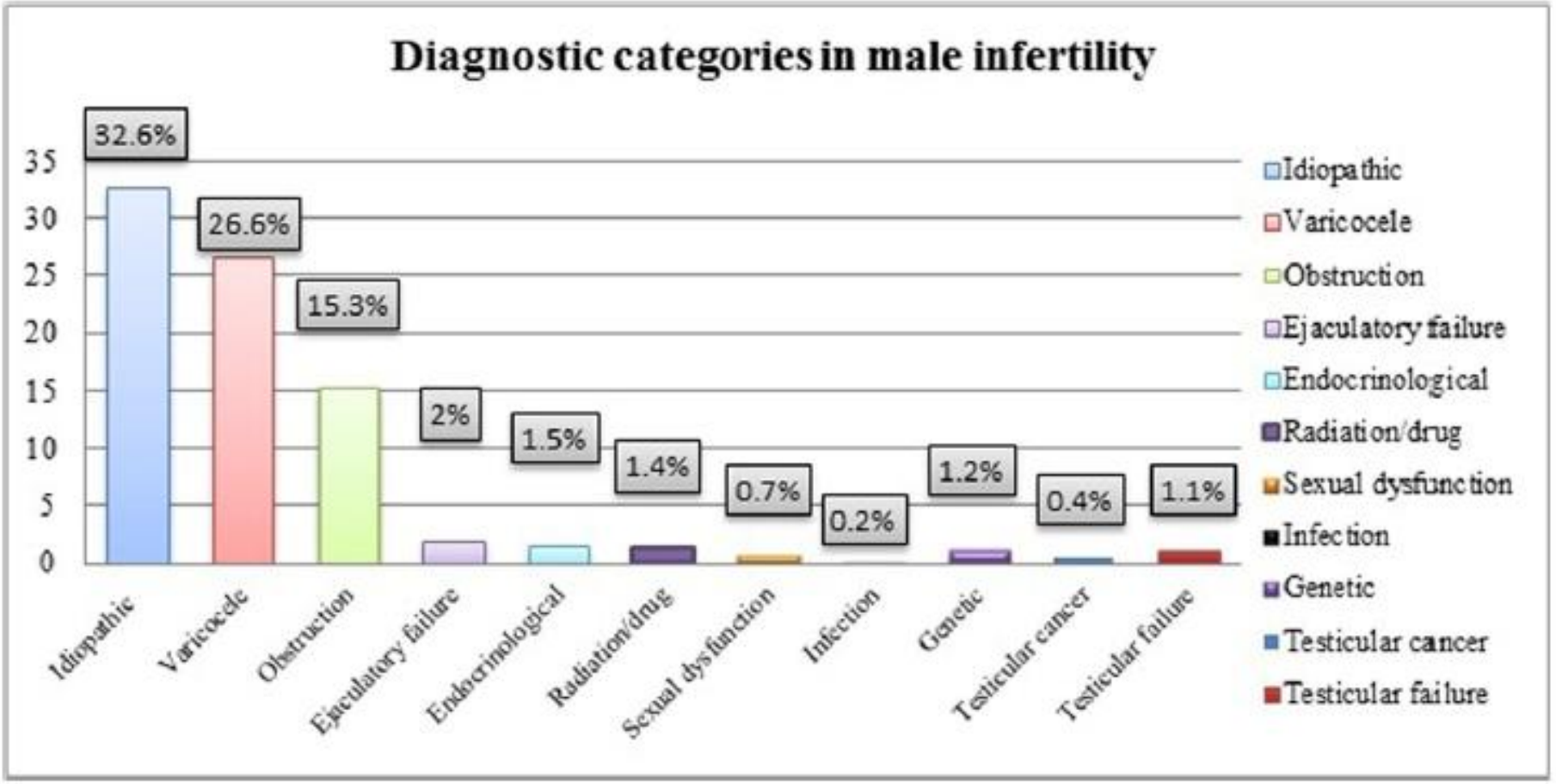




Infertility

- Def: inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in 1 year (WHO).
- Approximately 35% is due to male factors, 35% is due to female factors, 20% of cases have a combination of both male and female factors, and the last 10% are unexplained causes.

Causes and associated factors

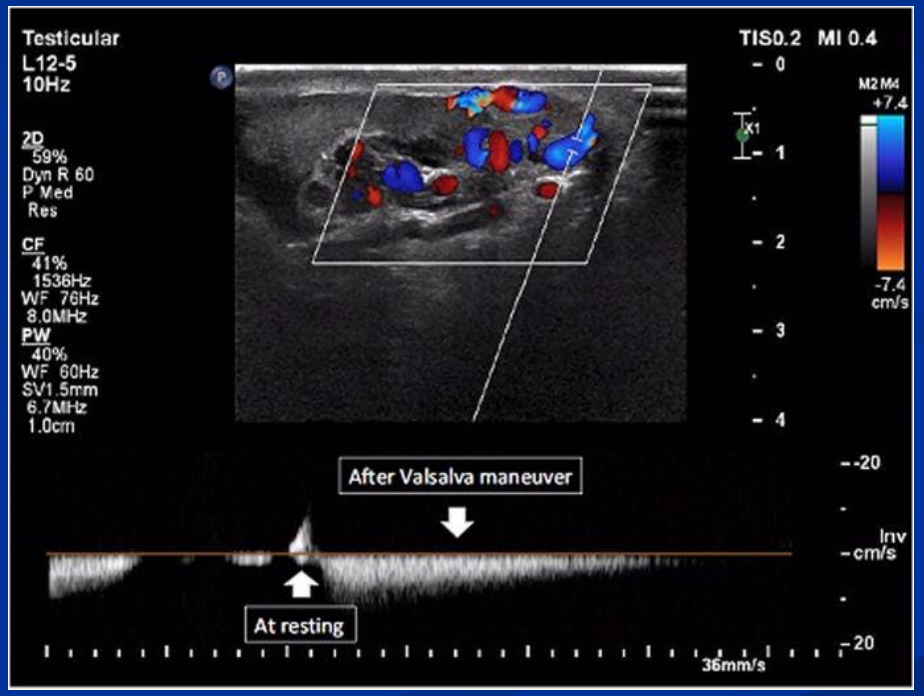


Diagnostic evaluation

- History
- P/E
- U/A
- Scrotal ultrasound. 3 cm (AP) x 2-4 cm (TR) x 3-5 cm (length), with a volume of 12.5-19 mL
- TRUS-P. (dilated seminal vesicle > 1.5 cm).Ejaculatory duct diameter range of 0.04 to 0.08 cm
- Semen analysis: at least 2
- Hormonal tests: Essential (FSH, T), + LH, Prolactin, estradiol

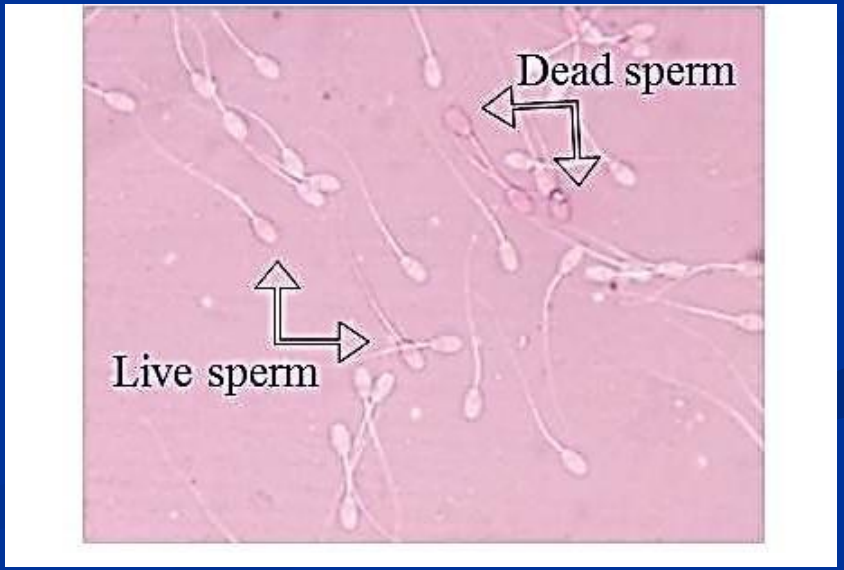
Varicocele

- Controversial in adults
- Spermatic vein diameter (>3mm or 2mm)
- Reversal of flow after Valsalva maneuvers
- Duration of venous reflux (>2s)
- Peak retrograde spermatic vein flow with Valsalva maneuvers (>38cm/s)



Semen analysis

- Collection: abstinence required, brough to lab within 2-3hr and maintained at 20C
- Physical properties: liquefaction, viscosity, volume, pH.
- Vitality: eosin-nigrosin test
- Number of spermatozoa
- Non-sperm cells
- Morphology
- Anti-sperm ab



Semen analysis

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 (10^6/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

CIs = confidence intervals; MAR = mixed antiglobulin reaction NP = non-progressive; PR = progressive.

Oligo-zoo-spermia: < 1.5 10^6
Astheno-zoo-spermia: <32% progressive motile
Terato-zoo-spermia: <4% norm form

Azoospermia

- Obstructive (OA) vs. Non-obstructive (NOA)
- Central NOA vs. Testicular NOA
- Generally, men with azoospermia, normal size testes and normal FSH levels have normal spermatogenesis are likely to have OA.
- Elevation in FSH is suggestive of testicular NOA.
- low gonadotropins and low T suggest s a central NOA.

Classification scheme of azoospermia based upon pre-testicular, testicular, and post-testicular etiologies.

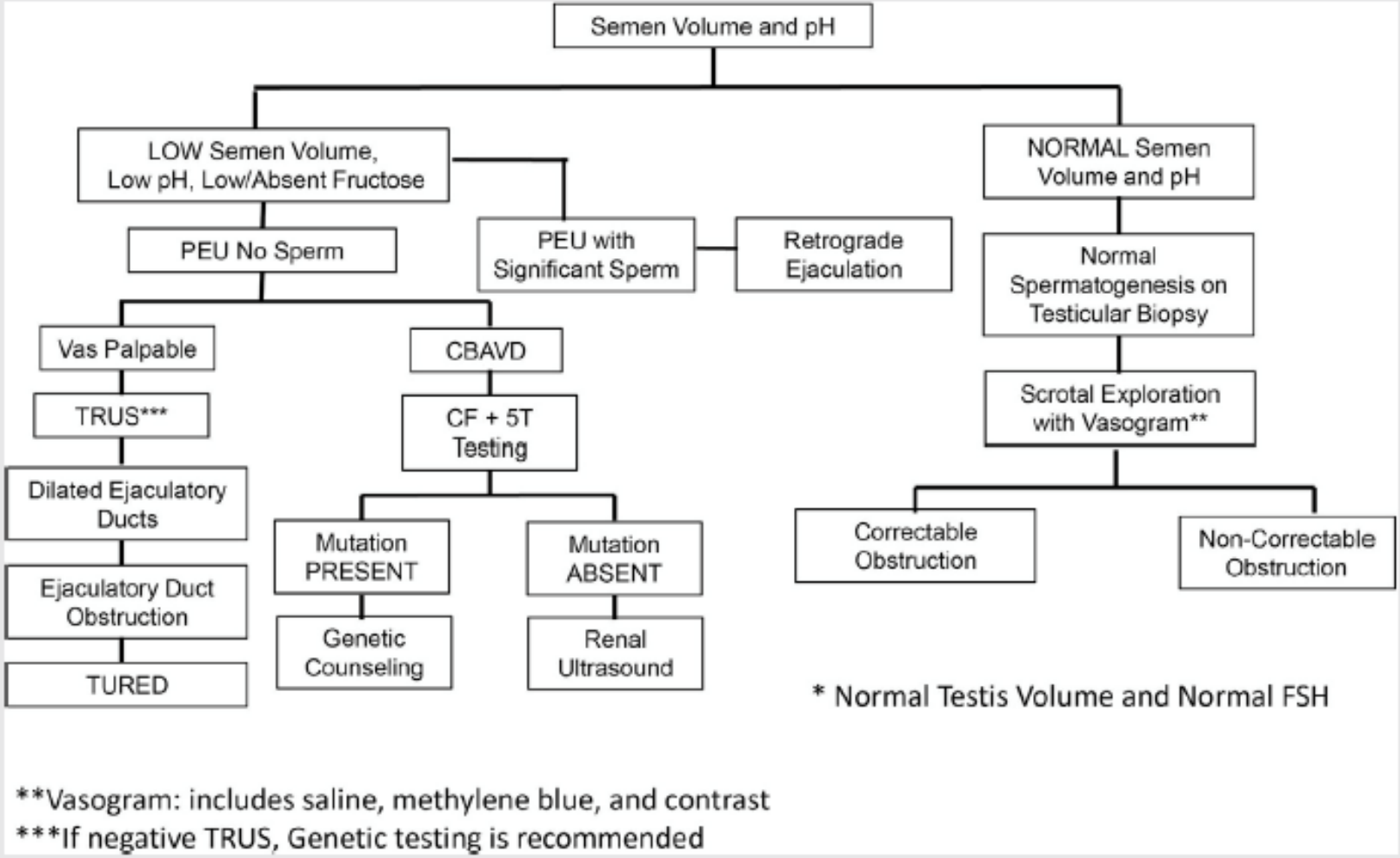
Etiology	Semen volume	T	FSH
Pre-testicular			
Hypogonadotropic hypogonadism	N / ↓	↓	↓
Exogenous androgens	N / ↓	↑ / N / ↓	↓
Testicular			
Primary testicular failure, genetic etiology, varicocele	N	↓	↑
Post-testicular			
Vasectomy, epididymal obstruction	N	N	N
Ejaculatory duct obstruction, ejaculatory dysfunction	↓	N	N / ↑

FSH = follicle-stimulating hormone, N = normal, T = testosterone.

ASRM. Evaluation of the azoospermic male. Fertil Steril 2018.

OA

- Low ejaculate volume (< 1.5mL) and normal FSH and testis volume => re-collection, post-ejaculate UA (retrograde ejaculation)
- Low ejaculate volume, palpable vas deferens, no retrograde ejaculation, semen pH < 7.2 => TRUS-P to evaluate seminal vesicles/ ejaculatory duct, + fructose (-)
- Approx. 10-15% of congenital bilateral absence of vas deferens (CBAVD) have unilateral renal agenesis.

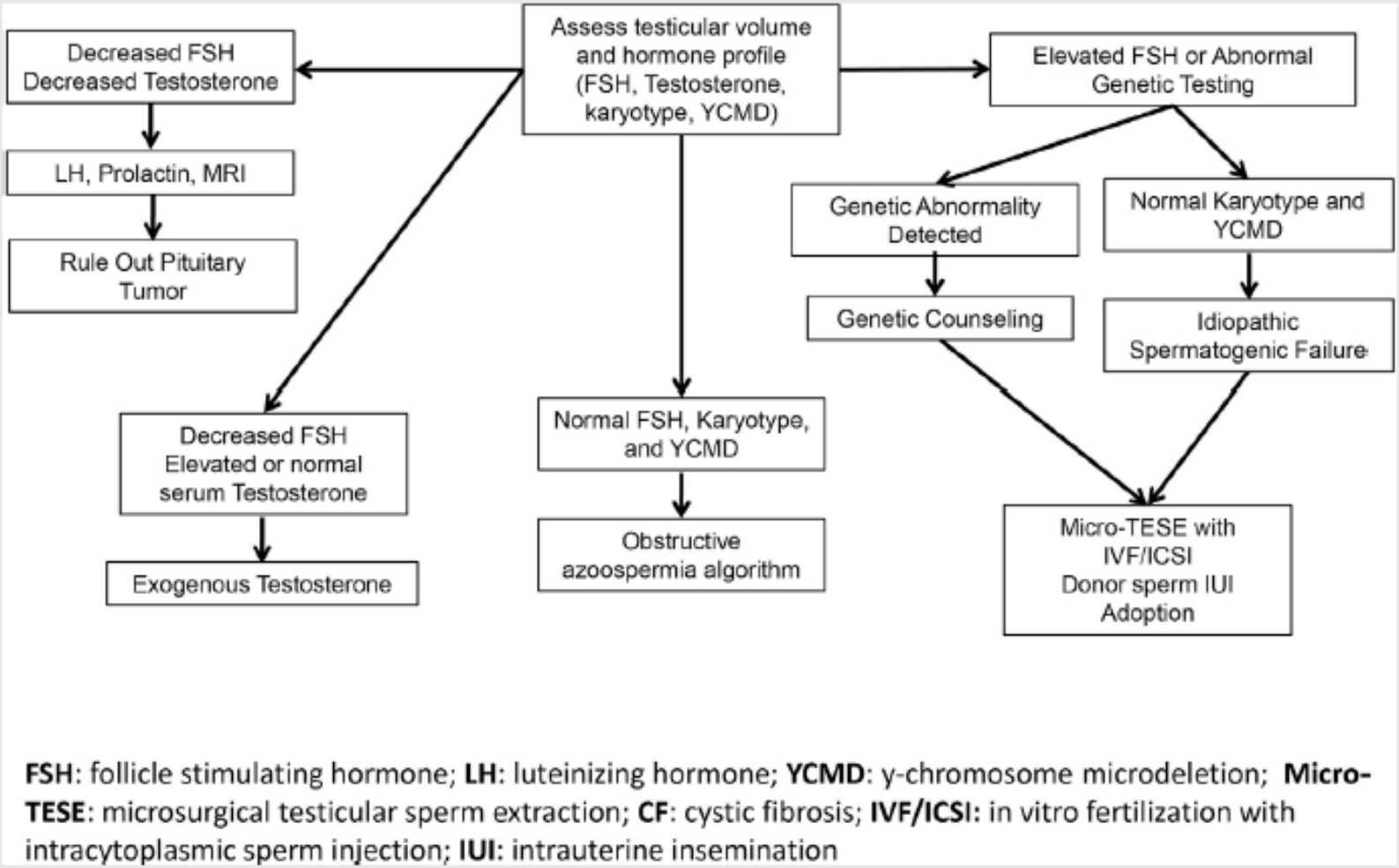


Algorithm for obstructive azoospermia.

ASRM. Evaluation of the azoospermic male. Fertil Steril 2018.

NOA

- An elevated FSH (>7.6 mIU/mL) and a normal/ low T + bilateral testicular atrophy => primary testicular failure. (genetic testing: chromosomal abnormalities, Y-chromsome microdeletions, YCMD)
- Low gonadotropins and bilateral testicular atrophy suggests hypogadotropic hypogonadism => hypothalamic disorders (ie. Kallmann syndrome)



Evaluation of nonobstructive azoospermia (normal semen volume).

ASRM. Evaluation of the azoospermic male. Fertil Steril 2018.

Genetic testing for NOA

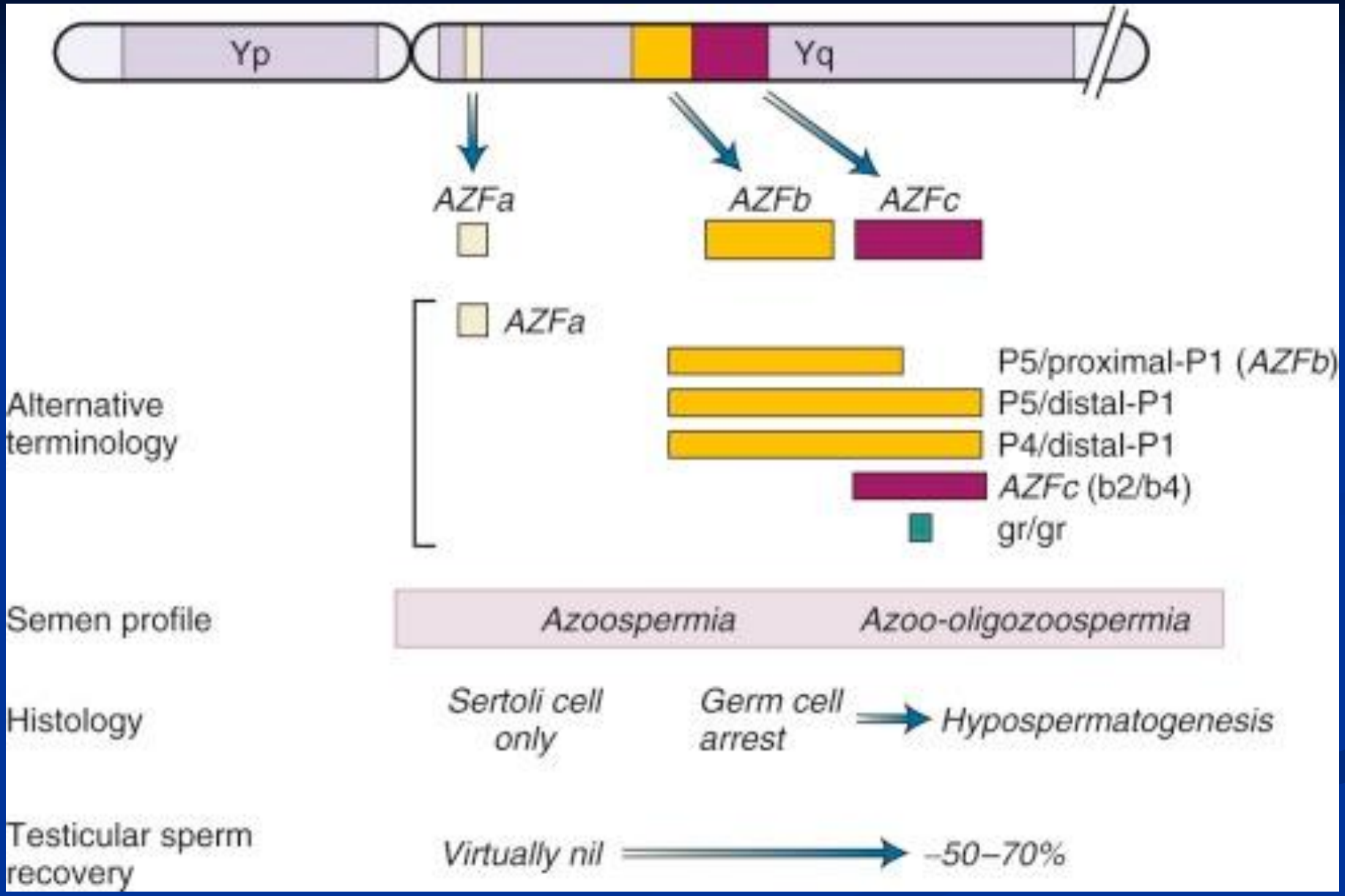
- Chromosomal abnormalities => impaired testicular function
- YCMD => isolated spermatogenic impairment

Karyotypic chromosomal abnormalities

- Chromosome deletion
- Translocation (有機會 sperm retrieval)
- Inversion (無機會)=> increased risk of miscarriages
- Sexual chromosomal aneuploidy (ie. Klinefeter syndrome 47 XXY; triad: small firm testes, azoospermia, gynecomastia, 70% successful rate by TESE)

Y-Chromsome micro deletions

- Most YCMD occur in long arm of Y => Azoospermia factor (AZF) a, b to c.
- Found in 10-15% of oligospermia patients (< 5 million spermatozoa/ mL)
- Men with deletion in AZFc (most common) can still have sperm present in ejaculate=> good sperm retrieval
- Deletion in AZFa or b => very poor sperm retrieval


Yp
Yq
AZFa
AZFb
AZFc
AZFa
P5/proximal-P1 (AZFb)
P5/distal-P1
P4/distal-P1
AZFc (b2/b4)
gr/gr
Alternative terminology
Semen profile
Azoospermia
Azoo-oligozoospermia
Histology
Sertoli cell only
Germ cell arrest
Hypospermatogenesis
Testicular sperm recovery
Virtually nil
~50–70%

Indications for testicular bx

- When sperm retrieval for ICSI is considered, a testicular bx for pathologic analysis should be considered.
- Diagnostic testicular bx or aspiration if there is uncertainty of OA or NOA.

Mx of OA

- Microsurgical reconstruction: vasovasostomy, vasoepididymostomy
- Sperm retrieval: microsurgical epididymal sperm aspiration, open testicular bx, percutaneous testicular sperm aspiration (TESA), (m)TESE,
- Cryopreservation
- Alpha-adrenergic agonist such as imipramine, ephedrine, pseudoephedrine used for retrograde ejaculation.

Mx of NOA

- Hormonal therapy in men with primary testicular failure
  - Clomophene citrate
  - hCG
- NOA with hypogonadotropic hypogonadism
  - Pulsatile: hCG (1500-3000 IU), 3 times/ week for 8-12 week
  - + FSH 75IU 3times/ week (if no effect to hCG)
  - Onset of spermatogenesis 3-6 months
- Sperm retrieval mTESE+ ICSI

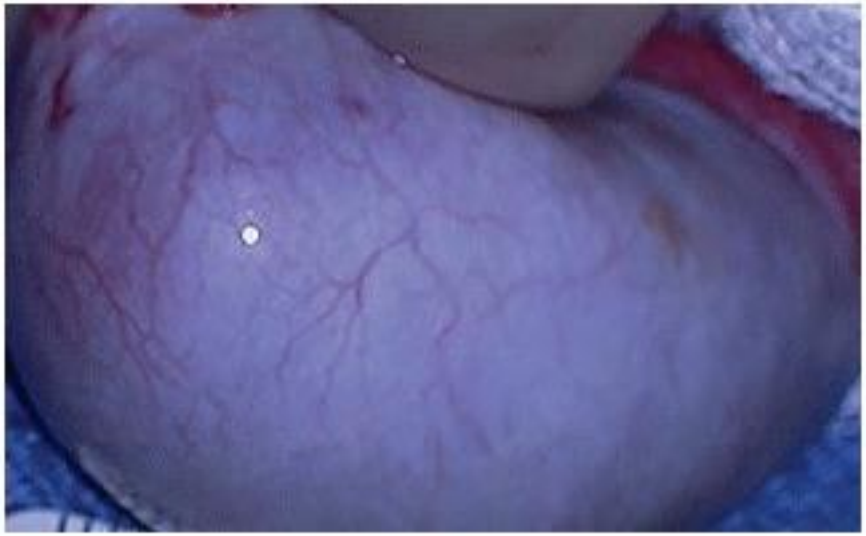


Figure 21-1. The appearance of the testis with its shiny tunica albuginea layer.

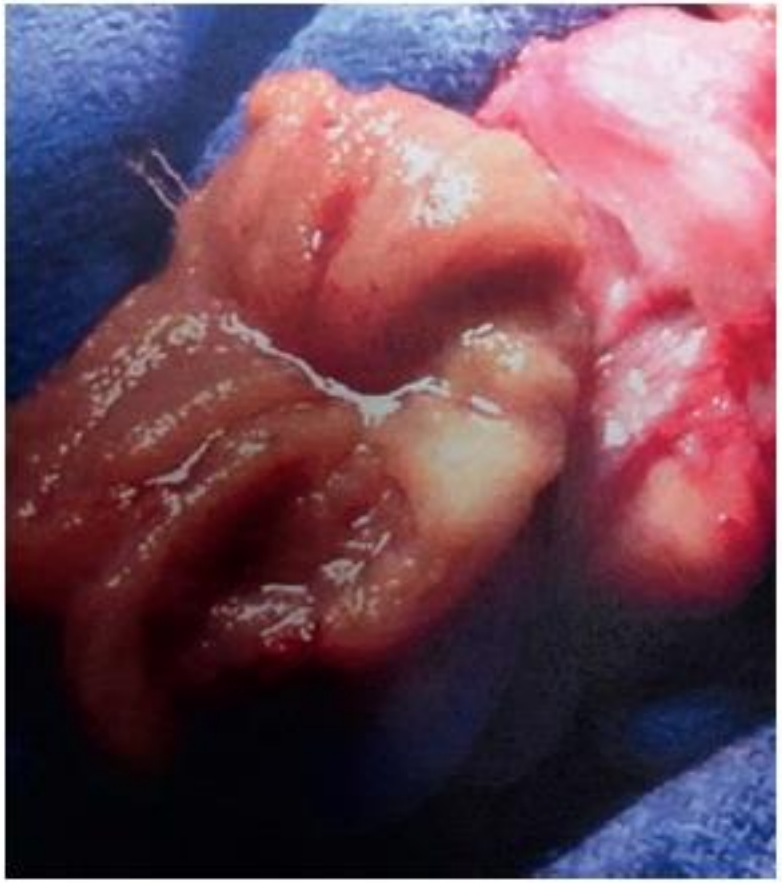


Figure 21-2. The appearance of the testicular parenchyma whe bivalved. The white nodule at the right inferior margin represents sarcoid nodule.

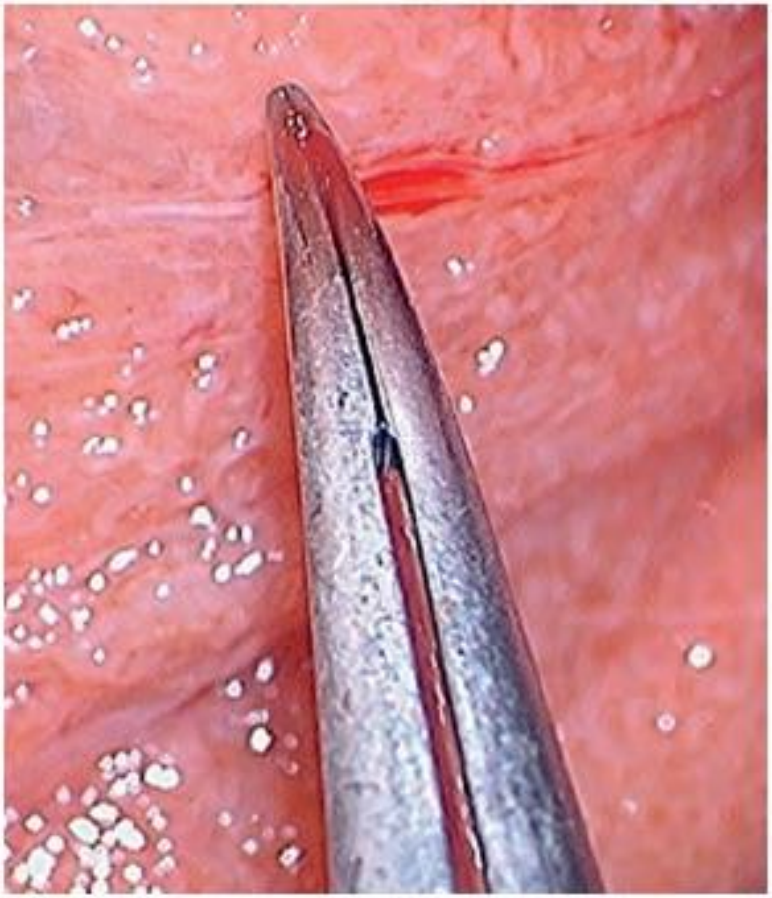


Figure 21-3. **Appearance of the seminiferous tubules under magnification.**

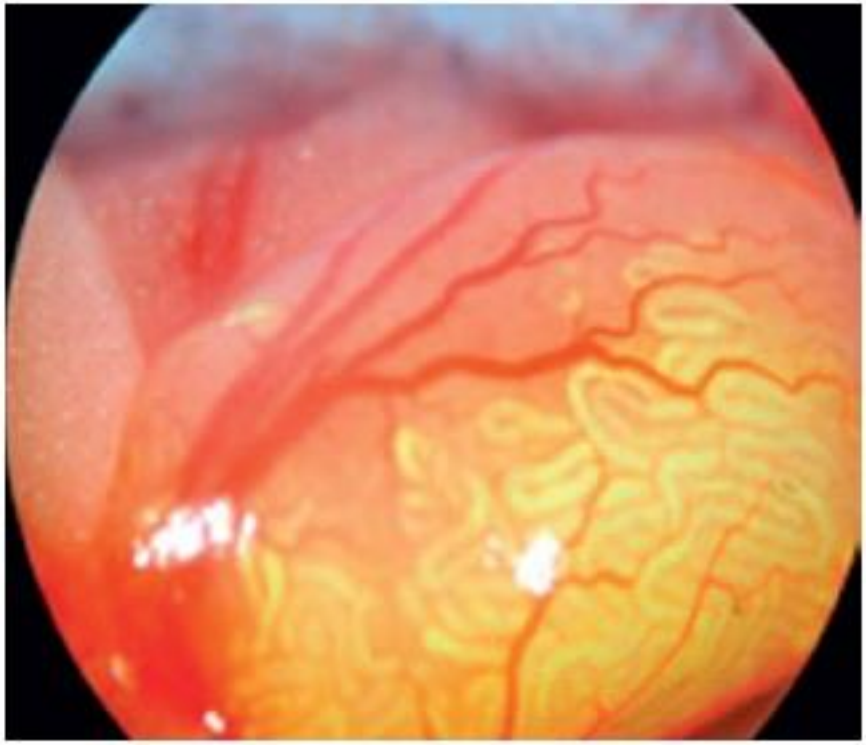


Figure 21-4. **Microbeads injected retrograde through the rete testis into the seminiferous tubules demonstrating the tubular structure. This is a mouse testis that has very similar architecture to the human testis. (Courtesy Jeffrey Lysiak, PhD.)**