Reproductive System

PHARMACOLOGY 432 TEAM

DRUGS USED IN MALE INFERTILITY

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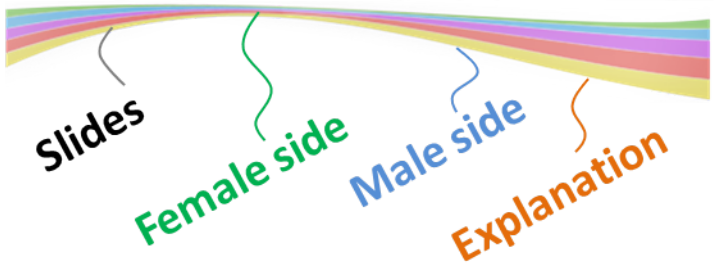
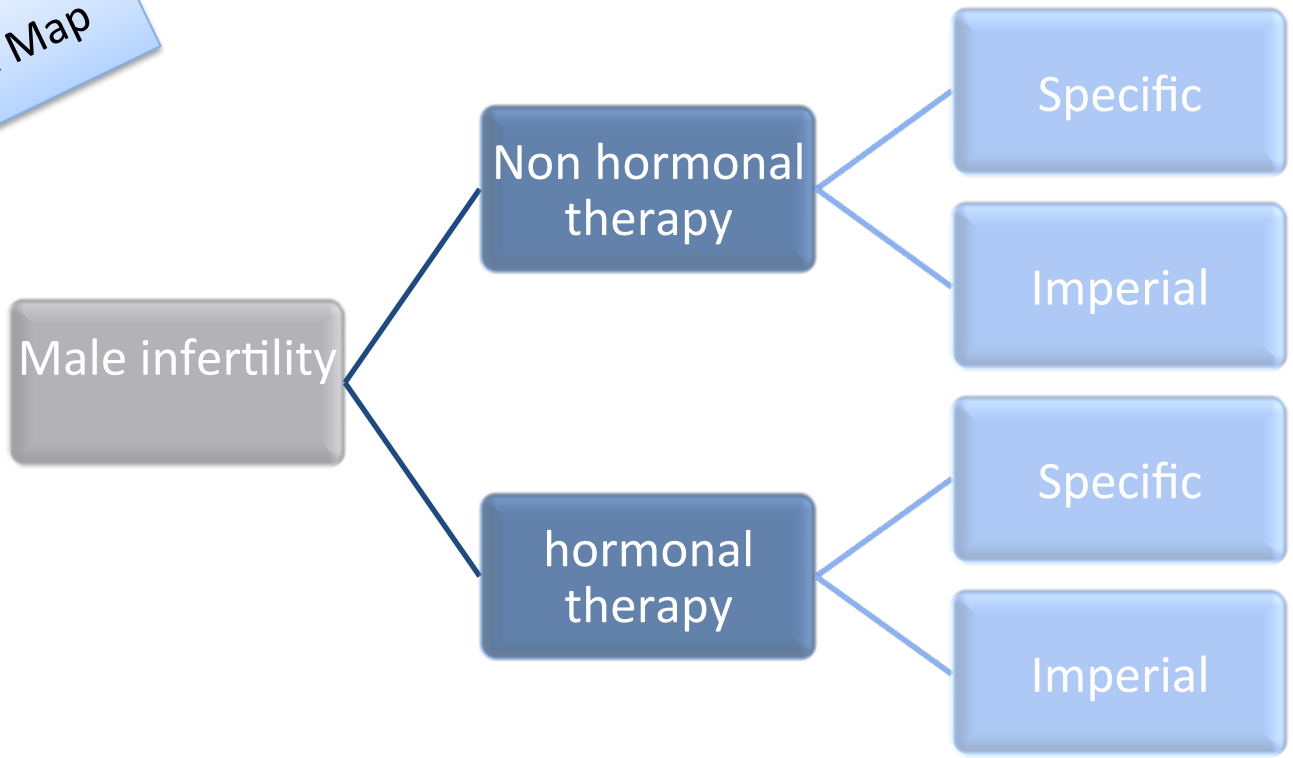


Learning Objectives:

- **Define male infertility .**
- **Recognize regulations contributing to male fertility & dysregulations leading to infertility.**
- **Classify hormonal & non-hormonal therapies used in male infertility whether being empirical or specific.**
- **Expand on the mechanism of action, indications, preparations, side effects, contraindications & interactions of most hormonal therapies.**
- **Highlight some potentialities of emperical non-hormonal therapies.**

Mind Map


Male infertility
Non hormonal therapy
hormonal therapy
Specific
Imperial
Specific
Imperial

❖ Introduction to male infertility :

Definition:

It is Inability of a male to achieve conception in a fertile woman after one year of unprotected intercourse.c.

Prevalence:

Approximately 15-20% of all cohabiting couples are infertile In up to ± 50% of such cases, males are responsible.

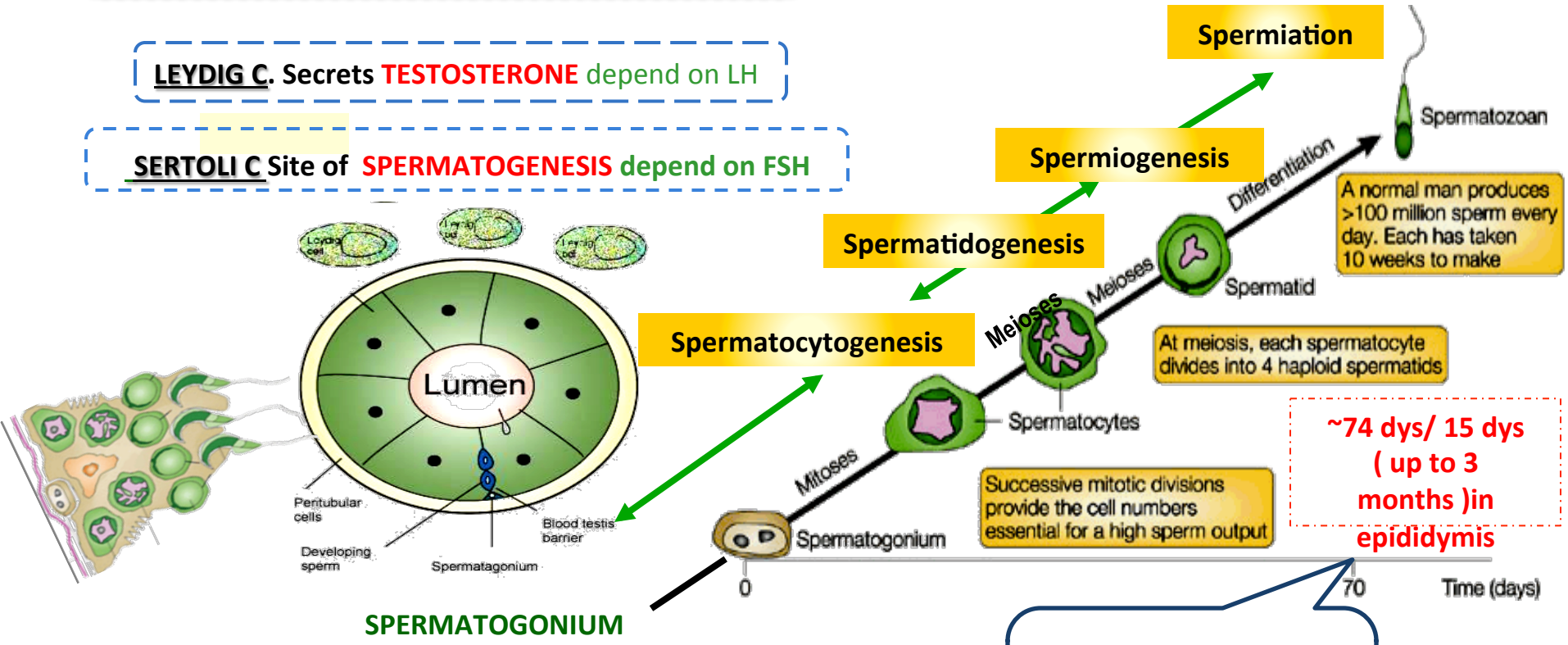
TESTIS

- Consist of Seminiferous Tubules
- Which is the Site of SPERMATOGENESIS

Mature Sperm / No motility / Sterile

LEYDIG C. Secrets TESTOSTERONE depend on LH

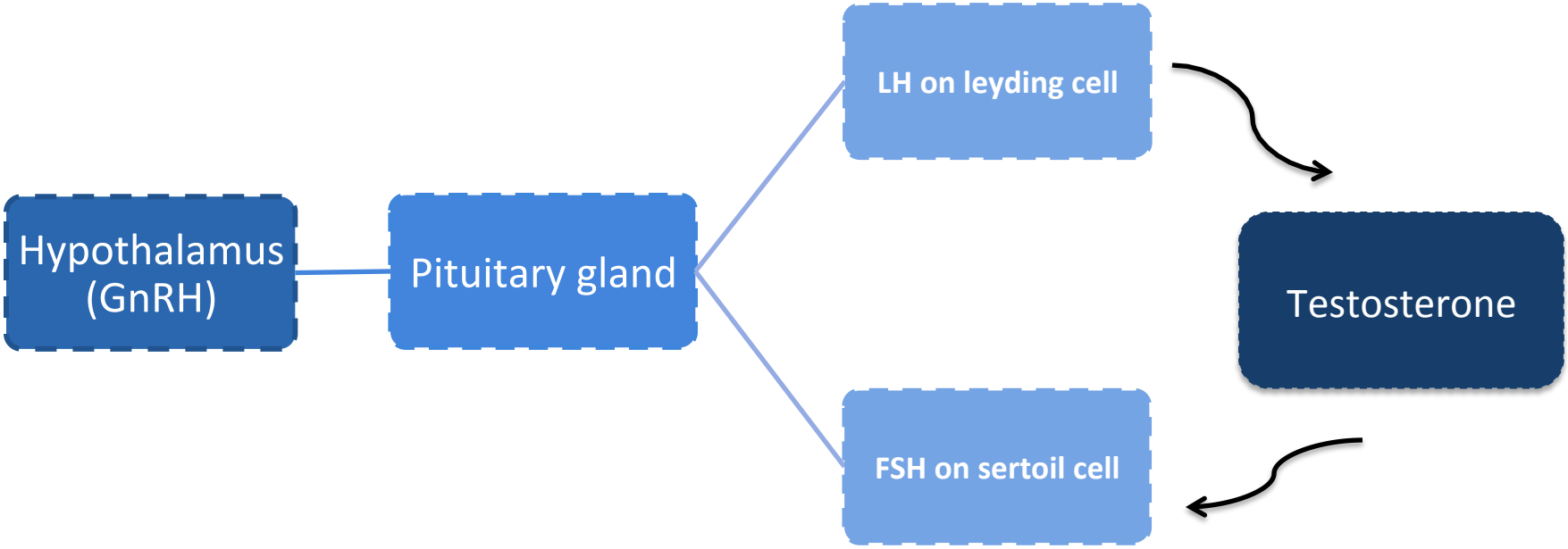
SERTOLI C Site of SPERMATOGENESIS depend on FSH



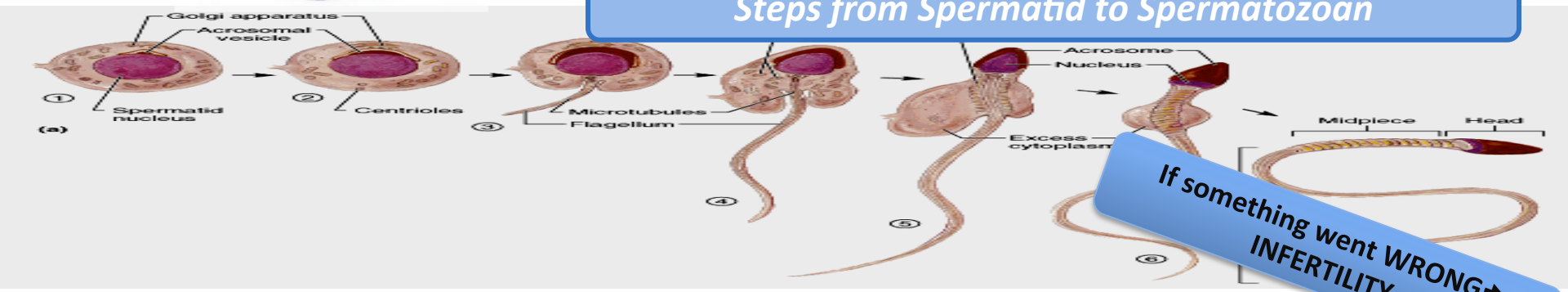
Nests ➔ **the** GERM CELLS

The effect of the drug appear After 5-6 monthes

- Communicate in a paracrine fashion.
- Separate them from rest of body by the blood-testicular barrier.
- Converts **Testosterone** to **Dihydrotestosterone [DHT]** & **Estradiol** to direct spermatogenesis.(act together)
- Secret androgen-binding-proteins **[ABP]** ➔ concentrate & ⬆testosterone in seminiferous tubules to stimulate spermiogenesis.



Steps from Spermatid to Spermatozoan



If something went WRONG → INFERTILITY

Proceed in **Seminiferous ducts.** → Then it goes to **Rete testis** → Then from Efferent ductules to **Epididymis**

DHT(active) will be converted into Testosterone ± Estradiol + other paracrine/ autocrine

[Develop Motility & Fertilizing ability of the sperms Protection + Storage in the epididymis] Till **Ejaculation.**

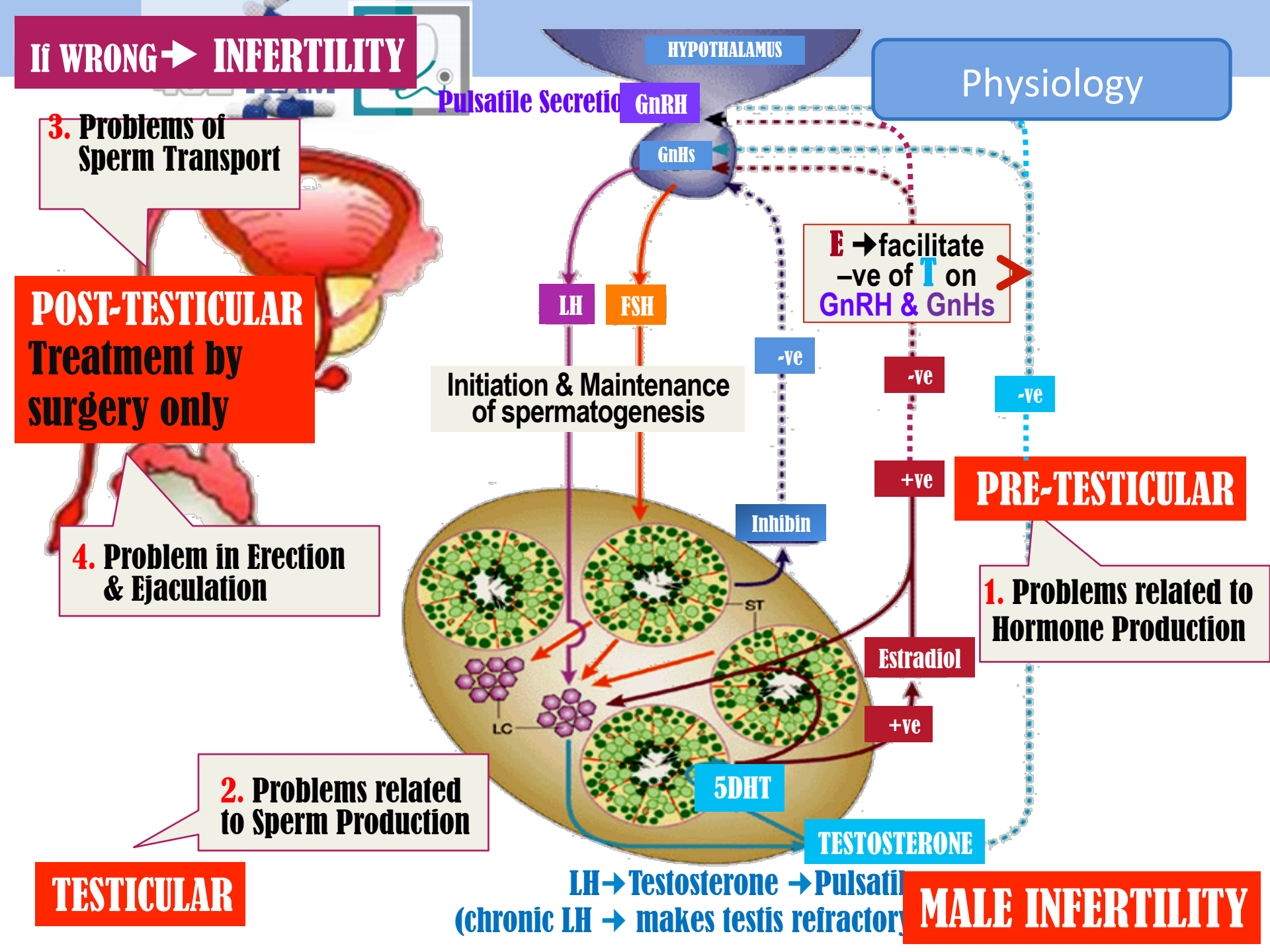
Prostatic & seminal secretions add to sperm functions

IN SEMINAL ANALYSIS

- Alteration in **sperm quantity**
  - **Low (oligospermia)**
  - **non (azoospermia)**
- Alteration in **both**
- Alteration in **sperm quality**
  - **Low motility (astheno(weak)spermia)**
  - **dead (necrospermia)**

If WRONG → INFERTILITY

Physiology



3. Problems of Sperm Transport

POST-TESTICULAR
Treatment by surgery only

4. Problem in Erection & Ejaculation

PRE-TESTICULAR

1. Problems related to Hormone Production

2. Problems related to Sperm Production

TESTICULAR

MALE INFERTILITY

DRUG TREATMENT OF MALE INFERTILITY

Needs 3 months before semen quality changes

HORMONAL THERAPY

this is the one we're concerned with in the lecture)

SPECIFIC

Not important

- Hyperprolactin-aemia → **DA_2 Agonists**
- Hypothyroidism → **Thyroxine**
- Congenital Adrenal Hyperplasia → ***Glucocorticoids***

IMPERICAL

1- Euogonadotrophic Hypogonadism

(↓Testesteron only or within the range)

Antiestrogens; .SERMs & Aromatase Is

2- Idiopathic →

Androgens , Antiestrogens,GnH(FSH)

3 - Hypogonadotrophic hypogonadism → 2ndry *Hypogonadism (Hypothalamo-Pituitary)*

(↓T & ↓ FSH / LH)

Pulsatile GnRH, hCG, hMG, Androgens,

NON-HORMONAL THERAPY

SPECIFIC

Not important

- Erectile Dysfunction → **PDE 5 Is, Alprostadil, Apomorphine…**
- Premature Ejaculation → **SSRIs**
- Retrograde Ejaculation → **aAD agonists**
- Leukocytospermia → **Antibiotic**

IMPERICAL

- **Pentoxiphylline**
- **Kallikrins**
- **Antioxidants; Vit E, C/ N-A Cystiene**
- **Zinc Supplements**
- **Folic a.**
- **L-Carnitine**

***Improve quality and quantity.**

Hypergonadotrophic Hypogonadism → Pry Hypogonadism (↓T &↑LH) Assisted Reproduction *(no therapy)*

Mesterolone

❖ It is oral synthetic androgen derived from DHT is more **safely given if the cause is :**

1- decrease in testosterone.

2- in 2ndry hypogonadism. **Why?** Because:

1. Not aromatised into **estrogens**/ no binding to estrogen receptors ➔ no –ve of GnHs ➔ **encourages natural testosterone production**+↓ SHBG(**Sex hormone-binding globulin**) from attaching to it ➔ spermatogenesis is enhanced

2. Unlike almost all other orals synthetic androgens it is **not hepatotoxic** ,not -alkylated but methylated ➔ **less hepatic complications** .

GnRH
- **LEUPROLIN**
- **GOSERELIN**

• **Used in hypothalamic dysfunction** ➔androgenization & spermatogenesis

• Given **as Pulsatile GnRH therapy** (4-8 ug subcut every 2 hours) using a portable pump. Less use by intranasal or intravenous routes.

• Exogenous excess of GnRH ➔ down-regulation of pituitary GnRH receptors & ↓ LH responsiveness.

Pulsatile: cancer
Continuous: treatment.

ADRs; Headache, depression, generalized weakness, pain & **gynecomastia** osteoporosis, neurological symptoms.(estrogenic effects)

Prostate cancer (on long term), yet can be prevented with the simultaneous use of antiandrogens for 2-4 weeks

GnHs
- **PREGNYL** (hCG)
- **MENOTROPN** ((hMG

•**Used in 2ndry hypogonadism (FSH or both FSH or LH absent)** ➔↑ spermatogenesis.

•GnHs replacement must be combined; **hCG** (3 x 2000 U/w. IM.➔**2 ms**.) followed by **hCG + hMG** (3x 75 to 3 x 150 U /w. IM. ➔**6 -12 ms**). rhFSH alone ➔ little efficacy

ADRs; Headache, local swelling (injection site), nausea, flushing, depression, gynecomastia, precocious puberty, **anaphylactic shock** (because it is combination therapy).

Antiestrogens	❖Because estrogens → –ve feedback on hypothalamus →↓ **GnRH pulse** frequency & pituitary responsiveness to GnRH , so antiestrogens → **used, with the rationale that absence of such feedback inhibition**→ ↑ GnRH & improve its pituitary response.	➢All are used for inducing spermatogenesis. in **oligozoospermia** ➢Given as daily dose over a period of 1–6 months. ➢Best to improve sperm count & motility with good pregnancy rates.
A.SERMs •Tamoxifen •Clomiphene	➢ Tamoxifen→↑ GnRH, but has its own estrogen agonistic property → feminizing side effects(gynecomastia). ➢ Clomiphene→ has **less** estrogenic agonistic property. Yet both drugs can induce libido & bad temper in men.	
B.Aromatase Inhibitors Anastrozole	.Blocks conversion of testosterone to estrogen **within the hypothalamus**	

NON-HORMONAL THERAPY	
Sometimes it is very promising, to improve sperm **quality > quantity**.	
ANTIOXIDANTS (Improve **quality and quantity**)	Protect sperm from **oxidative damage**.(used in inflammation) increase in phosphate.
KALLIKREIN **(Decreases the viscosity)**	Has proteolytic activity, cleaving kininogen to kinins➔ important for **sperm motility**
FOLIC ACID **quantity**	Plays a role in **RNA and DNA synthesis** during spermatogenesis & has **antioxidant properties**. **(Improve the cell division)**
ZINC	Plays an important role in **testicular development, spermatogenesis & sperm motility.**
L-CARNITINE	Is highly concentrated in the epididymis & is important for sperm metabolism & maturation.(help in oxidation of free fatty acids)

1. ANDROGENS

In NATURE

TESTOSTERONE

- by 5-a-REDUCTASE → DHT
  - in accessory sex organs
- by AROMATASE → Estradiol
  - in brain, bone , liver, adipose t.

Principle male sex hormone produced in testis, small amount in adrenals. It follows a circadian pattern→↑in early morning & ↓in evening

As Therapy

1. Testosterone

Derived from Testosterone
Esters(injectable form IM);
proprionate
, enanthate, cypionate

2. Synthetic Androgens;

derivatives as Fluoxymesterone, Methyltestosterone, Danazol (oral)

Derived from DHT;
Mesterolone

1. ANDROGENS

What does testosterone do ?

A. It or its DHT metabolite bind to Androgen Receptors [AR]

Not important

Like all other steroid hormones they act on;

1-Cytosolic ➔ GENOMIC Action (long action) ➔

mediates cell growth and differentation in AR responsive tissues; reproductive, those of 2ndry male sex characters, muscles

- ➢ Binding & Activation
- ➢ Nuclear translocation
- ➢ Dimerization on SRE
- ➢ Gene Transcription
- ➢ mRNA Translation
- ➢ New Protein Formation

2. Membranous

➔ NON-GENOMIC Action (short)

➔ mediates rapid responses ➔

on some brain, CVS, T cells functions

B. It aromatize to estradiol and binds to Estrogen Receptors [ER]

important

Estradiol rather than testosterone;

1. Responsible for feedback inhibition on hypothalamus (specially –ve LH secretion)
2. Induce maturation of cartilage ➔ leading to closure of epiphyses & conclusion of growth. Very important
3. Some CVS protective actions

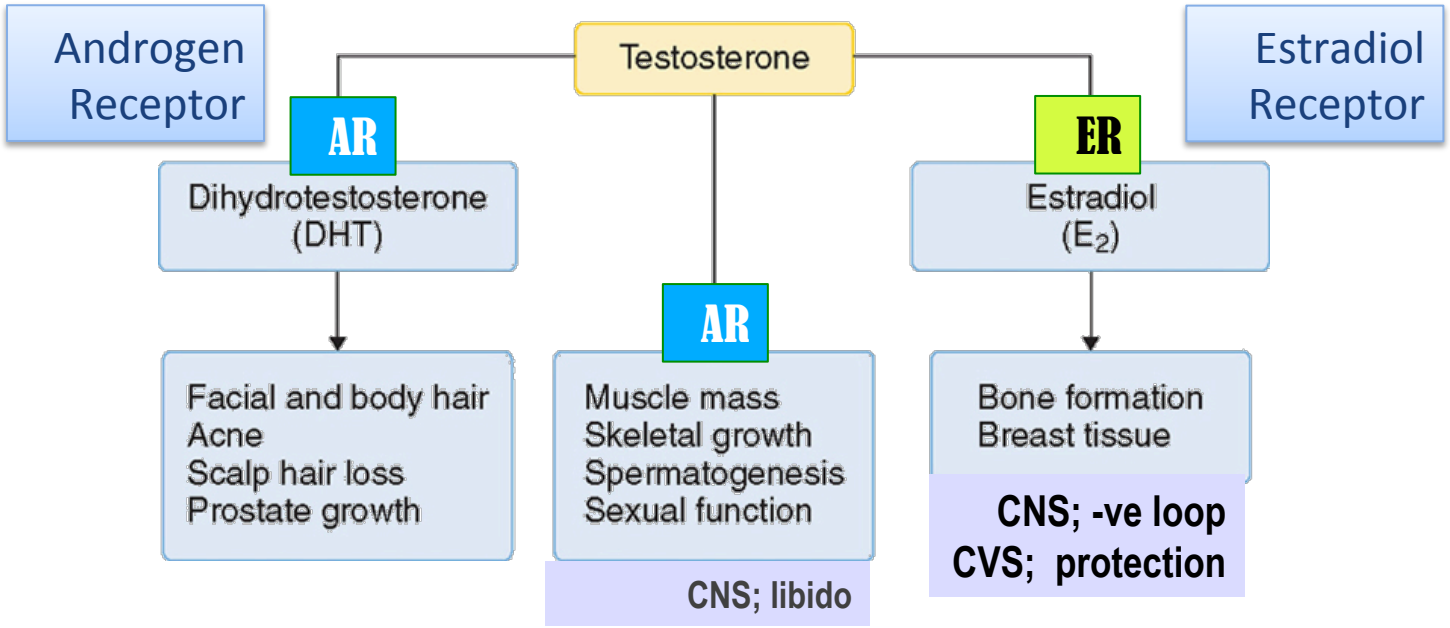
Androgens action

Not important

Testosterone & Synthetic Androgens

❖ Virilizing effects
Gonadotrpin regulation
Spermatogensis
Sexual dysfunction
Sexual restoration and development

❖ Protiien anabolic effects
(Not used in infertility)
bone density
muscle mass
blood cell mass


Androgen Receptor
Testosterone
Estradiol Receptor
AR
ER
Dihydrotestosterone (DHT)
Estradiol (E_2)
AR
Facial and body hair
Acne
Scalp hair loss
Prostate growth
Muscle mass
Skeletal growth
Spermatogenesis
Sexual function
CNS; libido
Bone formation
Breast tissue
CNS; -ve loop
CVS; protection

ANDROGENS

Kinetics

1-Binds to SHBG. (Sex hormone-binding globulin) 2- t1/2 = 10 –20 min.

3- Inactivated in the liver.; 90% of metabolites ➔ excreted in urine.

4-Synthetic androgens ➔ less rapidly metabolized & some are excreted unchanged in urine.

Administration

Testosterone	Synthetic Androgens	
ineffective orally(inactivated by 1st pass met.)➔ I.M or S.C. Skin patch (genital & no genital) & gels…. are also available	in oil for IM; every 2-3weeks Derived from Testosterone ▪Esters; proprionate, enanthate, cypionate	▪Orally; daily 1-Other derivatives as Fluoxymesterone, Methyltestosterone, Danazol ➔ 2-Derived from DHT;Mesterolone (DHT:dihydrotestosterone)

Indications

In adult Male Infertility		As Androgen Replacement Therapy
1. Low dose oral methyltestosterone 10-50 mg/day)or(fluoxymesterone 5-20 mg/day) may Improve epididymal function & ↑ sperm motility	2. High dose exogenous (risky they don't use this way anymore) testosterone given then abruptly stopped will 1st ➔ ↑ systemic T levels ➔ -ve feedback ➔ ↓ LH & ↓ endogenous testosterone production ➔ ↓ spermatogenesis. Or 2nd ➔ TESTOSTERONE REBOUND ➔ ↑ spermatogenesis after stoppage . The success rate is very low . Hazards are high ➔ many men become azoospermic for prolonged periods after. Now this is best avoided	1-In delayed puberty with hypogonadism ➔ give androgen slow & spaced for fear of premature fusion of epiphyses ➔ short stature

ANDROGENS

ADRS	Specific In Males ➢Prostatic hyperplasia → carcinoma specially in elder (give low dose) ➢2ndry Gn H suppression ; azoospermia, impotence, gynecomastia (if taken > 6 wks). ➢Short stature due to premature closure of epiphysis (before 18 years)	General ➢Behavioral changes; physiologic dependence ↑ aggressiveness, psychotic symptoms ➢Alteration in serum lipid profile: ↓HDL & ↑LDL; ↑risk of ACS ➢Salt & water retention ➢Hepatic dysfunction; ↑ AST levels, ↑alkaline phosphatase, ↑ bilirubin & cholestatic jaundice. Most oral preparations are hepatotoxic → adenomas & carcinomas ➢Polycythemia because of the anabolic effect
contrain dication	1-Male patients with cancer breast or prostate 2-Severe renal & cardiac disease → predispose to edema 3-Psychiatric disorders 4-Hypercoagulable states 5-Polycythemia	
Interactions	▪All forms + corticosteroids → oedema ▪All forms + warfarin → ↓metabolism → ↑ bleeding ▪Synthetic Androgens + insulin or oral hypoglycemics → hypoglycemia ▪ Testosterone + propranolol → ↑ propranolol clearance → ↓efficacy	
	Mesterolone→ oral synthetic androgen derived from DHT is more safely given if ↓ testosterone or in 2ndry hypogonadism. Why??? 1. Not aromatised into estrogens/ no binding to estrogen receptors→no –ve of GnHs → encourages natural testosterone production+↓ SHBG from attaching to it → spermatogenesis is enhanced 2. Unlike almost all other orals synthetic androgens it is not hepatotoxic; not -alkylated but methylated → less hepatic complications	

drug	Indication	ADRs	note
Mesterolone	safely given if the cause is decrease in testosterone or in 2ndry hypogonadism	_	Not hepatotoxic
GnRH ***LEUPROLIN ,*** ***GOSERELIN***	hypothalamic dysfunction	Headache, depression, generalized weakness, pain & gynecomastia osteoporosis, neurological symptoms. Prostate cancer (on long term),	yet can be prevented with the simultaneous use of antiandrogens for 2-4 weeks
GnHs ***PREGNYL*** ,hCG ***MENOTROPIN*** ,hMG	2ndry hypogonadism (FSH or both FSH or LH absent)	Headache, local swelling (injection site), nausea, flushing, depression, gynecomastia, precocious puberty, anaphylactic shock	
Tamoxifen	oligozoospermia	feminizing side effect induce libido & bad temper in men	Increases GnRH
Clomiphene		induce libido & bad temper in men	has less estrogenic agonistic property.
Anastrozole			Blocks conversion of testosterone to estrogen within the hypothalamus

Non-HORMONAL THERAPY	
ANTIOXIDANTS	**(used in inflammation)**
KALLIKREIN	**Has proteolytic activity→ important for sperm motility**
FOLIC ACID	**Plays a role in RNA and DNA synthesis during spermatogenesis & has antioxidant properties.**
ZINC	**Plays an important role in testicular development, spermatogenesis & sperm motility**
L-CARNITINE	**Is highly concentrated in the epididymis & is important for sperm metabolism & maturation.**

Summary

	1. ANDROGENS	2. GnRH LEUPROLIN ,GOSERELIN	3. GnHs PREGNYL (hCG) MENOTROPIN (hMG)	4- Antiestrogens	
				a. SERMs	b. Aromatase Inhibitors
		Given as Pulsatile GnRH therapy (4-8 ug subcut every 2 hours) using a portable pump.	GnHs replacement must be combined; hCG (3 x 2000 U/w. IM.➔2 ms.) followed by hCG + hMG (3x 75 to 3 x 150 U /w. IM. ➔6 -12 ms). rhFSH alone ➔ little efficacy	Tamoxifen➔↑ Gn RH, but has its own estrogen agonistic property . Clomiphene➔ has less estrogenic agonistic property	Blocks conversion of testosterone to estrogen within the hypothalamus . All Given as daily dose over a period of 1–6 months
Uses	1-In adult Male Infertility 2- As Androgen Replacement Therapy In delayed puberty with hypogonadism	hypothalamic dysfunction ➔androgenization & spermatogenesis	2ndry hypogonadism (FSH or both FSH or LH absent) ➔↑ spermatogenesis		used for inducing spermatogenesis in oligozoospermia Best to improve sperm count & motility with good pregnancy rates
adrs	Specific In Males: 1-Short stature 2-Azoospermia 3- carcenoma General : 4- Polycythemia 5-psychotic symptoms 6-Hepatic dysfunction 7-Salt & water retention 8-Alteration in serum lipid profile:	1-depression, 2-generalized weakness, pain 3-gynecomastia 4-osteoporosis, 5-neurological symptoms. 6-Prostate cancer (on long term), yet can be prevented with the simultaneous use of antiandrogen for 2-4 weeks	1-local swelling (injection site). 2-flushing, 3-depression , 4-gynecomastia , 5-precocious puberty, 6-anaphylactic shock.	both drugs can induce libido & bad temper in men Tamoxifen➔ feminizing side effects	.

1. **Patient with infertility has been given a hormonal therapy for long time. However now he is diagnosed with Prostate cancer , which one of the following drug that causes this side effect :**

   A. **KALLIKREIN**
   B. **PREGNYL**
   C. **LEUPROLIN**
   D. **Tamoxifen**

2. **Which one of the following drugs is safely given if the cause of the infertility is decreasing in testosterone :**

   A. **Tamoxifen**
   B. **KALLIKREIN**
   C. **LEUPROLIN**
   D. **Mesterolone**

Answers:1-c , 2-d

Questions

3. **Why do we slow & space androgen doses for under 18 year old patients :**
   3. Fear of Salt & water retention
   4. Fear of premature fusion of epiphyses
   5. Fear of allergic reaction
   6. Fear of Hepatic dysfunction

4. **Saud, a 35 year old male who has been married for two years and he didn't have children yet investigations showed decrease in sperm motility . we cant treat him with androgens because**
   3. He was diagnosed with prostate cancer
   4. He Is diabetic patient
   5. He Is asthmatic patient

Answers:3:B , 4: A

Questions

5. **8 yo male was brought to the clinic by his family, in the last FEW MONTHS they noticed some pubertal changes happening to the boy, on examination… the boy is aggressive, and his RBC Count is HIGHER than normal, which one of the following is the best possible explanation**:
   A. He is using Androgens as a therapy.
   B. He is suffering from 1ry hypogonadism.
   C. He is going through physiological puberty.
   D. A family member has been using a cream containing Androgens.

6. **2. Abbas was diagnosed with hypogonadotropic hypogonadism, which one of the following is the best treatment?**
   A. Gonadotropin formulation
   B. FOLIC ACID
   C. Mesterolone
   D. Zinc

Answers:5:D , 6: A

Reproductive System

PHARMACOLOGY 432 TEAM

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