King Saud University

College of Medicine

2nd Year,

Reproduction Block

PHARMACOLOGY 433

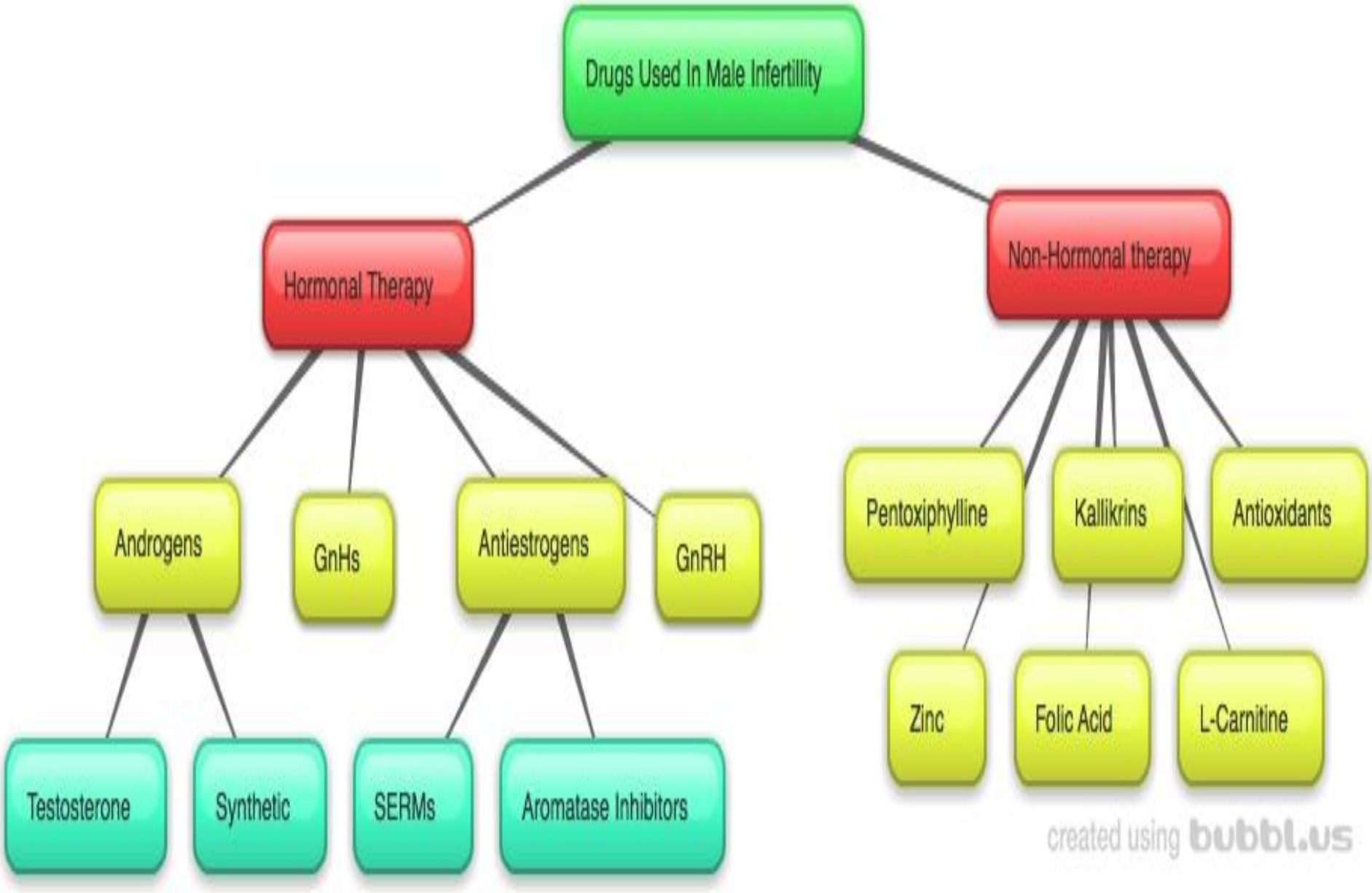
MED 433 Teams

L3- Drugs used in male infertility

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


Drugs Used In Male Infertility
Hormonal Therapy
Non-Hormonal therapy
Androgens
GnHs
Antiestrogens
GnRH
Pentoxiphylline
Kallikrins
Antioxidants
Testosterone
Synthetic
SERMs
Aromatase Inhibitors
Zinc
Folic Acid
L-Carnitine
created using bubbl.us

Introduction

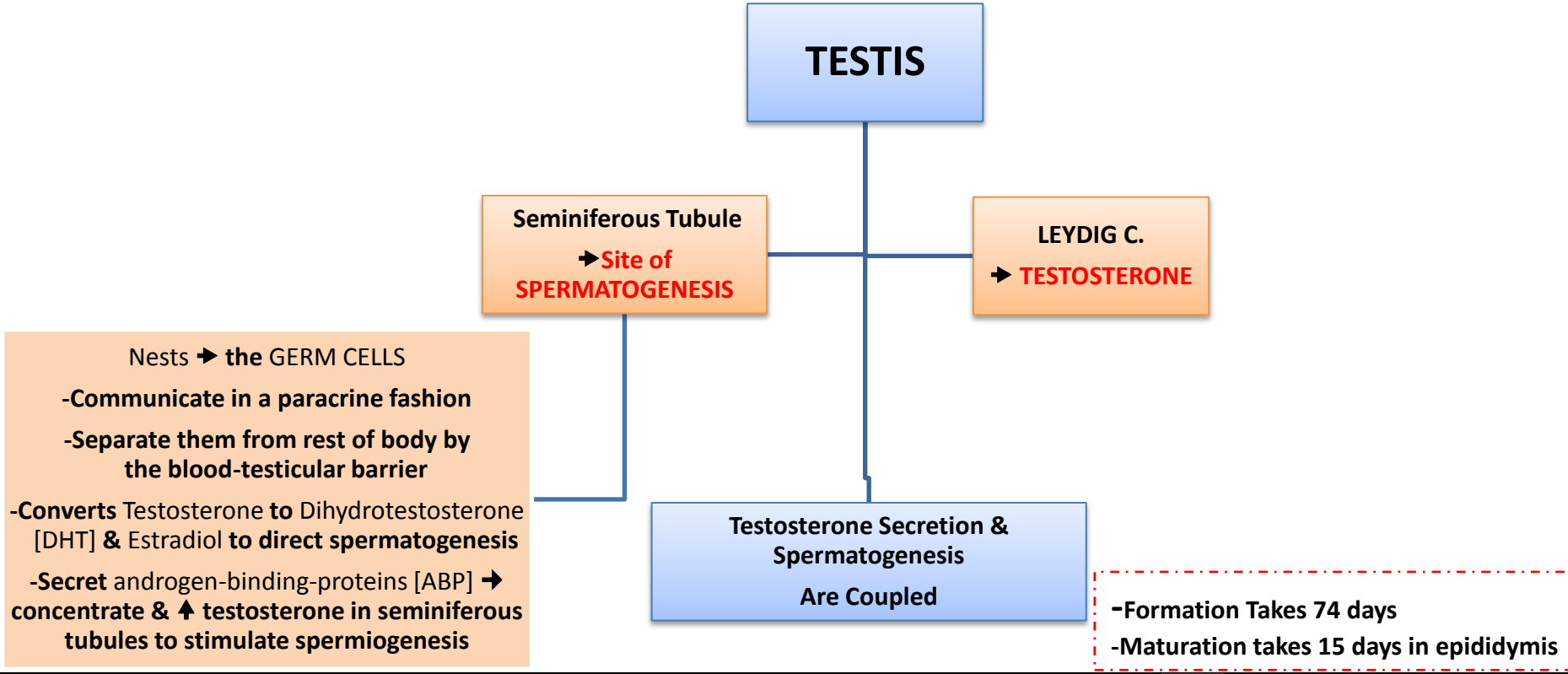
MALE INFERTILITY

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

Prevalence

Approximately 15-20% of all cohabiting couples are infertile

In up to ± 50% of such cases, males are responsible



slide | doctor's note | important | explanation

Introduction

Steps from Spermatid to Spermatozoan

Proceed ➔Seminiferous ducts➔Rete testis ➔ Efferent ductules ➔ Epididymis , DHT > Testosterone ± Estradiol + other paracrine/autocrine , Develop Motility & Fertilizing ability Protection + Storage Till Ejaculation , Prostatic & seminal secretions add to sperm functions.

If something went WRONG➔ INFERTILITY

IN SEMINAL ANALYSIS :

***Alteration in sperm quantity :**

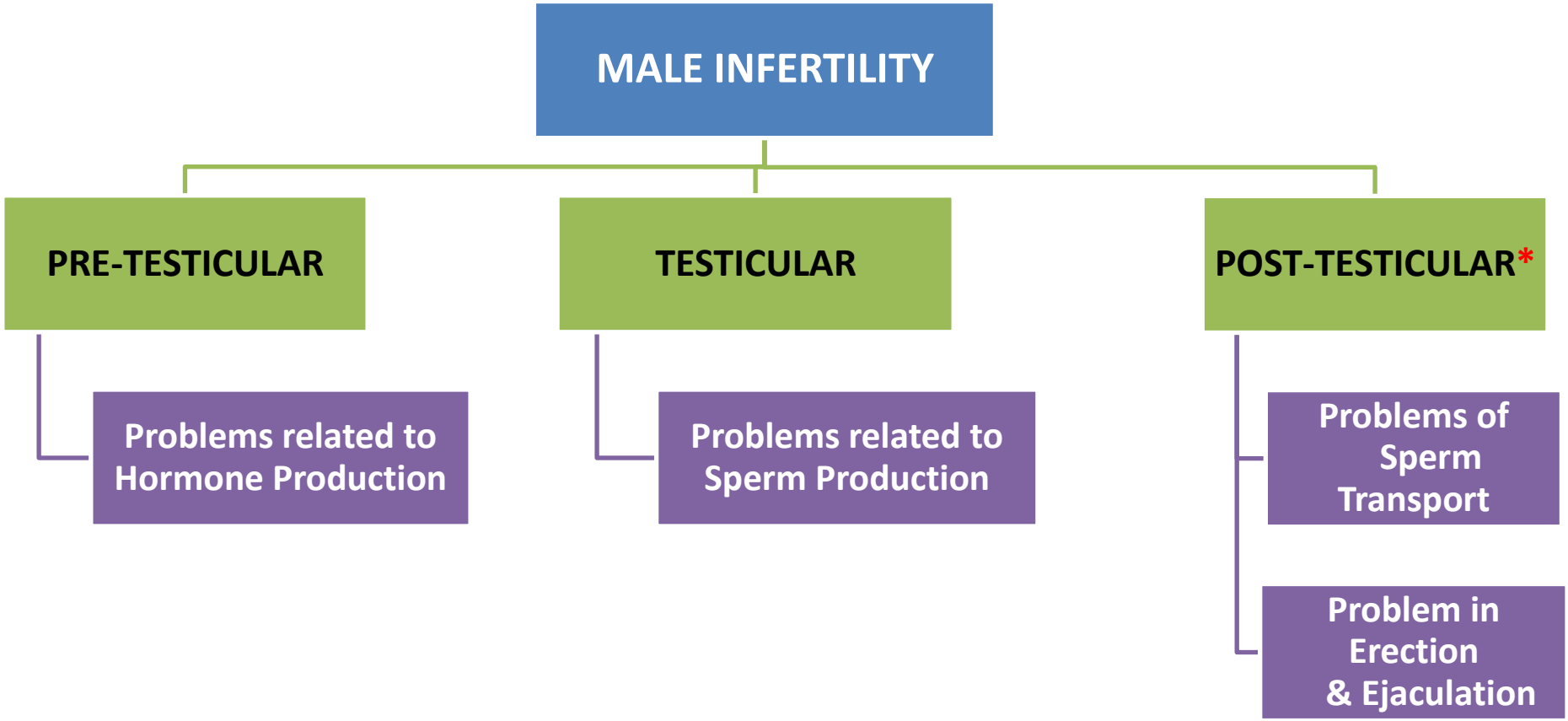
-Low (oligospermia) or non (azoospermia)

***Alteration in sperm quality :**

-Low motility (asthenospermia) or dead (necrospermia)

***Alteration in both.**

Introduction



* we cant do so much in such case with medication !

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Drug treatment of male infertility

Hormonal therapy

Specific*

-Hyperprolactinaemia → DA_2 Agonists

-Hypothyroidism → Thyroxine

-Congenital Adrenal Hyperplasia → Glucocorticoids

Imperical

-Euogonadotrophic Hypogonadism →

(↓T only) Antiestrogens; SERMs & Aromatase IS

-Idiopathic → Androgens, Antiestrogens,GnH (FSH)

-Hypogonadotrophic hypogonadism → 2ndry Hypogonadism (Hypothalamo-Pituitary) (↓T & ↓ FSH / LH)

Pulsatile GnRH, hCG, hMG, Androgens, Clomiphene

-Hypergonadotrophic Hypogonadism →

Pry Hypogonadism (↓T &↑LH) Assisted Reproduction

Non-hormonal therapy

Specific

Erectile Dysfunction → PDE 5 IS ,Alprostadil, Apomorphine

-Premature Ejaculation → SSRIs

-Retrograde Ejaculation → aAD agonists*

-Leukocytospermia → Antibiotics

Imperical

-Pentoxiphylline

-Kallikrins

-Antioxidants; Vit E, C/ N-A Cystiene

-Zinc Supplements

-Folic a.

-L-Carnitine

* Means first we have treat the disease that could cause infertility

*(alpha adrenergic agonists for example phenylephrine)

The treatment Needs 3 months at least. before semen quality changes

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1st Hormonal therapy: 1- androgens

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

androgens

In NATURE	As Therapy
1-androgen **with 5-a-REDUCTASE** enzyme converted into Dihydrotestosterone which work on accessory sex organs 2-Androgen **with AROMATASE** enzyme convert into estradiol which work on brain, bone, liver, adipose t.	1- Testosterone 2- Synthetic Androgens Either Derived from Testosterone Or Derived from DHT

Androgens In NATURE

Mechanism of Action	**1-Testosterone or DHT metabolite bind to Androgen Receptors [AR]** A-Cytosolic ➔GENOMIC Action ➔mediates cell growth & differentation in AR responsive tissues; reproductive, those of 2ndry male sex characters, muscles ▪ By Binding & Activation ▪ Nuclear translocation ▪ Dimerization on SRE ▪ Gene Transcription ▪ mRNA Translation ▪ New Protein Formation B-Membranous ➔ NON-GENOMIC Action ➔ mediates rapid responses ➔ on some brain, CVS, T cells functions	**2-Testosterone aromatize to estradiol and binds to Estrogen Receptors [ER]** A-Responsible for feedback inhibition on hypothalamus (**specially –ve LH secretion**) B-Induce maturation of cartilage ➔ leading to closure of epiphyses & conclusion of growth. C- Some CVS protective actions

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1- androgens

Androgens *Testosterone +DHT*

Action	**1-virilizing effect** Gonadotropins regulation Sexual dysfunction Spermatogenesis Sexual restoration	**2- protein anabolic effect** Red blood cells Bony mass Muscle mass } Not used in infertility
Pharmacokinetic	*Binds to SHBG *t1/2 = 10 –20 min *Inactivated in the liver.; 90% of metabolites ➔excreted in urine. *Synthetic androgens ➔ less rapidly metabolized & some are excreted unchanged in urine	
Method of Administration	**1-Testosterone** ▪ ineffective orally(inactivated by 1st pass met.) **so we give it I.M or S.C.** ▪ Skin patch (genital & no genital) & gels…. are also available	**2-Synthetic Androgens** **1-Derived from Testosterone** **2-Derived from DHT**

Synthetic Androgens

Derived from Testosterone	Derived from DHT
1. Esters; proprionate, enanthate, cypionate ➔in oil for **IM**; every 2-3 weeks = never given I.V (it will cause fat embolism) 2. Other derivatives as Fluoxymesterone, Methyltestosterone, Danazol ➔ given **Orally**; daily	Mesterolone ➔ given **Orally**; daily *slide 9*

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1- androgens

Androgens *Testosterone +DHT*

Indications	**1-In adult Male Infertility** ▪ **Low dose oral** (methyltestosterone 10-50 mg/day)or(fluoxymesterone 5-20 mg/day) may improve epididymal function & ↑ sperm motility ▪ High dose exogenous testosterone given then abruptly stopped will 1st → ↑ systemic T levels → -ve feedback → ↓ LH & ↓ endogenous testosterone production → ↓ spermatogenesis. 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	**2- As Androgen Replacement Therapy** **In delayed puberty with hypogonadism → give androgen slow & spaced for fear of premature fusion of epiphyses → short stature**
Contraindications	1. Male patients with cancer breast or prostate 2. Severe renal & cardiac disease → **predispose to edema** 3. Psychiatric disorders 4. Hypercoagulable states 5. Polycythemia = ↑ red blood cells	
Interactions	**1. All forms** + corticosteroids → oedema **2. All forms** + warfarin → ↓metabolism → ↑ bleeding **3. Synthetic Androgens** + insulin or oral hypoglycemics → hypoglycemia 4. **Testosterone** + propranolol → ↑ propranolol clearance → ↓efficacy	

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1- androgens

Androgens *Testosterone +DHT*

Side effect	**1-Specific In Males** 1. **Prostatic hyperplasia ➔ carcinoma specially in elder (give low dose)** 2. 2ndry Gn H suppression ; azoospermia, impotence, gynecomastia (if taken > 6 wks). 3. **Short stature due to premature closure of epiphysis (before 18 years)**	**2-General** 1. Behavioral changes; physiologic dependence,↑ aggressiveness, psychotic symptoms 2. Alteration in serum lipid profile: ↓HDL & ↑LDL; ↑risk of ACS 3. Salt & water retention 4. Hepatic dysfunction;↑ AST levels,↑alkaline phosphatase, ↑ bilirubin & **cholestatic jaundice.** Most oral preparations are hepatotoxic ➔ adenomas & carcinomas 5. Polycythemia

Mesterolone

oral synthetic androgen derived from DHT is more safely given if ↓ testosterone or in 2ndry hypogonadism

Why it is safe ?	**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

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2-GnRH

Leuprolin & goserelin

Indications	**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.
Side effect	1. Headache, depression, generalized weakness, 2. pain & gynecomastia osteoporosis, 3. neurological symptoms. 4. Prostate cancer (on long term), yet can be prevented with the simultaneous use of antiandrogens for 2-4 weeks

3- GnHs

Pregnyl *hCG* & menotropin *hMG*

Indications	**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 .
Side effect	1. Headache, local swelling (injection site), 2. nausea, flushing, 3. depression, gynecomastia, 4. precocious puberty, 5. anaphylactic shock.

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4-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→↑ Gn RH & improve its pituitary response

SERMs	
1-Tamoxifen	→↑ Gn RH, but has its own estrogen agonistic property → feminizing side effects.
2-Clomiphene	has less estrogenic agonistic property. Yet both drugs can induce libido & bad temper in men
Aromatase Inhibitors	
1-Anastrozole	Blocks conversion of testosterone to estrogen within the hypothalamus

1. All are used for inducing spermatogenesis in oligozoospermia
2. Given as daily dose over a period of 1–6 months.
3. Best to improve sperm count & motility with good pregnancy rates

2nd Non Hormonal therapy

As supplement

Sometimes it is very promising, to improve sperm quality > quantity.

1-antioxidants

Protect sperm from oxidative damage

2-kallikrein

Has proteolytic activity, cleaving kininogen to kinins➔ important for sperm motility

3-folic acid

Plays a role in RNA and DNA synthesis during spermatogenesis & has antioxidant properties.

4-zinc

Plays an important role in testicular development, spermatogenesis & sperm motility.

5-l-carnitine

Is highly concentrated in the epididymis & is important for sperm metabolism & maturation

SUMMARY

Hormonal Therapy

SPECIFIC	Hyperprolactinaemia	DA_2- Agonists
	Hypothyroidism	Thyroxine
	Congenital Adrenal Hyperplasia	Glucocorticoids
IMPERICAL	Euogonadotrophic Hypogonadism	Antiestrogens; SERMs & Aromatase Is
	Idiopathic	Androgens, Antiestrogens,GnH(FSH)
	Hypogonadotrophic hypogonadism	Pulsatile GnRH, hCG, hMG, Androgens, Clomiphene

Non-Hormonal Therapy

SPECIFIC	Erectile Dysfunction	PDE 5 IS ,Alprostadil, Apomorphine
	Premature Ejaculation	SSRIs
	Retrograde Ejaculation	aAD agonists (alpha adrenergic agonists for example phenylephrine)
	Leukocytospermia	Antibiotics

IMPERICAL

Pentoxiphylline, Kallikrins, Has proteolytic activity, cleaving kininogen to kinins→ important for sperm motility.

Antioxidants; Protect sperm from oxidative damage

Vit E, C/ N-A Cystiene,

Zinc Supplements:Plays an important role in testicular development, spermatogenesis & sperm motility

Folic acid: Plays a role in RNA and DNA synthesis during spermatogenesis & has antioxidant properties.

L-Carnitine: Is highly concentrated in the epididymis & is important for sperm metabolism & maturation

Antioxidants	Protect sperm from oxidative damage
Kallikrein	Important for sperm motility.
Folic acid	Plays a role in RNA and DNA synthesis during spermatogenesis & has antioxidant properties

SUMMARY

Synthetic Androgens:

Esters: proprionate, enanthate, cypionate			
DHT: Mesterolone			
Others: Fluoxymesterone, Methyltestosterone, Danazol			
Indications	epididymal function & ↑ sperm motility	fluoxymesterone	methyltestosterone
	↑ spermatogenesis	High exogenous testosterone after abruptly stopped of	
ADRs	Specific	Prostatic hyperplasia, 2ndry Gn H suppression (azoospermia, impotence, gynecomastia), Short stature	
	General	Behavioral changes, ↓HDL & ↑LDL, Salt & water retention, Hepatic dysfunction, Polycythemia	
Contrindications	▪ Severe renal & cardiac disease, Psychiatric disorders, Hypercoagulable states, Polycythemia		

Category	drugs	Indication	ADRs
Mesterolone		↓ testosterone or in 2ndry hypogonadism.	less hepatic complications
GnRH LEUPROLIN , GOSERELIN		Used in hypothalamic dysfunction→androgenization & spermatogenesis	Headache, depression, generalized weakness, pain & gynecomastia osteoporosis, neurological symptoms. Prostate cancer (on long term),
GnHs PREGNYL (hCG), MENOTROPIN (hMG)		Used in 2ndry hypogonadism (FSH or both FSH or LH absent) →↑ spermatogenesis	Used in 2ndry hypogonadism (FSH or both FSH or LH absent) →↑ spermatogenesis
4. Antiestrogens		used, with the rationale that absence of such feedback inhibition	
SERMs	Tamoxifen,	→↑ Gn RH	
	Clomiphene	less estrogenic agonistic property	
Aromatase Inhibitors Anastrozole		used for inducing spermatogenesis in oligozoospermia	

Quiz yourself

Q1: Witch of the following is a derivative of Dihydrotestosterone?

A. Fluoxymesterone
B. proprionate
C. Mesterolone
D. cypionate

Q2: Diabetic patient using infertility drugs developed hypoglycemia what is the most likely drug that he was using ?

A. Testosterone
B. Proprionate
C. SSRI
D. Clomiphene

Q3: Which of the following is important in sperm motility ?

A. Kallikerin
B. Folic Acid
C. L-Carnitine
D. A+B

Q4: Clinical investigation showed that a patent has no FSH what is the drug of choice to treat him infertility ?

A. Leuprolin
B. Menotropin
C. Testosterone
D. Tamoxifen

Q5: After using some male infertility drugs he developed gynecomastia and his voice got softer . Which of the following drugs was he taking ?

A. Tamoxifen
B. Clomiphene
C. Anastrozole
D. propanalol

Q6: Best way for testosterone admission is ?

A. Oraly
B. IV
C. IM
D. Sublingual

Q7: After using a drug to treat male infertility the male became violent and devoloped gynecomastia, depression and osteoporosis what drug is he using ?

A. Menotropin
B. Leuprolin
C. Testosterone
D. Tamoxifen

Q8: A patient with low hepatic function, what is the best drug for him ?

1. enanthate
2. Danazol
3. Cypionate
4. Mesterolone

Answers: 1-C 2-B 3-A 4-B 5-A 6-C 7-C 8-D

Done by

PHARMACOLOGY 433

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