Estrogens & androgens

أ.م.د.اسامة ايوب يعقوب

- Sex hormones produced by the gonads are necessary for
  - ✓ conception
  - ✓ embryonic maturation, and

- Several antagonists are effective in cancer chemotherapy

- All gonadal hormones are synthesized from the precursor, cholesterol, in a series of steps that includes shortening of the hydrocarbon side chain and hydroxylation of the steroid nucleus.

Estrogens

- ***Estradiol*** is the most potent estrogen produced and secreted by the ovary. It is the principal estrogen in the premenopausal woman.

- ***Estriol*** is another metabolite of *estradiol,* is significantly less potent than *estradiol.* It is present in significant amounts during pregnancy, because it is the principal estrogen produced by the placenta.

Estrogens

- Synthetic estrogens, such as *ethinyl estradiol* undergo less first-pass metabolism than naturally occurring steroids and, thus, are effective when administered orally at lower doses

- In the absence of ligand, the receptor is sequestered within the cell nucleus and maintained in an inactive state.

- Similarly to the other nuclear receptors, the protein is prevented from binding to DNA by heat shock proteins.

Estrogens

- Other pathways that require these hormones have been identified that lead to more rapid actions. For example

I. activation of an estrogen receptor in the membranes of hypothalamic cells has been shown to couple to a G protein

Therapeutic uses

1-Postmenopausal HT:

- For women who have an intact uterus, a progestogen is always included with the estrogen therapy, because the combination reduces the risk of endometrial carcinoma associated with unopposed estrogen.

- Lower dose required

- *Estradiol* transdermal patch is also effective in treating postmenopausal symptoms.

2-Contraception: The combination of an estrogen and progestogen provides effective contraception via the oral or transdermal route.

3-Estrogen therapy usually in combination with a progestogen, is instituted to stimulate development of secondary sex characteristics in young women (11 to 13 years of age) with primary hypogonadism.

4-Estrogen and progestogen replacement therapy is used for women who have premature menopause or premature ovarian failure.

5-Estrogen may be used for prevention of osteoporosis if other therapies are inappropriate or not tolerated.

Pharmacokinetics

- **Naturally occurring estrogens: These agents and their esterified** or conjugated derivatives are readily absorbed through the gastrointestinal tract, skin, and mucous membranes. Taken orally, *estradiol is rapidly metabolized*

Pharmacokinetics

- ✓ transdermal route (patch, topical gel, topical emulsion, or spray),
- ✓ intravaginally (tablet, cream, or ring),
- ✓ Or by injection.

- The parent estrogen drugs and their metabolites undergo excretion into the bile and are then reabsorbed through the enterohepatic circulation.

Adverse effects

I. Nausea and breast tenderness are the most common

II. Postmenopausal uterine bleeding can occur.

III. diethylstilbestrol has been implicated as the possible cause of a rare, clear-cell cervical or vaginal adenocarcinoma observed among the daughters of women who took the drug during pregnancy.

Selective Estrogen-Receptor Modulators

- class of estrogen-related compounds that display selective agonism or antagonism for estrogen receptors depending on the tissue type.

- This category includes
- tamoxifen,
- Bazedoxifene
- raloxifene,
- clomiphene, and
- ospemifene.

Selective Estrogen-Receptor Modulators

- ***Tamoxifen*** Considered to be the first SERM *it* competes with estrogen for binding to the estrogen receptor in breast tissue and uterus.

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- antagonism of estrogen receptors in the breast tissue. Therefore, some breast tumors regress following treatment with these agents

Selective Estrogen-Receptor Modulators

- Acts as an estrogen agonist in bone leading to decreased bone resorption, increased bone density, and decreased vertebral fractures

- has little to no effect on the endometrium and, therefore, may not predispose to uterine cancer.

- The drug reduces the risk of endometrial hyperplasia with estrogen use.

✓has antioestrogenic effects on breast and uterus but oestrogenic effects on bone, lipid metabolism and blood coagulation. It is used for prevention and treatment of postmenopausal osteoporosis

➢ ***Clomiphene*** acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus. So increases the secretion of gonadotropin-releasing hormone and stimulating ovulation.

Therapeutic uses

Tamoxifen

- used in the palliative treatment of metastatic breast cancer
- adjuvant therapy following mastectomy or radiation in breast cancer

Raloxifene

- prophylaxis of breast cancer in high-risk women
- for the prevention and treatment of osteoporosis in postmen-opausal women

Therapeutic uses

Clomiphene

- to treat infertility associated with anovulatory cycles,
- is not effective in women with ovulatory dysfunction due to pituitary or ovarian failure.
- Uses of clomiphene in male mechanism behind?

Adverse effects

tamoxifen

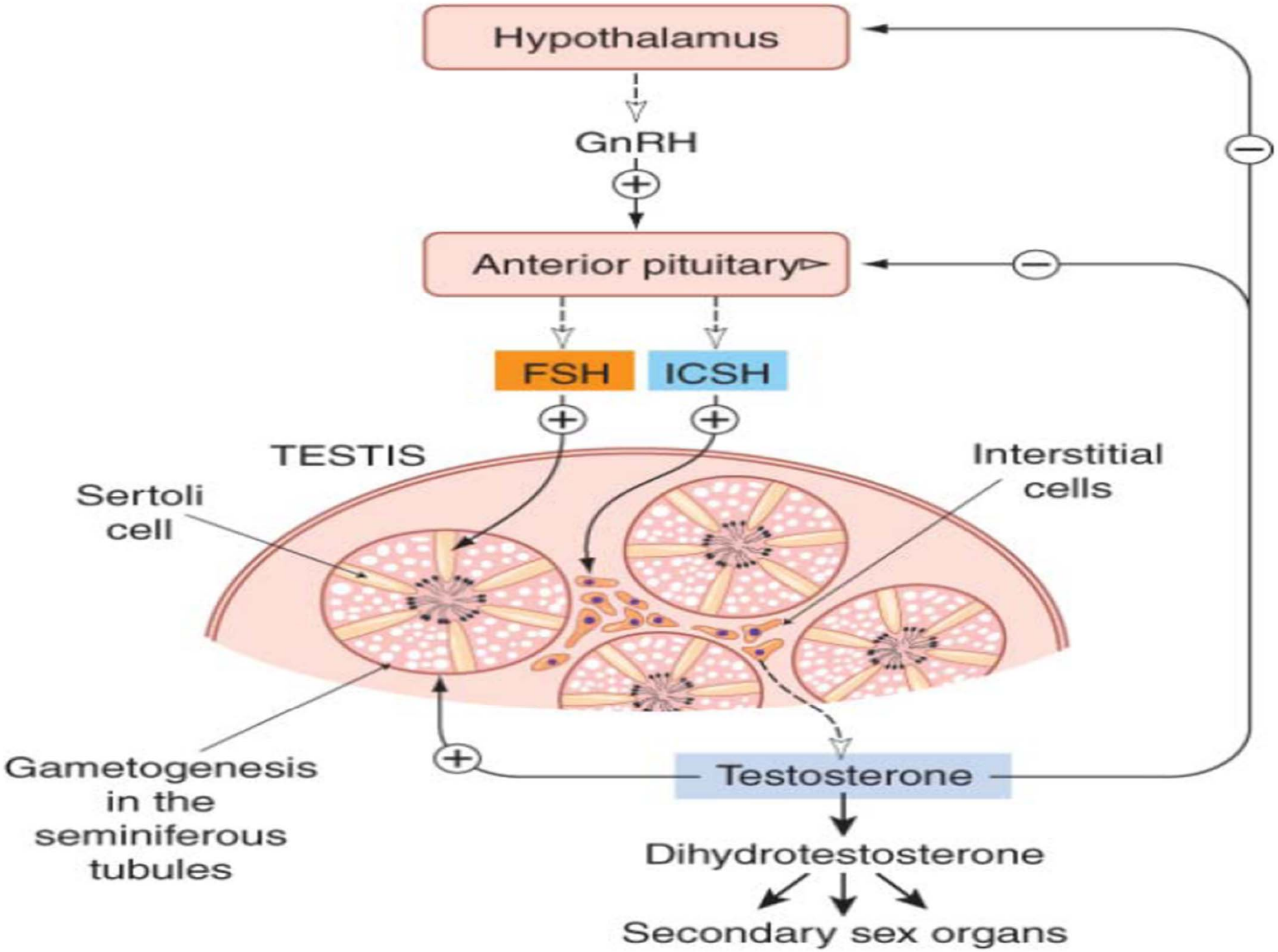
hot flashes and nausea.

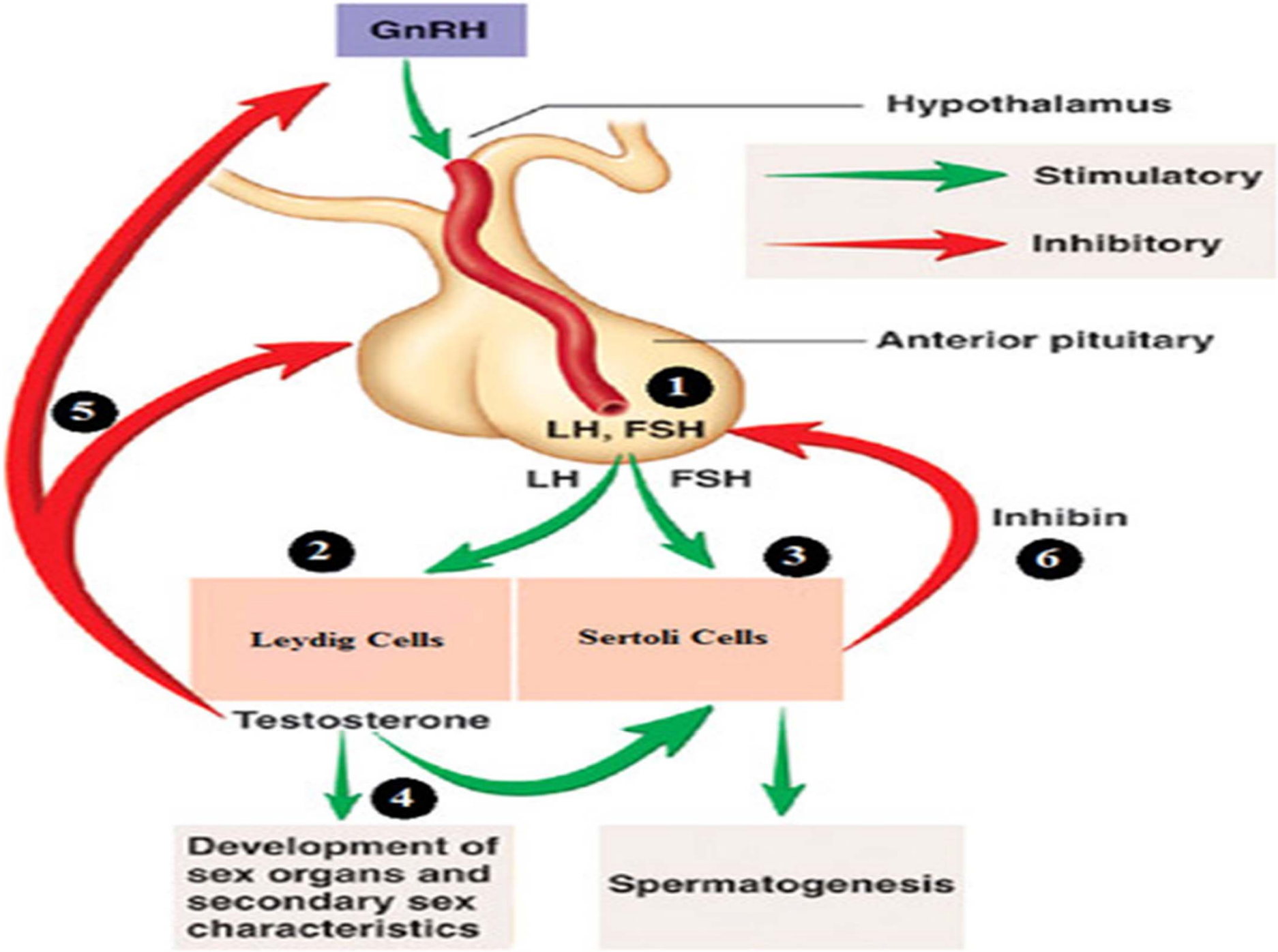
Because it is metabolized by various CYP450 isoenzymes, tamoxifen is subject to many drug interactions

Tamoxifen is also an inhibitor of P-glycoprotein.

Clomiphene

- dose related and include headache, nausea,, visual disturbances, and ovarian enlargement
- The risk of multiple births (twins or triplets) with *clomiphene* is 3 to 5 percent


Hypothalamus
GnRH
Anterior pituitary
FSH
ICSH
TESTIS
Sertoli cell
Interstitial cells
Gametogenesis in the seminiferous tubules
Testosterone
Dihydrotestosterone
Secondary sex organs


GnRH
Hypothalamus
Stimulatory
Inhibitory
Anterior pituitary
1
LH, FSH
LH
FSH
5
2
3
Inhibin
6
Leydig Cells
Sertoli Cells
Testosterone
4
Development of sex organs and secondary sex characteristics
Spermatogenesis

ANDROGENS

- LH stimulates steroidogenesis in the Leydig cells

- FSH is necessary for spermatogenesis in sertoli cells

- The androgens are **required for**

1) normal maturation in the male,
2) sperm production
3) increased synthesis of muscle proteins and hemoglobin, and
4) decreased bone resorption.

Mechanism of action

- bind to a specific nuclear receptor in a target cell
- testosterone itself is the active ligand in muscle and liver
- The hormone-receptor complex binds to DNA and stimulates the synthesis of specific RNAs and proteins.
- Testosterone analogs that cannot be converted to DHT have less effect on the reproductive system than they do on the skeletal musculature.

Therapeutic uses

1-Androgenic effects

2-Anabolic effects

3- Endometriosis:

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4-Unapproved use:

- ✓ Anabolic steroids are used to increase lean body mass, muscle strength, and endurance in athletes and body builders . use has been banned from the Olympics and in major professional and sports

- ❖ Testosterone is ineffective orally

- ❖ Testosterone and its C_{17}-esters (for example, testosterone cypionate or enanthate) are administered intramuscularly

- Transdermal patches, topical gels, and buccal tablets of testosterone are also available.
- Alkylation of the 17 position of testosterone allows oral administration of the hormone.

- Oxandrolone is another orally active testosterone derivative with anabolic activity 3 to 13 times that of testosterone

- Hepatic adverse effects have been associated with the alkylated androgens

Adverse effects

in females:

Masculinization

Acne

growth of facial hair

In males:

Priapism(painful, erection that lasts for more than four hours and occurs without sexual stimulation.)

impotence,

Adverse effects

- In children:

Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.

In athletes:

- ✓ premature closing of the epiphysis of the long bones(young)
- ✓ stunts growth and interrupts development(young)

hepatic abnormalities, increased aggression & mood disorders.

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Antiandrogens

- **Finasteride and dutasteride** agents used for the treatment of benign prostatic hypertrophy, inhibit 5α-reductase leads to a reduction in prostate size

- **Flutamide, bicalutamide and nilutamide** act as competitive inhibitors of androgens at the target cell effective orally for the treatment of prostate cancer.

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Antiandrogens

Cyproterone

- a derivative of progesterone and has weak progestational activity
- It is a partial agonist at androgen receptors, competing with dihydrotestosterone for receptors in androgen-sensitive target tissues.

- It is used as an adjunct in the treatment of prostatic cancer

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The end