Oestrogens and Anti- estrogens

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OESTROGENS

- **Two Endogenous Hormones secreted by Ovaries are :-**
- **1) Oestrogen, and 2) Progestin**
- **Responsible for both Physiological** and **Sexual Functions.**
- **Two Oestrogens receptors** are present in the **nucleus of target tissues / cells** :-
- **1) ER ? :- Uterus, Vagina, Ovary, Breasts, Bone, Vascular smooth muscles, Ant. Pituitary and Hypothalamus.**
- **2) ER ? :- Ovaries (Females)** and **Prostate (Males). Also in** Lungs, Brain and Vascular tissues.

Oestrogens

- **In Women,** Major Oestrogens produced are ;-

1) **Oestrone (E1) 2) Oestradiol (E2) and 3) Oestriol (E3).**

2) **In Premenopausal women, the main source of circulating Oestrogen (Oestradiol-E2) is the Ovaries (i.e. Graffian Follicles and Corpus Luteum).**
3) **In Post-menopausal women, the main source of oestrogen is Oestrone (E1) from Non-ovarian tissue (i.e. Adipose Tissues).**

1) **In Men, Oestrogen is produced by Testis.**

Synthesis of Oestrogen

Cholesterol

↓

Pregnenolone

↓

Androstenedione

↓

Aromatase Enyme

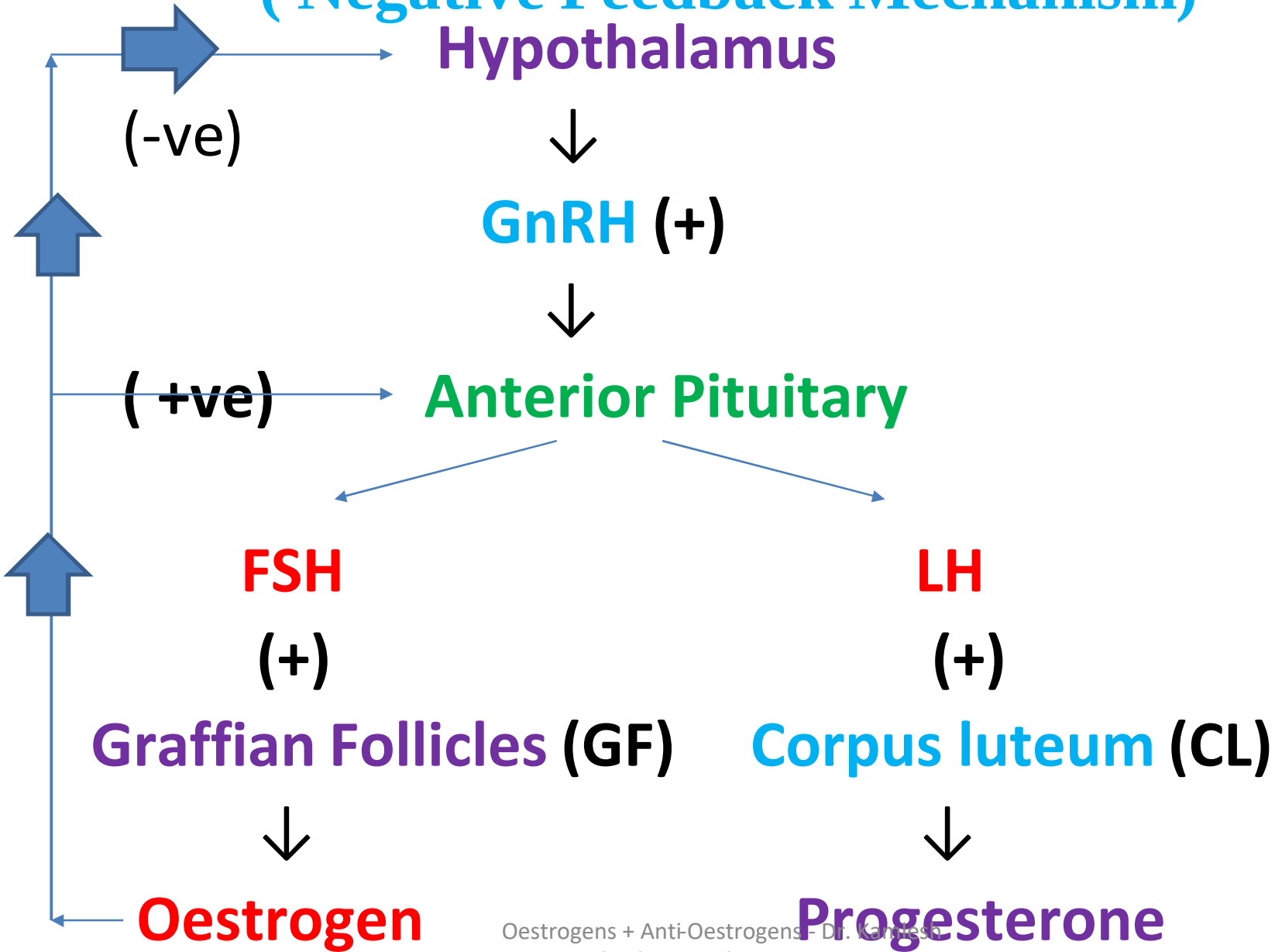
↓

Oestrone

Oestradiol **Oestriol**

Regulation Of Oestrogen Synthesis

(Negative Feedback Mechanism)



Actions of Oestrogens

1) **Growth and Development of Sex Organs in Females.**

2) **Stimulates the development of secondary sex characters**

3) **Responsible for the proliferative phase of Endometrium**

4) **Have negative feedback control mainly on anterior pituitary gland**

Actions of Oestrogens

5) Promotes rhythmic contractions of Fallopian tubes and myometrium

6) Makes cervical mucosa thin, secretion watery and alkaline to facilitates entry of spermatozoa

7) Stimulates the growth of ducts and stroma in Breast

8) Induces synthesis of Progesterone Hormone by sending positive signal to Anterior pituitary gland.

Actions of Oestrogens

9) Inhibit the activity of Osteoclast on Bones à Decreases rate of resorption of bone à Prevents Osteoporosis

10) ↑ HDL-C and ↓LDL-C levels in Plasma à Prevents atherosclerosis & CV arterial block.

11) Causes Sodium & Water Retention à producing Oedema à Mineralocorticoid activity

12) Enhances coagulability of blood by Clotting factors II,VII, IX & X & decreasing Anti-thromin III.

Therapeutic Uses of Oestrogens

1) **For Contraception :- Either as Transdermal Patch or most commonly as Combined Oral Contraceptive Pills along with Progestin.**

2) **In Senile Vaginitis à** as a Topical oestrogen preparations in the form of **cream, jelly or suppositories.**

3) **Dysmenorrhoea :- Oestrogens in combination with Progestins à To suppress ovulation in patients with Dysmenorrhoea. (The anovulatory cycles are painless)**

Therapeutic Uses of Oestrogens

4) Delayed Puberty in Girls :- In patients suffering from Hypo-pituitarism à oestrogens are used for the development of secondary sex characteristics à Avoids Osteoporosis.

Usually Cyclic treatment given.

5) Prostate Cancer :- Oestrogens acts as a Palliative. Prodrugs are used. Fosfestrol à converted to Stilbesterol by Acid Phosphatase in Prostate. Now, GnRH agonists (Leuprolide inj.) are preferred.

Therapeutic Uses of Oestrogens

11) Postmenopausal Hormone Replacement Therapy :- Required due to cessation of normal ovarian functions à Oestrogen deficiency à Increases risk of Osteoporosis in post- menopausal women.

1) **Short Term Therapy à Relieve menopausal symptoms like à** Hot flushes, night sweats, depression, irritability, sleeplessness etc…

Therapeutic Uses Of Oestrogens

2) **Long term therapy :-**

i) **To prevent or delay post menopausal osteoporosis (By decreasing rate of resorption of bones)**

ii) **To prevent or delay atherosclerosis & incidence of coronary artery disease (By Increasing HDL-C and Decreasing LDL-C plasma levels).**

iii) **To avoid risk of endometrial and breast cancer.**

iv) **Tibolone has oestrogenic, progestogenic and weak androgenic activities à No endometrium proliferation à Used continuously for HRT without cyclic progesterone administration.**

Adverse Effects of Oestrogens

1) **Nausea, vomiting**
2) **Breast tenderness**
3) **Water retention with oedema, Weight Gain**
4) **Thromboembolic complications**
5) **Increased incidence of Gall stones** and **Liver disease**
6) **Increased incidence of Endometrial and Breast Carcinoma**

Anti-estrogens

- Competes for natural Oestrogens for receptors in target organs.

- This includes :-

i) Clomiphene citrate

ii) Tamoxifene citrate

iii) Centchroman

iv) Fulvestrant

Clomiphene citrate

- Is non-steroidal antiestrogenic compound
- Is a ovulation inducing agent in females with anovulation causing infertility
- Is orally Estrogen Receptor Modulator with both agonist and antagonist properties
- It binds to both ER? and ER? receptors in anterior pituitary gland
- Acts as a pure estrogen antagonist
- Blocks negative feedback effect of estrogen on hypothalamus à stimulates Gonadotropins secretion (?FSH &? LH)à induces ovulation

Mechanism of Action – Clomiphene citrate

Clomiphene citrate (Pure antagonist)

↓

Competitively blocks oestrogen receptors (Erα and Erβ) in anterior pituitary gland

↓

Abolishes or opposes negative Feedback Effect of Estrogens

↓

Stimulates Gonadotropin secretion (↑FSH & ↑LH)

↓

Induces ovulation in anovulating women

Pharmacokinetics: Clomiphene citrate

- Well absorbed orally
- Is highly bound to plasma protein
- Has long plasma half life
- Undergoes Entero-hepatic cycling
- Accumulates in fatty tissues

Therapeutic Uses : Clomiphene citrate

1) Infertility in Females due to Anovulation

Cyclical therapy is recommended for not more than 6 cycles

- Schedule of therapy is as under:-

a) Dose :- **50 mg tab. once daily for 5 consecutive days, starting from 5th day of menstruation.** If, conception does not occur, continue the same dosage schedule up to 3 cycles.

Even after 3 cycles treatment if conception does not occur, then double the dose. i.e.

b) Dose :- **100mg tab. once daily for 5 consecutive days, starting from 5th day of menstruation for next three months.**

(Total treatment should not exceed more than 6 cycles due to increase risk of ovarian cancer).

Therapeutic Uses : Clomiphene citrate

2) In vitro fertilization

3) **Gamate Intrafallopian Transfer(GIFT) technique**

4) Assisted Reproduction Therapy**(ART)**

5) **Male Infertility due to Oligospermia**

Dose :- 25 mg Tab once daily for 25 consecutive days . Then 5 days drug free interval. Continue treatment for 6 to 9 months.

Clomiphene à increases Testosterone secretionà Increases sperm count and sperm motilityà increases chances of conception

Adverse effects : Clomiphene Citrate

- Multiple Pregnancy (Twins, Triplet born)
- Ovarian hyper - stimulation
- Ovarian cyst
- Ovarian malignancy
- Weight gain, Breast discomfort
- Hot flushes, nausea and vomiting
- Headache, Hair loss (Alopecia)

Tamoxifen Citrate

- Is Selective Estrogen Receptor Modulator (SERM)
- Has both **agonist** and **antagonist** action on estrogen receptors on different target tissues of the body
- Has **estrogen agonist** action on à **Uterus, bone, and plasma lipid**
- Has **estrogen antagonist** action on à Breast carcinoma cells, blood vessels and peripheral sites

Tamoxifen Citrate

USES :-

1) **In advanced metastatic Breast cancer due to its anti-estrogenic action on breast cancerous cells (In both premenopausal and postmenopausal women)**

Adverse Effects :-

1)Increase risk of endometrial carcinoma and venous thromboembolism

2)Vaginal bleeding and discharge

3)Fluid and water retention and oedema

4) Nausea, vomiting, hot flushes

Fulvestrant

- Is 1st member of 'Selective Estrogen Receptor Downregulators' **(SERDs)**
- Is pure Estrogen antagonist
- **Is SERM with no known agonist action on ER**
- Is longer acting à t1/2 of one month
- Is administered as 250 mg I.M. injection once every month
- It inhibits ER dimerizationà **prevents ER interaction with DNA à Enhances Receptor Degradation à Downregulates ER à resulting into complete suppression of ER responsive gene function**

Fulvestrant

- **USES :-**
- In Tamoxifen resistant ER positive Breast Cancer in postmenopausal women

Centchroman (Ormeloxifene)

- **Is nonsteroidal estrogen antagonist**
- **Is SERM developed by CDRI India**
- **Is introduced in National Family welfare Programme à to be distributed as an oral contraceptive under the brand name SAHELI**
- **Available as 30 mg tab of centchroman**
- **Dose is Twice in a week for first three months, then once in a week as long as contraception is required.**

Centchroman (Ormeloxifene)

- **Dose :**
- **1st tab on 1st day of menstruation (eg. Sunday).**
- **Then, 2nd tab on 4th day (i.e. Wednesday).**
- **Subsequent tab on Sunday and Wednesday for 1st 3 months followed by once a week on same day**

Centchromane (Ormeloxifene)

- **Is SERM**
- **Has Antagonist Effect on Breast And Uterus**
- **Useful in treatment of Dysfunctional Uterine Bleeding**
- Other uses under Evaluation are :-
- **i) Post menopausal osteoporosis**
- **Ii) Breast carcinoma**
- **Iii) endometrial carcinoma**