



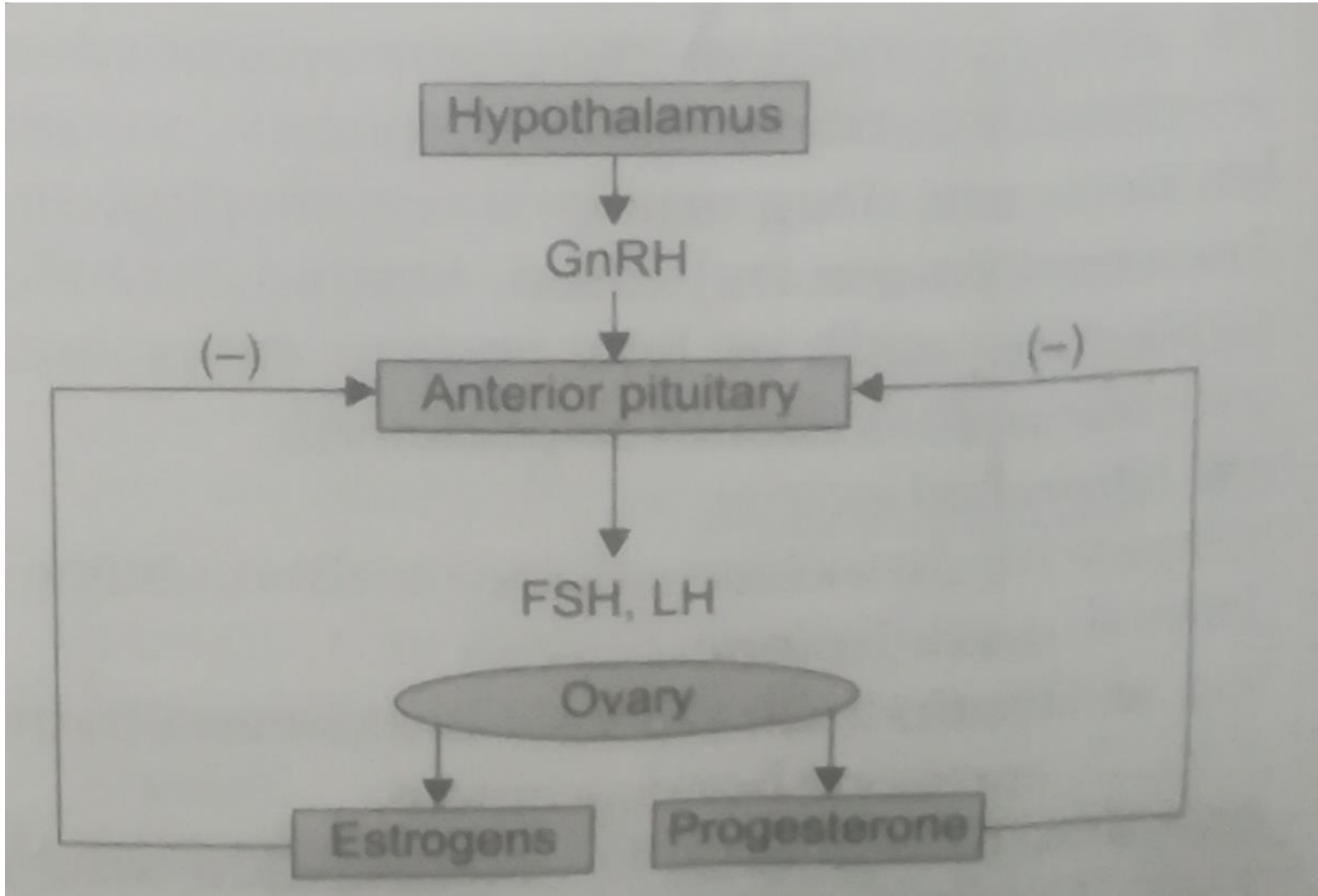
# **FEMALE SEX HORMONES & INHIBITORS**

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# HORMONES

- 🕒 Estrogen
- 🕒 Progesterone
- 🕒 FSH
- 🕒 LH
- 🕒 GnRH





# ESTROGEN

🕒 Natural estrogens: Estradiol, estrone, estriol

🕒 Synthetic: ethinyl estradiol, stilboestrol

🕒 MOA:

it enters into cell, bind to cytosolic receptors and translocate of receptor hormone complex into nucleus where it modulates gene expression.



- **Estradiol** has **low oral bioavailability**
- **micronized form** for oral use.
- transdermal patch, vaginal cream, or intramuscular injection.
  
- **Estradiol cypionate. Longer acting , I/M**
- **Ethinyl estradiol and mestranol. B/A increased**



# ESTROGEN

## Effects;

- 🕒 Growth of normal genital structure
- 🕒 Secondary sex characters
- 🕒 Reduce bone resorption
- 🕒 Enhances blood coagulability
- 🕒 Increase triglycerids
- 🕒 Reduces LDL



# CLINICAL USES OF ESTROGEN

- 🕒 Treatment of hypogonadism
- 🕒 Use in HRT (hormone replacement therapy)
- 🕒 Premature ovarian failure
- 🕒 Preventing bone loss and osteoporosis
- 🕒 Hormonal contraceptives
- 🕒 CA prostate
- 🕒 Dysmennorrhhea



# TOXICITY OF ESTROGEN

- ⌚ In hypogonadal girl, premature closure of epiphyses of long bones.
- ⌚ Increased risk of endometrial cancer
- ⌚ Small increase risk of stroke and breast cancer
- ⌚ Dose dependent toxicity is nausea, vomitings headache, breast tenderness, migraine, gall bladder disease, hypertension and hypertriglyceridemia.
- ⌚ orally administered estrogens will have a high ratio of hepatic to peripheral effects.
- ⌚ Diethylstilbestrol (DES)???





# PROGESTINS

**Natural:** progesterone

**Synthetic :**

- L-norgestrel
- Medroxyprogesterone
- Norgestimate
- Norethisterone



# PROGESTRONE

- 🕒 Secetory changes in endometrium
- 🕒 Maintaince of pregnancy
- 🕒 Affect carbohydrate metabolism and stimulate fat deposition
- 🕒 High doses suppress gonadotrophins and cause anovulation
- 🕒 Cervix, thick secretions
- 🕒 Breast changes, rise in body temperature



# CLINICAL USES

- 🕒 Contraception
- 🕒 In HRT
- 🕒 Endometrial hyperplasia /cancer
- 🕒 DUB (dysfunctional uterine bleeding)
- 🕒 Premenstrual syndrome
- 🕒 Threatened abortion



# TOXICITY OF PROGESTRONE

- 🕒 Increase blood pressure, headache, acne
- 🕒 Decrease HDL
- 🕒 Delayed resumption of ovulation after therapy
- 🕒 Decrease in bone density
- 🕒 Teratogenic



Estrogen refers to a steroid hormone that is important in the reproductive development in females

Produced by the growing Graafian follicle

Secreted by ovaries prior to ovulation; also produced by the placenta during pregnancy

Secretion is regulated by FSH

Involved in the formation and maintenance of secondary sex characteristics; also important in bone resorption

Involved in the enlargement of the uterus and breasts during pregnancy

Progesterone refers to a steroid hormone that prepares the uterus for pregnancy

Produced by the corpus luteum

Secreted by the ovaries after the ovulation; also produced by the placenta during pregnancy

Secretion is regulated by LH

Involved in the formation and maintenance of endometrium and uterus

Involved in the reduction of contractility of the uterus and stimulates the growth of mammary glands



## Classification

- Selective Estrogen Receptor

Modulator (SERM)

Tamoxifen, Toremifene, Raloxifen

Clomiphene

- Pure Estrogen Receptor

Antagonist:

Fulvestrant

- 

## Aromatase Inhibitors

(Estrogen synthesis inhibitors)

Anastrozole, Letrozole ,

Exemestane , Fadrozole

- Progesterone Antagonist

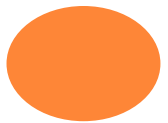
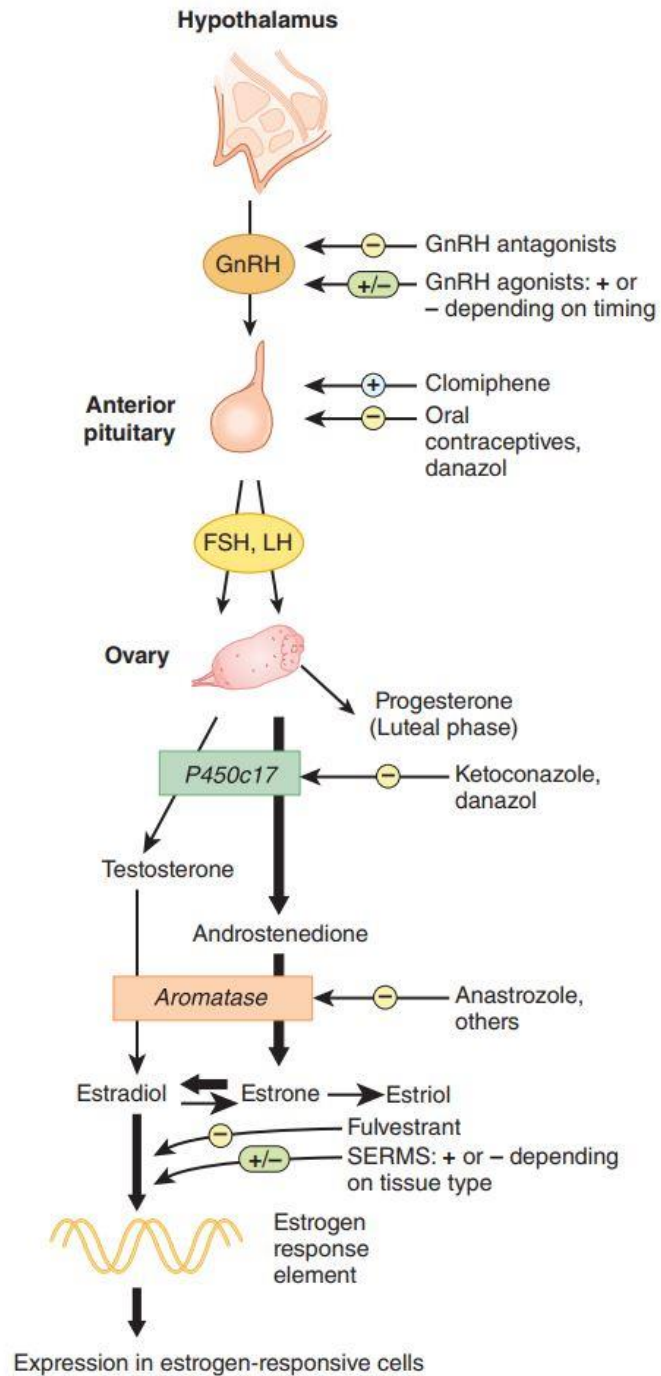
Mifepristone

- Anti-estrogen, Anti-progestin,

Anti-androgenic activity:

- Danazol





# SERMs

- 🕒 Stands for **selective estrogen receptors modulators**
- 🕒 At some receptors act as agonists and on others as antagonists
- 1. Tamoxifen
- 2. Raloxifen
- 3. clomiphene





# TAMOXIFEN

## MOA

- ⌚ As antagonists on breast tissues
- ⌚ While agonist at endometrial receptors
- ⌚ Agonist on bones

## Clinical use

- ⌚ Used in hormone responsive breast cancer
- ⌚ Used prophylactically in women at high risk
- ⌚ osteoporosis



# RALOXIFEN

## MOA

- 🕒 Act as **antagonist on breast tissue** so reduce chances of breast cancer
- 🕒 No/low effect on endometrial tissue
  
- 🕒 **Used** in osteoporosis in postmenopausal women
- 🕒 **Side effects** hot flushes and venous thrombosis



# CLOMIPHENE

- ⌚ Non steroid compound having tissue selectivity

## MOA

- ⌚ It **blocks estrogen receptors in pituitary**,
- ⌚ reduces negative feedback and increase FSH AND LH levels.
- ⌚ Increase gonadotrophins **stimulates ovulation**.

## Clinical use

- ⌚ Ovulation Induction in treatment of infertility in females with polycystic ovarian disease



# ADVERSE EFFECTS

- • Incidence of multiple pregnancies is 10 %
- • Nausea, vomiting.
- • Hot flashes
- • Burred vision (Intensification & prolongation of afterimages), may cause trouble while driving.
- • Headache, can trigger migraine
- • Allergic skin reactions
- • Reversible hair loss • Weight gain



# FULVESTRANT

- Pure estrogen receptor antagonist
- Effective in the treatment of breast cancer in patients who become resistant to Tamoxifen



# ESTROGEN AND PROGESTERONE SYNTHESIS INHIBITORS OR ANTAGONISTS

1. Mifepristone
2. Danazol
3. Aromatase inhibitors



# MIFEPRISTONE

- 🕒 Orally **active antagonist of progesterone**
- 🕒 It also antagonise the glucocorticoids

- 🕒 **Used as abortifacient**(within 49 days)

It is given along prostaglandin E or F analogue(reduce toxicity)

- 🕒 Also **used as postcoital contraceptive**

- 🕒 Other uses are endometriosis , cushing`s syndrome , breast cancer

**Adverse effects:** • Vomiting , diarrhea , abdominal or pelvic pain



# AROMATASE INHIBITORS

- 🕒 Anastrozole and related compounds letrozole
- 🕒 **Inhibitors of aromatase**
- 🕒 Aromatase is enzyme required for estrogen synthesis, aromatization of **androgens(testosterone) into estrogens**
- 🕒 **Inhibit excessive estrogen synthesis in patients with polycystic ovarian disease**
  - Prevent the negative feedback and increase synthesis of FSH,LH and **result in ovulation induction in females** and spermatogenesis in males





## CLINICAL USES

- **Used in treatment of breast cancer**

- **Treatment of infertility**

Ovulation induction in females having polycystic ovarian disease

- **To increase sperm count in male patients**



# DANAZOL

- 🕒 **Partial agonist of glucocorticoids and androgens**
- 🕒 Inhibit p450 enzyme(synthesis of gonadal hormones)
- 🕒 **Treatment of endometriosis and fibrocystic disease of breast.**

## **Adverse Effects**

- 🕒 • Weight gain • Edema • Acne • Hirsutism • Headache • Hot flashes • Muscle cramps



# OVULATION INDUCING AGENTS (DRUGS USED FOR TREATMENT OF INFERTILITY)

- **Clomiphene** (50-100mg once daily from day 2 to day 5)
- **Gonadotropins(FSH,LH)** given I/M for ovulation at day 14 of menstrual cycle Menotropins, Urofollitropin
- **Aromatase inhibitors:** Letrozole, Anastrozole

