السنة الثالثة

تأثير الأدوية 2

د.رامز ونوس

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Sex hormones and drugs

Pharmacology II

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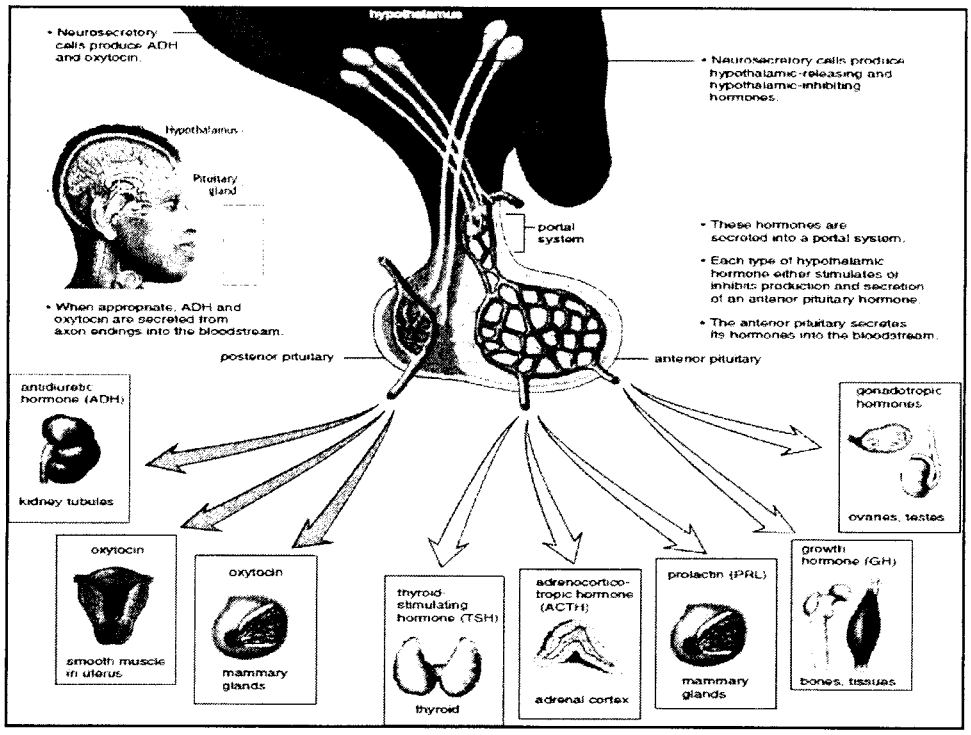
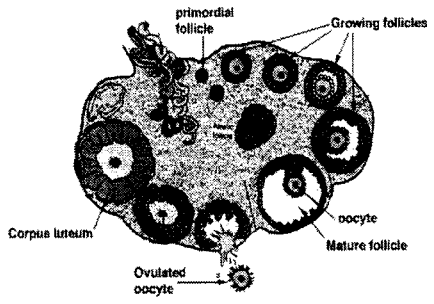
2017



- Hormones affecting the reproductive system are peptide, glycopeptides or steroid hormones.
- Peptide hormones include those produced by hypothalamus.
- Glycopeptides (glycoproteins) hormones include those produced by pituitary.
- Steroids are mainly produced from gonads (ovaries/testis) and adrenal glands (adrenal cortex).
- Steroid hormones include oestrogen, progestogens and androgens.

Oestrogens



Oestrogens

Oestrogens include the natural hormones as well as semi-synthetic and synthetic agents

The three major **naturally** occurring estrogens in women are :

- Estradiol (E2) is the predominant estrogen during reproductive years both in terms of absolute serum levels as well as in terms of estrogenic activity.
- Estrone (E1) is the predominant circulating estrogen During menopause
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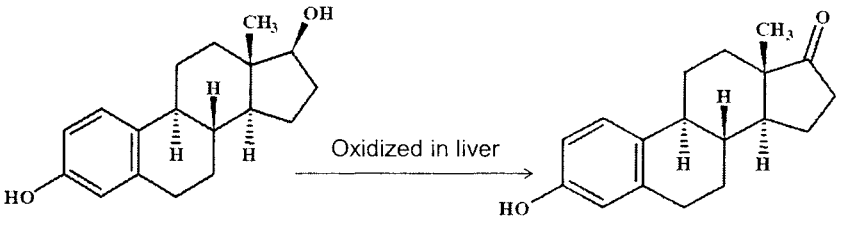
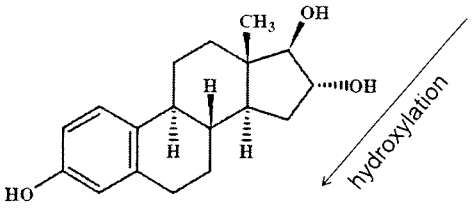
- Estriol (E3) is the predominant circulating estrogen during pregnancy in terms of serum levels.
- Estradiol is the strongest with a potency of approximately 80 times that of estriol

Natural Oestrogens



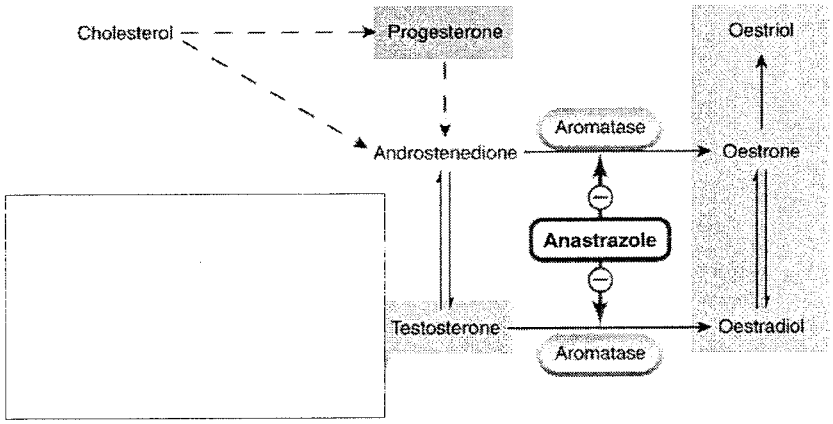
1. ESTRADIOL

2. ESTRONE



3. ESTRIOL

Biosynthetic pathway for the androgens and oestrogens

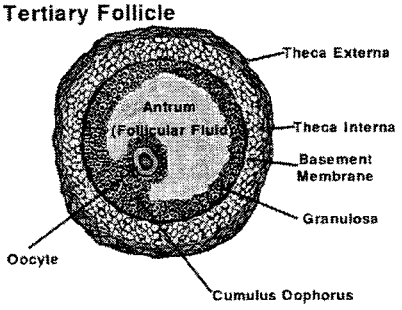


The **theca folliculi** comprise a layer of the ovarian follicles.

The theca are divided into two layers, the **theca interna** and the **theca externa**.

- The **theca interna** is responsible for the production of **androstenedione**, and indirectly the production of 17β estradiol by supplying the neighboring granulosa cells with androstenedione that with the help of the enzyme aromatase can be used as a substrate for this type of estradiol.
- FSH induces the granulosa cells to make aromatase that converts the androgens made by the theca interna into estradiol.
- The theca interna is highly vascular and possesses LH receptors, not FSH.
- Estradiol promotes the formation of LH receptors on granulosa cells, which also have FSH receptors.

Tertiary Follicle

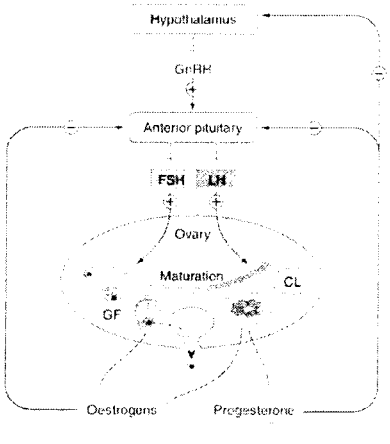


- After rupture of the mature ovarian follicle, the theca interna cells differentiate into the theca lutein cells of the corpus luteum. Theca lutein cells secrete androgens and progesterone.

Synthetic oestrogens

- Steroidal:
  - Ethinyl estradiol, Mestranol and Tibolone
- Nonsteroidal:
  - Diethinylstilbestrol, Hexestrol and Dienestrol

Regulation of Secretion



Hormonal control of the female reproductive system.
The Graafian follicle (GF) is shown developing on the left, then involuting to form the corpus luteum (CL) on the right, after the ovum (•) has been released. FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinising hormone.

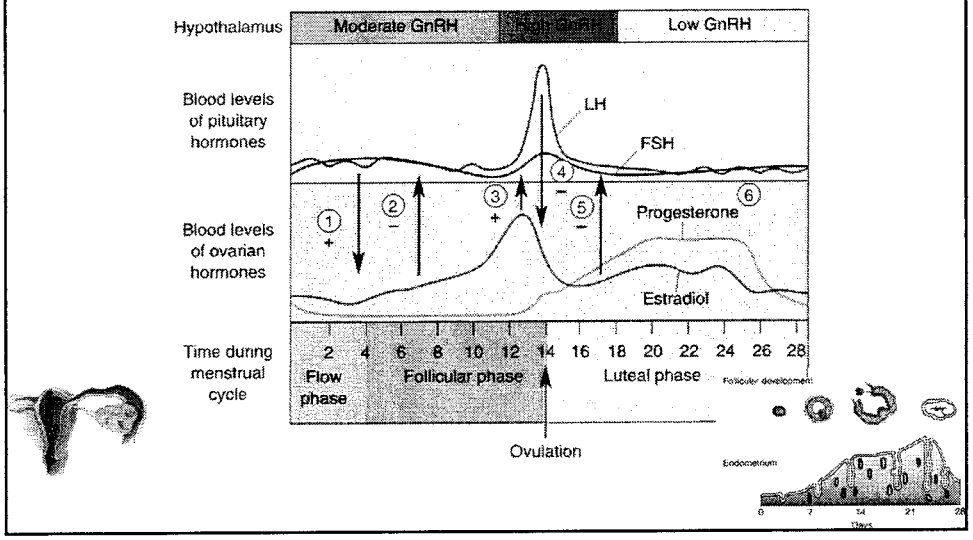
- Daily secretion: 10 to 100 mcg per day
- During pregnancy – large quantity by placenta – upto 30 mg per day
- Post menopausal: 2 – 10 mcg per day only

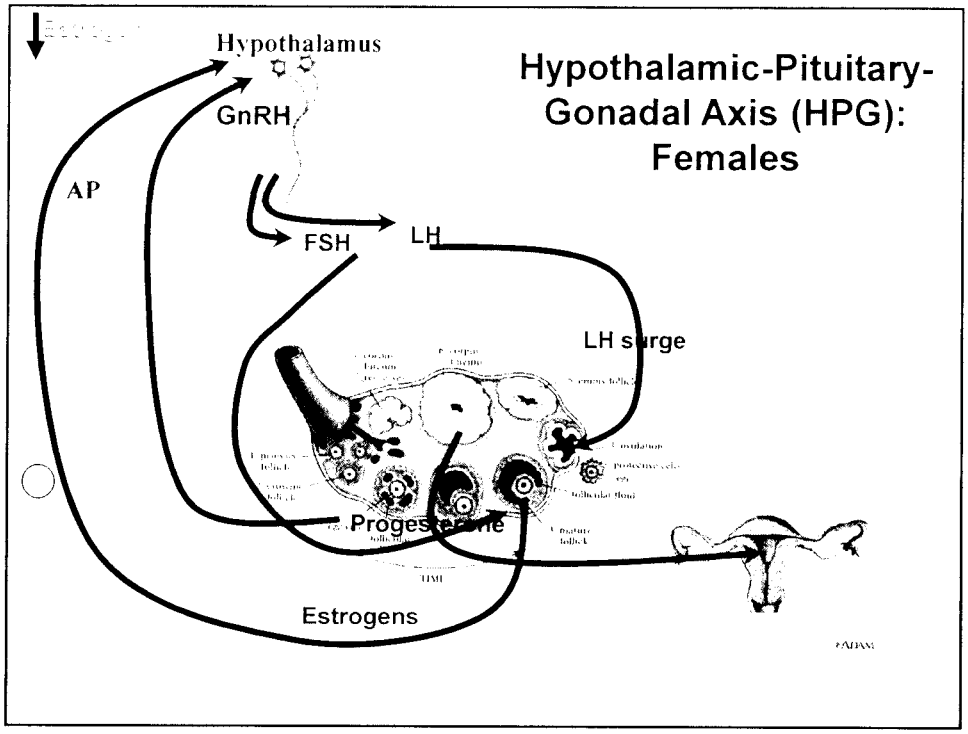
Hormonal control of the female reproductive system

- The **menstrual cycle** starts with menstruation.
- Gonadotrophin-releasing hormone (GnRH), released from the hypothalamus, acts on the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinising hormone (LH).
- FSH and LH stimulate follicle development in the ovary. FSH is the main hormone stimulating oestrogen release. LH stimulates ovulation at mid-cycle and is the main hormone controlling subsequent progesterone secretion from the corpus luteum.
- Oestrogen controls the proliferative phase of the endometrium and has negative feedback effects on the anterior pituitary. Progesterone controls the later secretory phase, and has negative feedback effects on both hypothalamus and anterior pituitary.
- If a fertilised ovum is implanted, the corpus luteum continues to secrete progesterone.
- After implantation, human chorionic gonadotrophin (hCG) from the chorion becomes important, and later in pregnancy progesterone and other hormones are secreted by the placenta.

Oestrogens Physiology

- Hormonal regulation of oogensis and ovulation





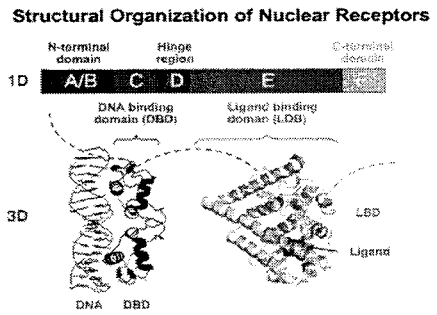
Actions of Oestrogens

- On sexual organs (primary and secondary sexual characteristics)
- In menstrual cycle
  - Increases the endometrium in thickness and vascularity
  - Rhythmic contractions of uterus and fallopian tube
  - Increase of cervical mucous and alkaline watery secretion with a lowered viscosity favoring sperm access
- Metabolic effects: Anabolic
  - Bone: Important for maintaining bone mass
  - Oedema – salt and water retention
  - Increased HDL and decreased LDL level
  - Increased coagulability: II, VII, IX and X

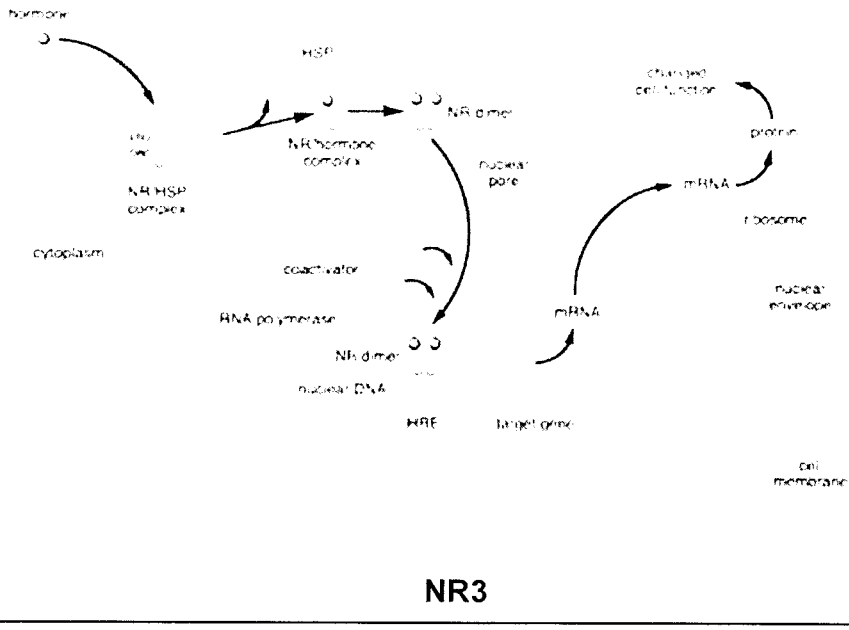
Oestrogen - Kinetics

- Natural as well as synthetic oestrogens are well absorbed in the gastrointestinal tract and metabolised in the liver by P450 where synthetic oestrogens are degraded less rapidly.
- There is a variable amount of enterohepatic cycling, which forms the basis for drug interaction, because broad-spectrum antibiotic use alters bowel flora and can thereby render oral contraception ineffective.
- Most oestrogens are readily absorbed from skin and mucous membranes.
- In the plasma, natural oestrogens are bound to albumin and to a sex hormone-binding globulin (SHBG).
- Natural oestrogens are excreted in the urine as glucuronides and sulfates.

Mechanism of Action (MOA)



- 2 ERs are – ERα and ERß
- ERß – Prostate and Ovaries
- ERα - uterus, vagina, breast and blood vessels
- Work via a steroid hormone mechanism.
  - Entering the target cells and binding to specific cytosolic receptors
  - Translocating of The steroid-receptor complex to the nucleus
  - Interacting with coactivator proteins or corepressor proteins
  - Altering the expression of target genes



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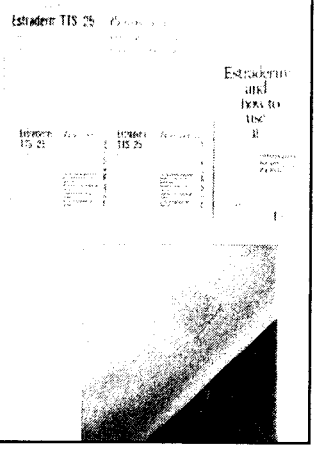
Oestrogen preparations

- Many preparations are available (oral, transdermal, intramuscular, **implantable** and topical)
- Preferred route is **oral**, but sometimes **parenteral** when large doses are required
- Topically in the vagina as **creams** or **pessaries** for local effect.
- Some examples:
  - Ethinylestradiol (EE) : 0.01, 0.05, 1 mg tab
  - Mestranol: 0.1 mg tabs
  - Estriol succinate: 1mg/gm cream
- **Transdermal patches (TTS)**

Sizes: 5, 10 and 20 cm^2 0.025, 0.05 and 1 mg/day

Usual dose: 0.5 mg/day

Estrogen + Progestin patches



Clinical use of oestrogens and antioestrogens

Oestrogens

- Replacement therapy:
  - primary ovarian failure (e.g. Turner's syndrome)
  - secondary ovarian failure (menopause) for flushing, vaginal dryness and to preserve bone mass.
- Contraception.

Antioestrogens

➢ To treat oestrogen-sensitive breast cancer (tamoxifen).
➢ To induce ovulation (clomiphene) in treating infertility.

Therapeutic Uses

- Hormone Replacement Therapy to Menopause woman

- Problems of menopause:
  - **Vasomotor disturbances**
  - **Urogenital atrophy**
  - **Osteoporosis and fractures**
  - **Dermatological changes**
  - **Risk of cardiovascular diseases**

- Dosage: Oestrogen equivalent to 0.625 mg of EE/day
  - Progestin preparation (medroxy progesterone /norethisterone) is used – 2.5 mg daily
  - TTS preparations may be preferred

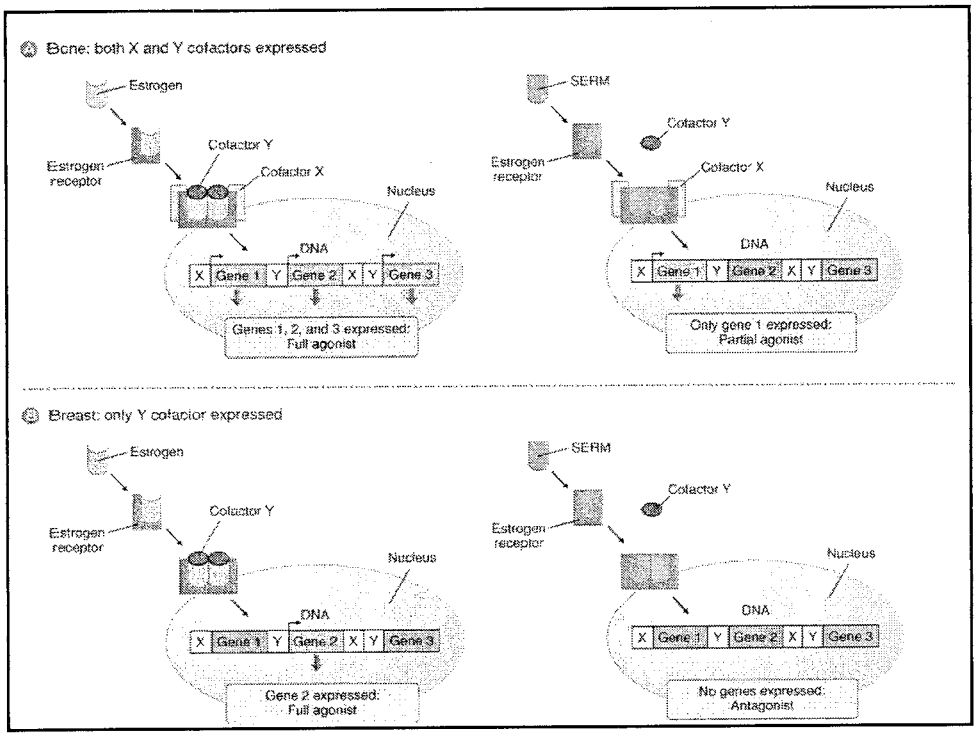
Estrogens Side Effects

- Increase risk of breast, vaginal and uterine cancers.
- Increase risk of thromboembolic and vascular problems.
- Hypertension
- Nausea, vomiting, headache, menstrual disturbances and weight gain.

Selective Estrogen Receptor Modulators (SERMs)

- Are mixed agonists/antagonists.
- SERMs are tissue-specific.

- Clomifene – used to induce ovulation. Is an ER antagonist in hypothalamus and anterior pituitary, but a partial agonist in ovaries.
- Tamoxifen – an ER antagonist in breast, but a partial agonist in endometrium and bone.
- Raloxifene – ER agonist in bone, but an antagonist in both breast and endometrium.



Clomiphene Citrate (Antiestrogen)

- The "Fertility pill" - pure antagonist of estrogen receptor in all human tissues
  - Used in women with unexplained infertility or anovulatory infertility
  - Inhibits oestrogen binding in the anterior pituitary, so preventing the normal modulation by negative feedback and causing increased secretion of GnRH and gonadotrophins.

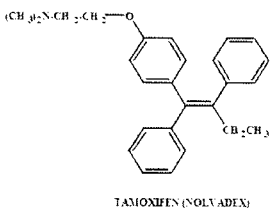
➢ Dosage:

- 50 mg OD from 5th day onwards for 5 days
- Continued for 2-3 cycles
- Conception occurs within 4-6 cycles

Tamoxifen (SERM)

- Actions:
  - Is a competitive antagonist to estrogen at receptors in the breast.
  - Partial agonist at other estrogen receptors (thus minimizing side effects due to estrogen deprivation) - bone, uterus, liver and pituitary
  - Hot flushes – antiestrogenic action
  - Improvement in bone mass and lipid profile
- Kinetics:
  - Absorbed orally and has long duration of action
  - Excreted in Bile
  - Dose is 10 to 20 mg BD

Tamoxifen – contd.



TAMOXIFEN (NOLVADEX)

- Uses:
  - Breast carcinoma of pre and post menopause
  - Adjuvant therapy in early cases
  - Palliative therapy
  - Infertility:

- in women with anovulatory disorders (given at days 3–7 of a woman's cycle).

- in males by disinhibiting the hypothalamic-pituitary-adrenal axis (via ER antagonism) and thereby increasing the secretion of LH and FSH and increasing testicular testosterone production.

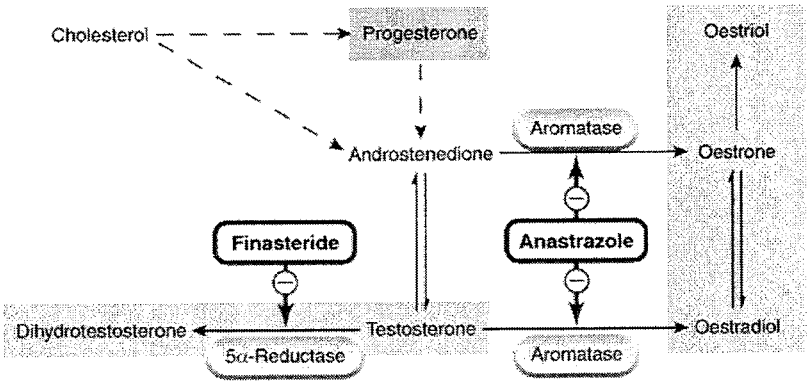
- Side effects.

-The drug has a low incidence of adverse reactions

-Hot flashes, nausea, vomiting, rash, menstrual irregularities and bleeding, infrequent depression, headache, hypercalcemia, and edema

-Less toxic than anticancer drugs

Aromatase Inhibitors



Biosynthetic pathway for the androgens and oestrogens

Aromatase Inhibitors

- <u>Letrozole, Anastrozole and Exemestane</u>
- MOA: Letrozole
  - Non steroidal compound, reversible inhibition of aromatization all over the body
  - Suppression of proliferation of estrogen dependant breast carcinoma cells
  - Rapid oral absorption – 100% bioavailability, t1/2 – 40 Hrs
- Uses:
  - Early breast carcinoma and Advanced breast carcinoma in postmenopausal