Estrogens and Androgens

Hypothalamus and Pituitary Regulation of Female Reproductive System

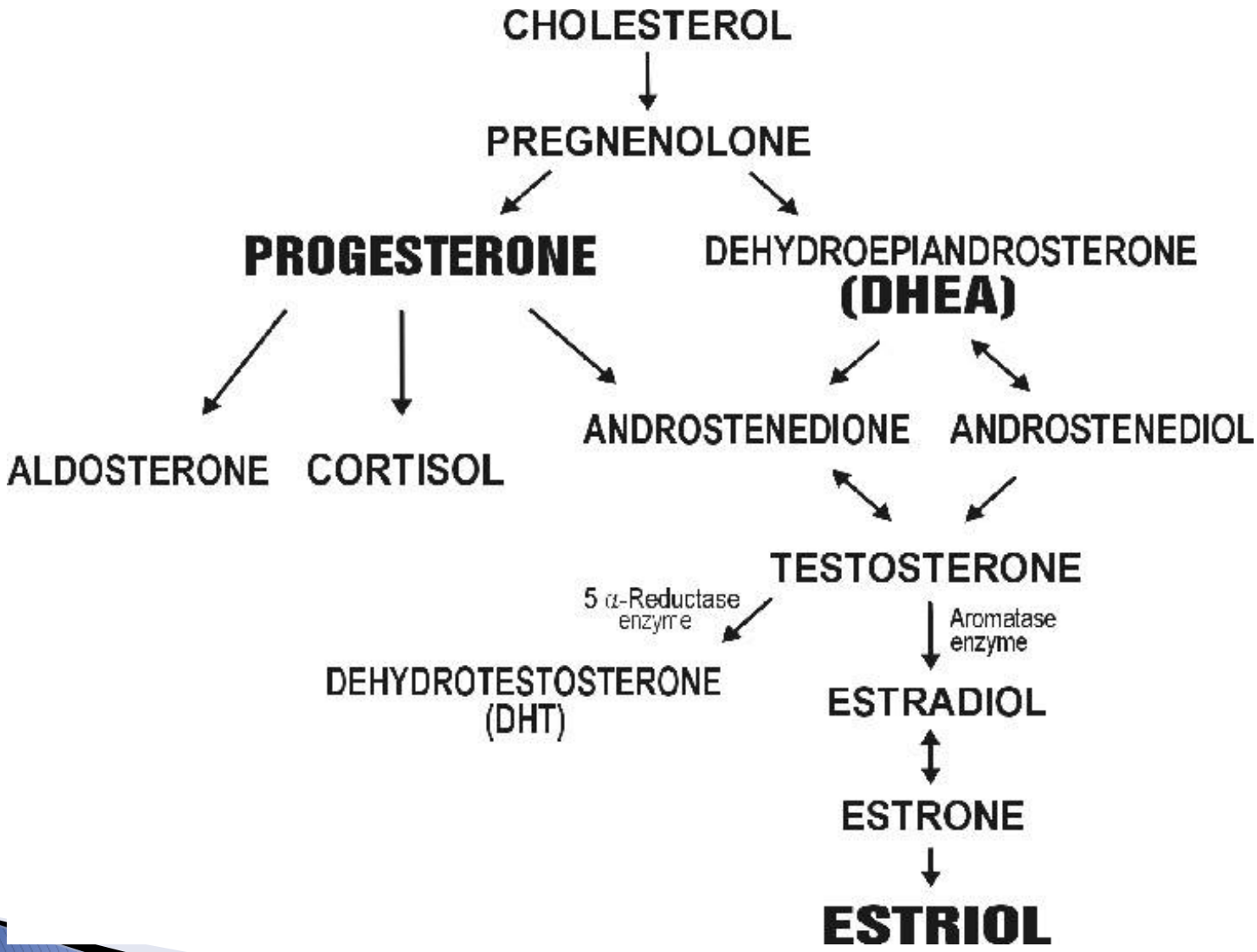
- Hypothalamus secretes gonadotropin-releasing hormone (GnRH)
  - Stimulates pituitary to secrete FSH and LH
    - Act on ovary and cause immature ovarian follicles to begin developing to dominant follicles
  - Pituitary hormones
    - Rising and falling levels create two interrelated cycles: ovarian and uterine

- Sex hormones produced by the gonads are necessary for:
  - Conception
  - Embryonic maturation
  - Development of primary and secondary sexual characteristics at puberty

- Activity in target cells is modulated by receptors

- Therapeutic uses of gonadal hormones:
  - Replacement therapy
  - Contraception
  - Management of menopausal symptoms
  - Several antagonists are effective in cancer chemotherapy

- All gonadal hormones are synthesized from cholesterol, in a series of steps that includes
  - Shortening of the hydrocarbon side chain
  - Hydroxylation of the steroid nucleus
  - Aromatization is the last step in estrogen synthesis


CHOLESTEROL
PREGNENOLONE
PROGESTERONE
DEHYDROEPIANDROSTERONE
(DHEA)
ALDOSTERONE
CORTISOL
ANDROSTENEDIONE
ANDROSTENEDIOL
TESTOSTERONE
5 α-Reductase enzyme
Aromatase enzyme
DEHYDROTESTOSTERONE
(DHT)
ESTRADIOL
ESTRONE
ESTRIOL

Estrogens

- Estradiol
  - The most potent estrogen produced and secreted by the ovary
  - The principal estrogen in the premenopausal woman
- Estrone
  - A metabolite of estradiol that has approximately one third potency of estradiol
  - Primary circulating estrogen after menopause
  - Generated from conversion of androstenedione in peripheral tissues

Estrogens

- Estriol
  - A metabolite of estradiol
  - Significantly less potent than estradiol
  - Present in significant amounts during pregnancy
  - Produced by the placenta

- Plant-derived conjugated estrogen products are also available

Estrogens

- Ethinyl estradiol
  - Synthetic estrogen
  - Undergo less first-pass metabolism than naturally occurring steroids
  - Effective when administered orally at lower doses

Estrogens

- Selective estrogen-receptor modulators (SERMs)
  - Nonsteroidal compounds that bind to estrogen receptors and exert either estrogenic or antiestrogenic effects on target tissues
  - Include tamoxifen and raloxifene and clomiphene

Estrogens mechanism of action

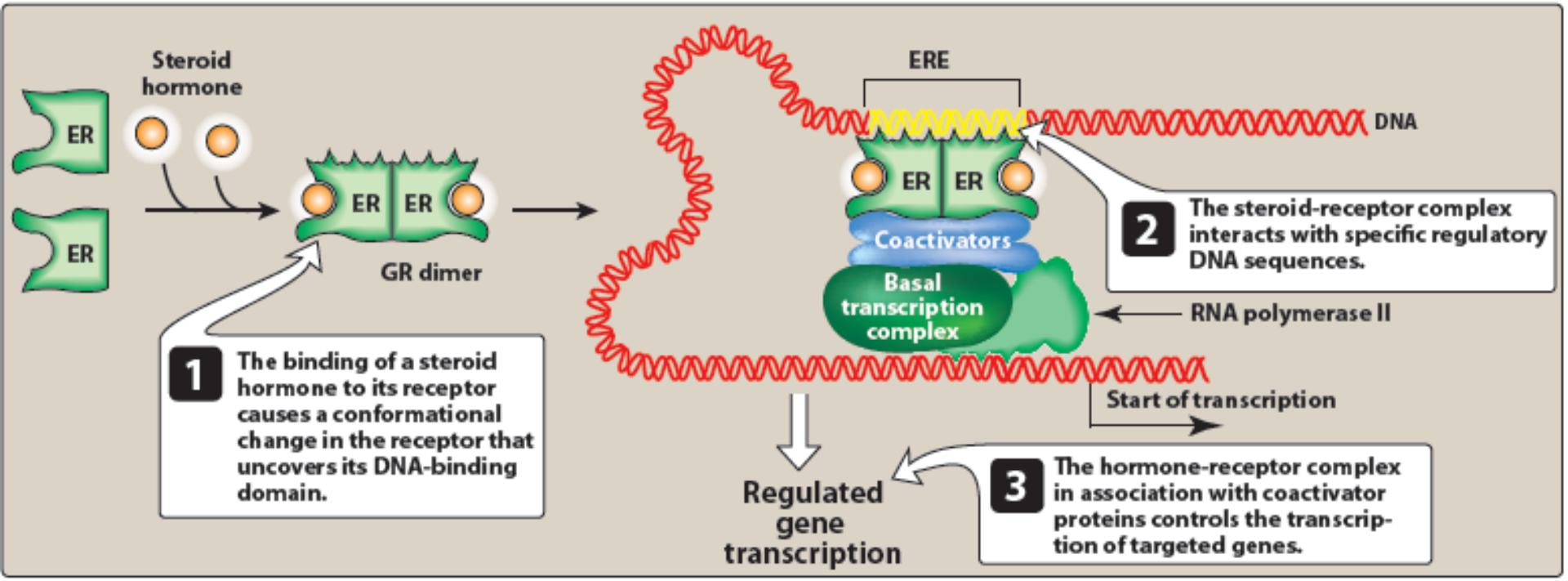
- Steroid hormones diffuse across the cell membrane and bind to specific nuclear-receptors
- Two estrogen-receptor subtypes, α and β, mediate the effects of the hormone
- The α-receptor contains a region that promotes transcription activation
- The β-receptor contains a repressor domain

Estrogens mechanism of action

- The transcriptional properties of the α and β estrogen receptors are different
- Affinity for the receptor type varies with the particular estrogen
- The receptor isoforms vary in structure, chromosomal location, and tissue distribution

Estrogens mechanism of action

- Activated steroid-receptor interacts with nuclear chromatin to initiate RNA synthesis and synthesis of specific proteins that mediate physiologic functions
- The steroid hormones are both receptor and tissue specific and result in different RNA species in diverse target tissues
- Activation of an estrogen receptor in the membranes of hypothalamic cells has been shown to couple to a G protein initiating a second-messenger cascade
- Estrogen-mediated dilation of coronary arteries occurs by the increased formation and release of nitric oxide and prostacyclin in endothelial cells


Steroid hormone
ER
ER
ER ER
GR dimer
1 The binding of a steroid hormone to its receptor causes a conformational change in the receptor that uncovers its DNA-binding domain.
ERE
DNA
ER ER
Coactivators
Basal transcription complex
RNA polymerase II
2 The steroid-receptor complex interacts with specific regulatory DNA sequences.
Start of transcription
Regulated gene transcription
3 The hormone-receptor complex in association with coactivator proteins controls the transcription of targeted genes.

Estrogens therapeutic uses

- Estrogens are used for contraception and postmenopausal hormone therapy (HT)
- Due to concerns over the risks of HT, the National American Menopause Society recommends that HT be prescribed at the lowest effective dose for the shortest possible time to relieve menopausal symptoms
- Extended use of HT may be appropriate for some women in whom the relief of symptoms outweighs the risk of continuation of HT

Estrogens therapeutic uses

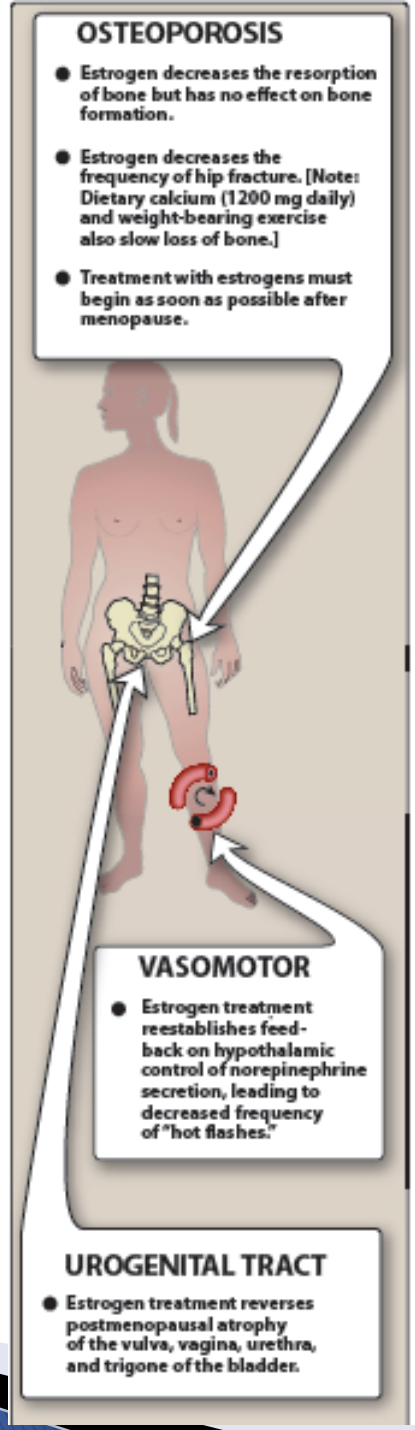
- Estrogens were previously widely used for prevention of osteoporosis, but current guidelines recommend use of other therapies such as alendronate over estrogen
- Estrogen may be used for prevention of osteoporosis if other therapies are inappropriate or not tolerated
- Estrogens are also used extensively for replacement therapy in premenopausal patients who are deficient in this hormone
- Estrogen deficiency can be due to inadequate functioning of the ovaries (hypogonadism), premature menopause, or surgical menopause

Postmenopausal HT

- The primary indication for estrogen therapy in postmenopausal women is menopausal symptoms, such as vasomotor instability and vaginal atrophy
- For women who have an intact uterus, a progestogen is always included with the estrogen therapy, to reduce the risk of endometrial carcinoma
- For women who have undergone a hysterectomy, unopposed estrogen therapy is recommended because progestins may unfavorably alter the beneficial effects of estrogen on lipid parameters

Postmenopausal HT

- The amount of estrogen used in replacement therapy is less than the doses used in oral contraception
- The adverse effects of estrogen replacement therapy are less severe than the adverse effects seen in women who are taking estrogen for contraception
- Delivery of estradiol by trandermal patch is also effective in treating postmenopausal symptoms
- Women who only have urogenital symptoms, such as vaginal atrophy, should be treated with vaginal rather than systemic estrogen


OSTEOPOROSIS
Estrogen decreases the resorption of bone but has no effect on bone formation.
Estrogen decreases the frequency of hip fracture. [Note: Dietary calcium (1200 mg daily) and weight-bearing exercise also slow loss of bone.]
Treatment with estrogens must begin as soon as possible after menopause.
VASOMOTOR
Estrogen treatment reestablishes feed-back on hypothalamic control of norepinephrine secretion, leading to decreased frequency of "hot flashes."
UROGENITAL TRACT
Estrogen treatment reverses postmenopausal atrophy of the vulva, vagina, urethra, and trigone of the bladder.

Estrogen uses

- Contraception:
  - The combination of an estrogen and progestogen provides effective contraception via the oral or transdermal route
- Estrogen therapy mimicking the natural cyclic pattern, and in combination with a progestogen, is used to stimulate development of secondary sex characteristics in young women with primary hypogonadism
  - Continued treatment is required after growth is completed
- Estrogen and progestogen replacement therapy is used for women who have premature menopause or premature ovarian failure
  - Replacement therapy is usually continued until about age 50

Estrogens

- Naturally occurring estrogens and their esterified or conjugated derivatives are readily absorbed through the GIT, skin, and mucous membranes
- Synthetic estrogen analogs such as **ethinyl estradiol** and **mestranol** are well absorbed after oral administration
- Mestranol is demethylated to ethinyl estradiol which is metabolized more slowly than the naturally occurring estrogens
- Being fat soluble, they are stored in adipose tissue, from which they are slowly released
- Synthetic estrogen analogs have a prolonged action and a higher potency compared to natural estrogens

Estrogens

- Estrogens are transported in the blood bound to serum albumin or sex hormone–binding globulin
- Bioavailability of estrogen taken orally is low due to first-pass metabolism in the liver
- To reduce first-pass metabolism, estrogens may be administered via the transdermal route (patch, topical gel, topical emulsion, or spray), intravaginally (tablet, cream, or ring), or by injection
- In individuals with liver damage, serum estrogen levels may increase due to reduced metabolism, causing feminization in males or signs of estrogen excess in females

Estrogens adverse effects

- Nausea
- Breast tenderness
- Postmenopausal uterine bleeding can occur
- Risk of thromboembolic events
- Myocardial infarction, and breast and endometrial cancer is increased with estrogen therapy
- The increased risk of endometrial cancer can be reduced by including a progestogen along with the estrogen therapy

Adverse effects of estrogens

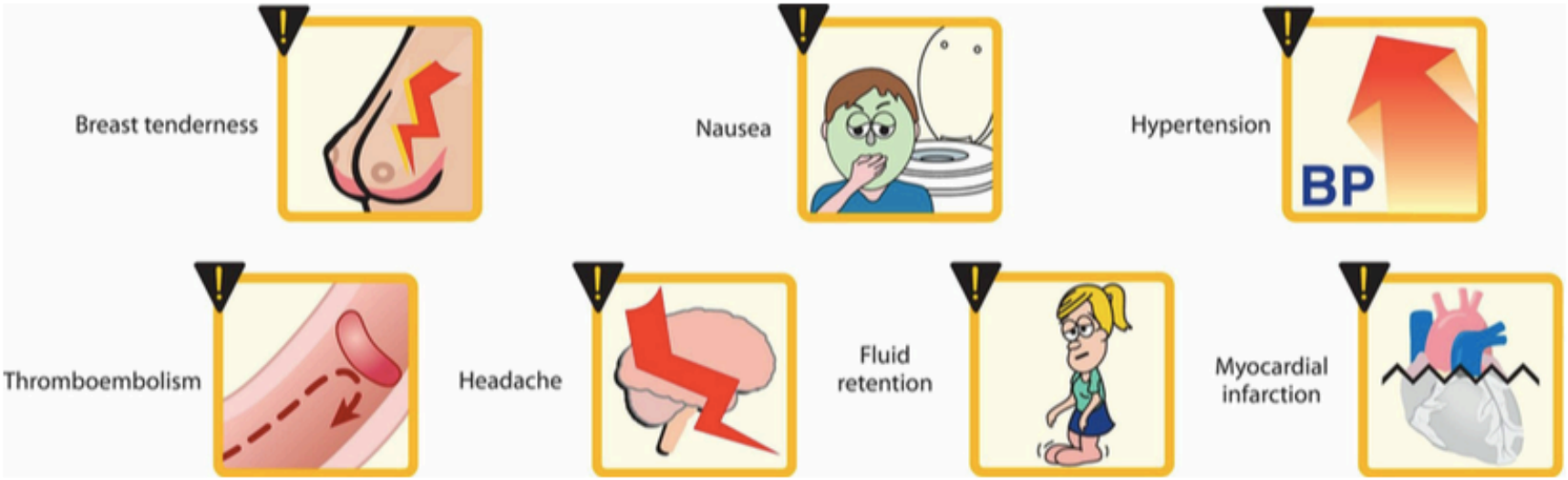


Figure 25.4 Some adverse effects associated with estrogen therapy. BP = blood pressure.

Selective Estrogen-receptor Modulators (SERMs)

- Selective estrogen-receptor modulators (SERMs) are a class of estrogen related compounds that interact at estrogen receptors

- Have different effects depending on the tissues (display selective agonism or antagonism according to the tissue type)

Selective Estrogen-receptor Modulators (SERMs)

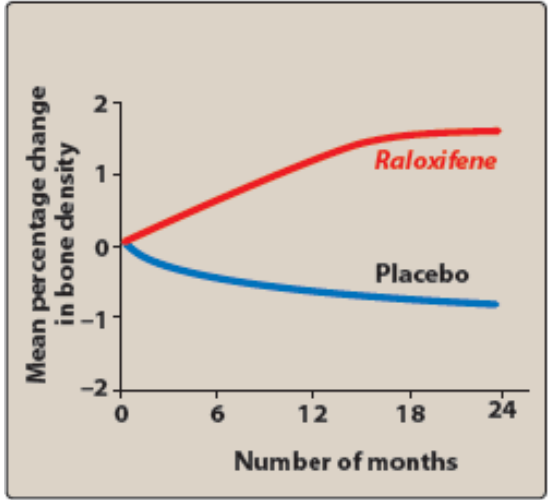
- Tamoxifen (Nolvadex®, Valodex®)
- Raloxifene (Evista®)
- Clomiphene (Ikaclomin®)

Tamoxifen

Mechanism of action

- Competes with estrogen for binding to the estrogen receptor in breast tissue
- Normal breast growth is stimulated by estrogens
- Some breast tumors regress following treatment with tamoxifen

Raloxifene



Mechanism of action

- A second-generation SERM
- Antagonist estrogen receptors in the breast tissue
- Also decreases bone resorption and overall bone turnover
- Bone density is increased, and vertebral fractures are decreased
- Unlike estrogen and tamoxifen, raloxifene has little to no effect on the endometrium and, may not predispose to uterine cancer
- Raloxifene lowers total cholesterol LDL in the serum
- It has no effect on HDL or triglyceride levels

Clomiphene

Mechanism of action

- Acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus

- This effect increases the secretion of gonadotropin-releasing hormone and gonadotropins leading to stimulating ovulation

SERMs therapeutic uses

- Tamoxifen
  - Currently used in the palliative treatment of metastatic breast cancer in postmenopausal women
  - Used as adjuvant therapy following mastectomy or radiation in breast cancer
  - Used as prophylactic therapy to reduce the risk of breast cancer in high risk patients
- Raloxifene
  - Prophylaxis of breast cancer in high-risk women
  - Prevention and treatment of osteoporosis in postmenopausal women
- Clomiphene
  - Used to treat infertility associated with anovulatory cycles
  - **Not** effective in women with ovulatory dysfunction due to pituitary or ovarian failure

SERMs

- Administered orally
- Tamoxifen is extensively metabolized by CYP450
- Raloxifene is rapidly converted to glucuronide conjugates through first-pass metabolism
- Raloxifene is >95% bound to plasma proteins
- All three agents undergo enterohepatic cycling
- The primary route of excretion is through the bile into feces

SERMs adverse effects

- Adverse effects of tamoxifen:
  - Hot flashes
  - Nausea
  - Menstrual irregularities and vaginal bleeding
  - Due to its estrogenic activity in the endometrium, hyperplasia and malignancies have been reported in women who have been maintained on tamoxifen
  - This has led to recommendations for limiting the length of time on the drug
- Tamoxifen is subject to many drug interactions
  - Some CYP450 inhibitors may prevent the formation of active metabolites of tamoxifen and possibly reduce the efficacy (for example, amiodarone, haloperidol, risperidone)

SERMs adverse effects

- Adverse effects of raloxifene:
  - Hot flashes
  - Leg cramps
  - Increased risk of deep-vein thrombosis, pulmonary embolism, and retinal-vein thrombosis
    - Women who have a past or active history of venous thromboembolic events should not take the drug
- Should be avoided in women who are or may become pregnant (Category X)
- Coadministration with cholestyramine can reduce the absorption of raloxifene by 60% (Should not be used together)

SERMs adverse effects

- Adverse effects of clomiphene
  - Headache
  - Nausea
  - Vasomotor flushes
  - Visual disturbances
  - Ovarian enlargement

- Multiple births chance (twins or triplets) with clomiphene is 3 to 5%

Progestogens

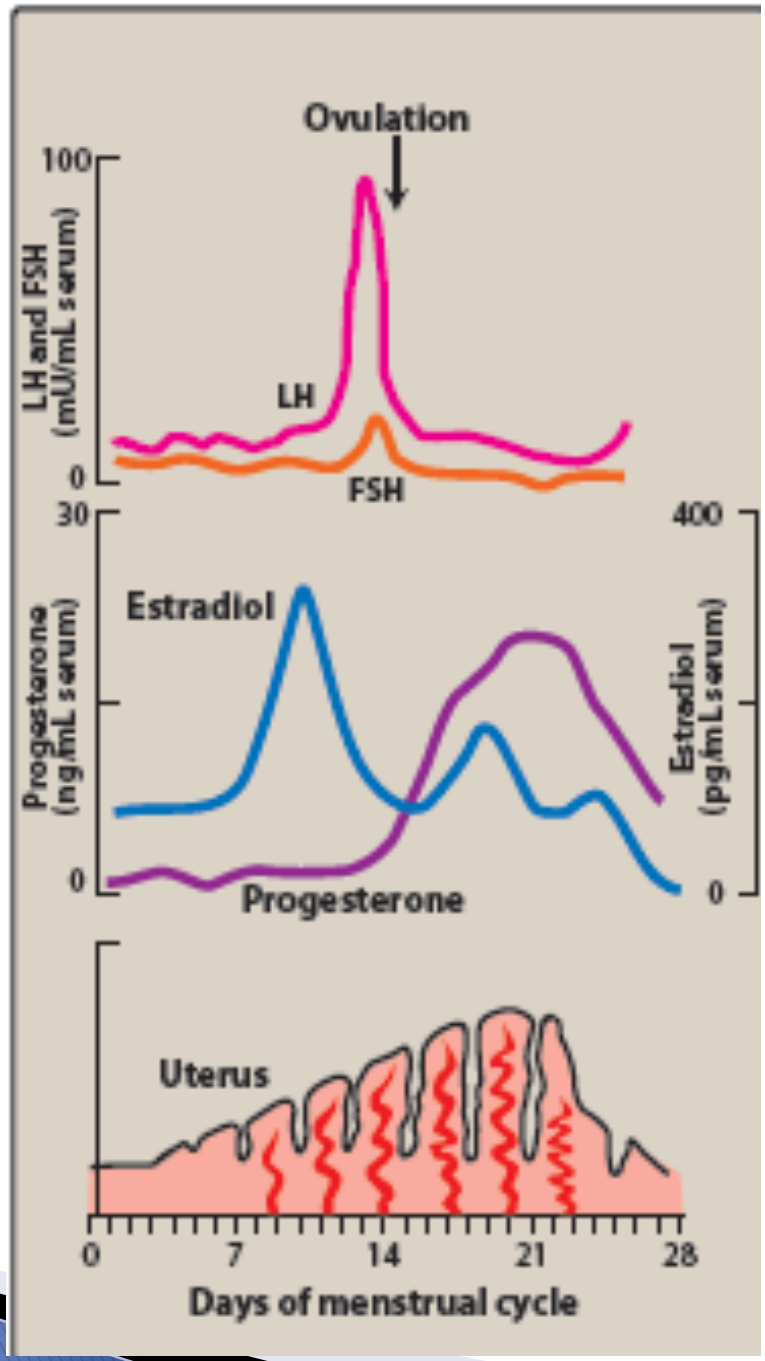
Progesterone

- Natural progestogen produced in response to LH
  - Females (secreted by the corpus luteum, primarily during the second half of the menstrual cycle, and by the placenta)
  - Males (secreted by the testes)
  - Also synthesized by the adrenal cortex in both sexes
- In females, progesterone promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo

Progestogens

Progesterone

- The high levels of progesterone that are released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin and further ovulation
- If conception takes place, progesterone continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions
- If conception does not take place, the release of progesterone from the corpus luteum ceases which stimulates menstruation


Ovulation
100
LH and FSH (mU/mL serum)
LH
FSH
0
30
Progesterone (ng/mL serum)
Estradiol
Progesterone
0
400
Estradiol (pg/mL serum)
0
Uterus
0
7
14
21
28
Days of menstrual cycle

Progestogens

- Progestogens cause:

1) Increase in hepatic glycogen

2) Decrease Na+ reabsorption in the kidney due to competition with aldosterone at the mineralocorticoid receptor

3) Increase body temperature

4) Decrease in plasma amino acids

5) Increase in excretion of urinary nitrogen

Progestogens therapeutic uses

- Treating hormonal deficiency
- Contraception
  - Generally used with estrogens
  - Progesterone by itself is not used widely as a contraceptive therapy because of its rapid metabolism, resulting in low bioavailability
  - Synthetic progestogens (progestins) used in contraception are more stable to first-pass metabolism, allowing lower doses when administered orally
  - Medroxyprogesterone acetate is an injectable contraceptive
- Oral medroxyprogesterone acetate form is a common progestin component of postmenopausal HT
- Control of dysfunctional uterine bleeding
- Treatment of dysmenorrhea
- Management of endometriosis
- Infertility

Synthetic progestogens (progestins)

- Norethindrone
- Norethindrone acetate (Primolut-Nor)
- Medroxyprogesterone (Depo-Provera®, Provera®, Sayana®)
- Norgestrel
- Levonorgestrel (Mirena®, Norlevo®)
- Desogestrel
- Norgestimate
- Drospirenone

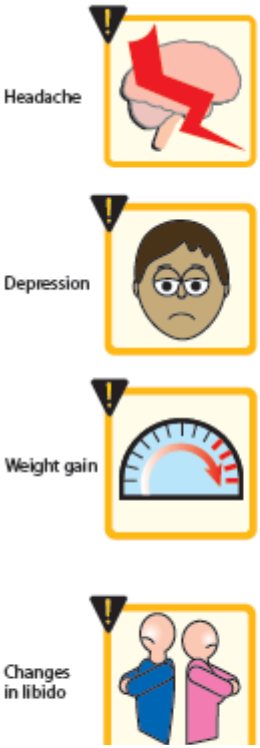
- Estradiol+norgestrel (Progyluton®)
- Ethinylestradiol+levonorgestrel (Microgynon®, Nordette®)
- Desogestrel+ethinylestradiol (Microdiol®)
- Ethinylestradiol+norgestimate (Ortho-Cyclen®)

Progestogens

- A micronized preparation of progesterone is rapidly absorbed after oral administration
- Progesterone has a short half-life in the plasma and is almost completely metabolized by the liver
- Synthetic progestins are less rapidly metabolized
- Oral medroxyprogesterone acetate has a half-life of 30 days
- IM or SC medroxyprogesterone has a half-life of about 40 to 50 days and provides contraception for about 3 months
- The other progestins have half-lives of 1 to 3 days, allowing for once-daily dosing

Adverse effects of progestins

- Headache
- Depression
- Weight gain
- Changes in libido
- Injectable medroxyprogesterone acetate has been associated with increased risk of osteoporosis
  - Duration of use is limited to 2 years unless other forms of contraception are unsatisfactory



Antiprogestin

Mifepristone (RU-486)

- Progesterone antagonist with partial agonist activity
- Has potent antiglucocorticoid activity
- Administration of this drug to females early in pregnancy usually results in abortion of the fetus due to interference with the progesterone needed to maintain pregnancy
- Mifepristone is often combined with the prostaglandin analog misoprostol (administered orally or intravaginally) to induce uterine contractions
  - This combination increases the chance for successful termination of pregnancy
- The major adverse effects are significant uterine bleeding and the possibility of an incomplete abortion
- Mifepristone has also been investigated as an oral contraceptive and an emergency contraceptive agent

Contraceptives

- Drugs that decrease fertility by different mechanisms
  - Preventing ovulation
  - Impairing gametogenesis or gamete maturation
  - Interfering with gestation

- Interference with ovulation is the most common pharmacologic intervention for preventing pregnancy

Major classes of contraceptives

- Combination oral contraceptives
- Transdermal patch
- Vaginal ring
- Progestin-only pills
- Injectable progestin
- Progestin implants
- Progestin intrauterine device
- Postcoital contraception (emergency contraception)

Combination oral contraceptives

- Products containing a combination of an estrogen and a progestin
- Most common type of oral contraceptives
- Active pills are taken for 21 days followed by 7 days of placebo
- Monophasic combination pills contain a constant dose of estrogen and progestin given over 21 days
- Triphasic oral contraceptive products attempt to mimic the natural female cycle and most contain a constant dose of estrogen with increasing doses of progestin given over three successive 7-day periods
- Withdrawal bleeding occurs during the hormone-free interval

Combination oral contraceptives

- The most common estrogen in the combination pills is **ethinyl estradiol**
- The most common progestins are **norethindrone**, **norethindrone acetate**, **norgestrel**, **levonorgestrel**, **desogestrel**, **norgestimate**, and **drospirenone**
- Highly effective in achieving contraception

Transdermal patch

- An alternative to combination oral contraceptive pills
- Transdermal contraceptive patch contain **ethinyl estradiol** and the progestin **norelgestromin**
- One contraceptive patch is applied each week for 3 weeks to the abdomen, upper torso, or buttock
- Week 4 is patch free and withdrawal bleeding occurs
- Similar adverse effects to OCPs

Vaginal ring

- Contains **ethinyl estradiol** and **etonogestrel**
- The ring is inserted into the vagina and is left in place for 3 weeks
- Week 4 is ring free, and withdrawal bleeding occurs
- Efficacy, contraindications, and adverse effects are similar to those of OCPs

Progestin-only pills

- Usually contain **norethindrone**
- Called a “mini-pill”
- Taken daily on a continuous schedule
- Deliver a low, continuous dosage of drug
- Less effective than the combination pill
- May produce irregular menstrual cycles more frequently than the combination pills

Progestin-only pills

- May be used in breastfeeding women (Progestins do not affect on milk production), intolerance to estrogen, smokers, or in contraindications to estrogen

Injectable progestin

- **Medroxyprogesterone**
- Administered every 3 months
- Available IM and SC
- Adverse effect:
  - Weight gain
  - Amenorrhea because it provides high sustained levels of progestin
  - Return to fertility may be delayed for several months after discontinuation
  - May contribute to bone loss and predispose patients to osteoporosis and/or fractures
- Should not be continued for more than 2 years unless the patient is unable to tolerate other contraceptive options

Progestin implants

- A subdermal implant containing **etonogestrel** offers long-term contraception
- One 4-cm capsule is placed subdermally in the upper arm
- Provides contraception for 3 years
- The implant is nearly as reliable as sterilization
- The effect is reversible when surgically removed
- Adverse effects
  - Irregular menstrual bleeding
  - Headache

Progestin intrauterine device

- A levonorgestrel-releasing intrauterine system offers a highly effective method of long-term contraception
- Provides contraception for up to 5 years
- It is a suitable for women who already have at least one child and do not have a history of pelvic inflammatory disease or ectopic pregnancy

Emergency contraception

- Emergency contraception uses high doses of progestin (for example, 0.75 mg of **levonorgestrel**) or high doses of estrogen (100 µg of **ethinyl estradiol**) plus progestin (0.5 mg of **levonorgestrel**) administered within 72 hours of unprotected intercourse (the "morning-after pill")
  - A second dose of emergency contraception should be taken 12 hours after the first dose
- A newer progestin-only regimen consists of a one-time dose of 1.5 mg **levonorgestrel**
- For maximum effectiveness, emergency contraception should be taken as soon as possible after unprotected intercourse (preferably within 72 hours)
- A single dose of **mifepristone** has also been used for emergency contraception

Contraceptives

Mechanism of action

- The mechanism of action for hormonal contraceptives is not completely understood
- It is likely that the combination of estrogen and progestin administered over 3-weeks inhibits ovulation
- Estrogen provides a negative feedback on the release of LH and FSH preventing ovulation
- Progestin inhibits LH release and thickens the cervical mucus affecting the transport of sperm
- Withdrawal of the progestin stimulates menstrual bleeding during the placebo week

Contraceptives adverse effects

- Most adverse effects occur due to the estrogen component but cardiovascular effects reflect the action of both estrogen and progestin
- The incidence of adverse effects with oral contraceptives is relatively low and is determined by the specific compounds and combinations used

Major adverse effects:

- Depression
- Fluid retention
- Headache
- Nausea
- Vomiting

Contraceptives adverse effects

Cardiovascular adverse effects:

- The most serious adverse effect of oral contraceptives
- Rare
- Most common among women who smoke and who are older than age 35 years, although they may affect women of any age
- Include thromboembolism, thrombophlebitis, hypertension, MI, and cerebral and coronary thrombosis

Contraceptives adverse effects

Carcinogenicity:

- The incidence of cervical cancer may be increased with oral contraceptives
  - Because women are less likely to use additional barrier methods of contraception that reduce exposure to human papilloma virus (the primary risk factor for cervical cancer)

Metabolic:

- Abnormal glucose tolerance is sometimes associated with oral contraceptives
- Weight gain
  - Less with oral contraceptives containing drospirenone

Serum lipids:

- Estrogen causes an increase in HDL and a decrease in LDL
- Progestins may negate some of the beneficial effects of estrogen
  - Estrogen- dominant preparations are best for individuals with elevated serum cholesterol

Contraceptives

- **Contraindications:**
  - Cerebrovascular and thromboembolic disease
  - Estrogen dependent neoplasms
  - Liver disease
  - Pregnancy
  - Combination oral contraceptives should not be used in patients over the age of 35 who are heavy smokers

Androgens

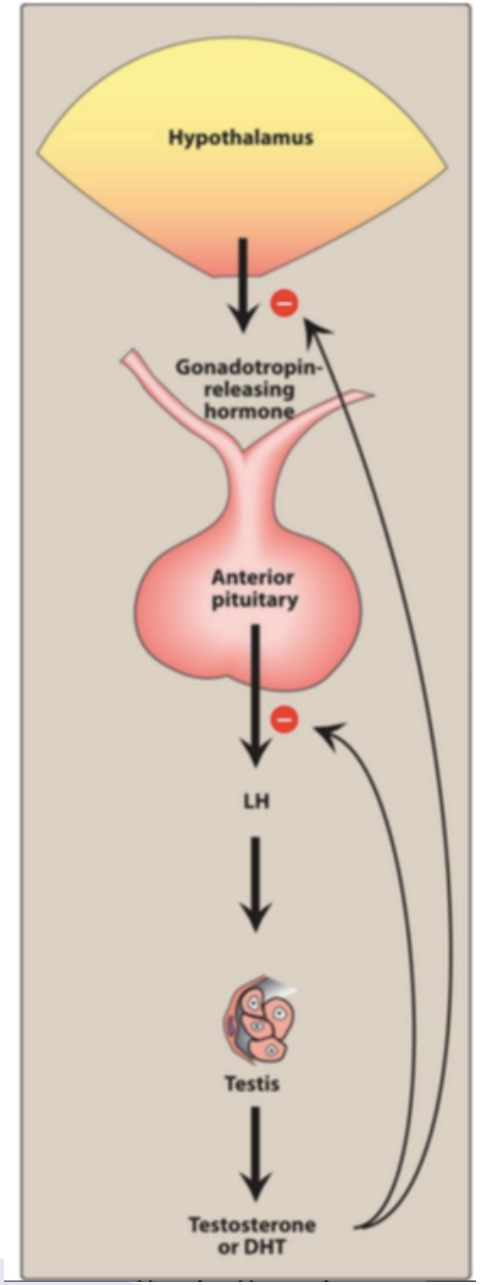
- A group of steroids that have anabolic and/or masculinizing effects in both males and females
- Testosterone the most important androgen in humans, synthesized by:
  - Leydig cells in the testes
  - Thecal cells in the ovary of the female in smaller amounts
  - Adrenal gland in both sexes

Androgens

- Other androgens secreted by the testes:
  - 5α-dihydrotestosterone (DHT)
  - Androstenedione
  - Dehydroepiandrosterone (DHEA) in small amounts

Androgens

- In adult males, testosterone secretion by Leydig cells is controlled by GnRH from the hypothalamus, which stimulates the anterior pituitary gland to secrete FSH and LH
- LH stimulates steroidogenesis in the Leydig cells
- FSH is necessary for spermatogenesis
- Testosterone or its active metabolite, DHT, regulate testosterone production, they inhibit production of these specific trophic hormones through negative feedback


Hypothalamus
Gonadotropin-releasing hormone
Anterior pituitary
LH
Testis
Testosterone or DHT

Androgens

- Androgens are required for:

1) Normal maturation in the male
2) Sperm production
3) Increased synthesis of muscle proteins and hemoglobin
4) Decreased bone resorption

Androgens

Synthetic modifications of the androgen structure modify solubility and susceptibility to enzymatic breakdown (prolonging the half life of the hormone) and to separate anabolic and androgenic effects

Androgens

Mechanism of action

- Androgens bind to a specific nuclear receptor in a target cell
- Testosterone is the active ligand in muscle and liver
- Testosterone is metabolized by 5α-reductase to DHT
- Testosterone is biotransformed to estradiol by CYP450 aromatase
- The hormone-receptor complex binds to DNA and stimulates the synthesis of specific RNAs and proteins

Androgens Therapeutic uses

- **Androgenic effects**:
  - Androgenic steroids are used for males with inadequate androgen secretion (Hypogonadism)

- **Anabolic effects**:
  - Anabolic steroids can be used to treat senile osteoporosis and chronic wasting associated with HIV or cancer
  - Also used as adjunct therapy in severe burns and to speed recovery from surgery or chronic debilitating diseases

Androgens Therapeutic uses

- **Endometriosis:**
  - Danazol: a mild androgen, is used in the treatment of endometriosis
  - Danazol also possess antiestrogenic activity
  - It inhibits release of FSH and LH
  - Adverse effects:
    - Weight gain
    - Acne
    - Deepening voice
    - Increased hair growth

Androgens

Unapproved use:

- Anabolic steroids are used to increase lean body mass, muscle strength, and endurance in athletes and body builders

Androgens

- Testosterone is ineffective orally because of inactivation by first-pass metabolism
- C17-esters of testosterone (for example, **testosterone cypionate** or **enanthate**) are administered IM
- Transdermal patches and buccal tablets of testosterone are also available
- Testosterone derivatives (e.g. **fluoxymesterone, oxandrolone**) can be administered orally

Androgens

Adverse effects

- **In females**: Androgens can cause masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, excessive muscle development, and menstrual irregularities
- **In males**: Excess androgens can cause, impotence, decreased spermatogenesis, androgens can also stimulate growth of the prostate
- **In children**: Androgens can cause abnormal sexual maturation and growth disturbances
- Androgens increase serum LDL and lower serum HDL levels
- Androgens can also cause fluid retention, leading to edema

Antiandrogens

- Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors

- At high doses, the antifungal drug ketoconazole inhibits several of the CYP450 enzymes involved in steroid synthesis

Antiandrogens

- **Finasteride** and **dutasteride** are used for the treatment of benign prostatic hypertrophy
  - They inhibit 5α-reductase
  - The resulting decrease in formation of dihydrotestosterone in the prostate leads to a reduction in prostate size

Antiandrogens

- **Flutamide** act as competitive inhibitors of androgens at the target cell
- Flutamide is used in the treatment of prostatic carcinoma in males
- **Bicalutamide** and **nilutamide** are effective orally for the treatment of prostate cancer