MECHANISM OF ESTROGEN ACTION:

1. Most effects produced through interaction with nuclear receptors
   - Two types now known: ERα and ERβ
   - Both located in nucleus in inactive form
2. Binding of hormone causes dissociation of corepressor proteins and dimerization of receptor, which then binds to specific DNA sites, called estrogen response elements (ERE)
3. The estrogen-receptor complex then recruits coactivator proteins, allowing transcription to be initiated, leading to mRNA & protein synthesis

MENSTRUAL CYCLE:

1. At the beginning of the cycle, gradual increase in FSH initiates follicular growth and development. Estradiol, secreted in increasing amounts by the follicles, first inhibits the secretion of LH and FSH. At the peak of its secretion, however, there is a sudden surge in the production of LH and to a lesser extent, FSH.
2. In response to LH, follicular cells decrease production of estradiol and begin production of progesterone. LH also results in ovulation, and formation of the corpus luteum.
3. The corpus luteum produces increasing amounts of progesterone and estrogens, which inhibit secretion of FSH and LH. In the absence of LH and if the ovum is not fertilized, the corpus luteum regresses, levels of estrogen and progesterone fall, and menstruation occurs.
4. When levels of progesterone and estrogen fall, the hypothalamus is released from the negative feedback and levels of FSH and LH slowly begin to rise. The cycle then repeats itself.

REGULATION OF ESTROGEN AND PROGESTIN PRODUCTION:

Positive feedback occurs during days 12 through 14.

Negative feedback occurs throughout most of the cycle.

SYNTHESIS OF ESTROGENS AND PROGESTERONE:

Cholesterol → Pregnenolone → 17-Hydroxyprogrenolone → Progesterone → Androsterone → Testosterone → Estrone → Estradiol → Estriol

MAJOR ESTROGENS:

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>17β-estradiol (E2)</td>
<td>Most potent naturally occurring estrogen</td>
</tr>
<tr>
<td>Estrone (E1)</td>
<td>Major secretory product of the ovaries &amp; major circulating estrogen in pre-menopausal women (60% of total)</td>
</tr>
<tr>
<td>Estriol (E3)</td>
<td>Produced in ovaries, peripheral tissues and liver; also by placenta in pregnancy</td>
</tr>
<tr>
<td>Estabol (E4)</td>
<td>Major estrogen in post-menopausal women, produced in adipose tissue from adrenal androgens</td>
</tr>
</tbody>
</table>

ACTIONS OF ESTROGENS IN FEMALES:

- Female maturation: Stimulate development of vagina, uterus and fallopian tubes, as well as secondary characteristics (hair growth, body fat distribution)
- Breasts: Stimulate growth and development of the breasts
- Endometrium: Cause growth of endometrium during first half of the menstrual cycle
  - Action normally opposed by progesterone released during second half of cycle
  - If unopposed, can cause endometrial hyperplasia, leading to increased risk of endometrial cancer
- Brain: Regulate areas that prepare body for reproduction
  - May influence behavior and libido
  - May help protect memory and cognition
- Bone: Limited effect to promote linear growth, but promote closure of epiphyses (termination of bone growth) and help to maintain density by decreasing resorption
- CV events: Alterations in serum lipids (↑ HDL, ↓ LDL)
  - Increased blood coagulation, through enhanced hepatic production of clotting factors

THERAPEUTIC USES OF ESTROGENS:

- Oral contraception (with progestins)
- Replacement therapy in estrogen deficiency states:
  - Primary hypogonadism
  - Hypogonadotrophic hypogonadism
  - In young girls, estrogen therapy at appropriate time replicates events of puberty and stimulates growth
  - Menopause

MENOPAUSE:

- Defined as the cessation of menstrual cycles for 12 months
- Preceded by an interval known as perimenopause, during which symptoms such as hot flashes and night sweats begin
- Results from depletion of ovarian follicles, associated with a reduction in oocyte quality – since follicles are responsible for secretion of hormones, estrogen and progesterone levels fall
- Onset: late 40 – early 50s (median age is 51)

POTENTIAL CONSEQUENCES OF MENOPAUSE:

- Early sx: Hot flashes, night sweats (up to 75%)
  - Most severe during first 2 post-menopausal years
  - Sudden onset of upper body vasodilation associated with feeling of intense heat and sweating
  - Frequency up to 1/hour, last for 2-3 mins
  - Due to re-setting of hypothalamic thermostat
  - Insomnia, irritability, mood disturbances

- Physical changes:
  - Urogenital atrophy (thinning of tissues lining vagina and bladder)
  - Predisposes to dryness, itching, painful intercourse (dyspareunia), infection
  - Skin atrophy

- Diseases:
  - Osteoporosis
  - Cardiovascular disease
**Lecture 1**

**SELECTIVE ESTROGEN RECEPTOR MODIFIERS (SERMs):**

**MECHANISM OF ACTION:**
- Bind to nuclear estrogen receptors (ER) and competitively inhibit the binding of estrogen, antagonizing the actions of estrogen in some tissues but mimicking the actions of estrogen in others.
- On binding, change the conformation of the ER differently than estradiol, and depending on the tissue:
  - Change its interaction with coactivators or allow it to interact with corepressors (preventing transcription).
  - Allow it to interact with non-ERE in some tissues, producing an estrogen-like effect.

**IDEAL SERM WOULD:**
- Strengthen bone
- Raise HDL and lower LDL
- Suppress hot flashes

**SERMS TREATMENT:**

<table>
<thead>
<tr>
<th>SERM</th>
<th>Use</th>
<th>AEs</th>
</tr>
</thead>
</table>
| Tamoxifen| First line hormonal treatment of breast cancer in pre-menopausal women
- As adjunct (with surgery or chemo) in early stage breast cancer
- Alone in advanced breast cancer
- Used prophylactically - lowers incidence of breast cancer in both pre- and post-menopausal women at high risk | Hot flashes, risk of VTE, endometrial cancer |
| Raloxifene| Reduces risk of invasive breast cancer in post-menopausal women at high risk
- In post-menopausal osteoporosis – reduces risk of vertebral fracture, but not hip fracture | Hot flashes, weight gain, increased risk of VTE, no increased risk of endometrial cancer |

**COMPARISON OF ESTROGEN AND SERMS:**

<table>
<thead>
<tr>
<th></th>
<th>Oral estrogen</th>
<th>Raloxifene</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td>↓↓↓</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Prevention of post-menopausal bone loss</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Favorable pattern of serum lipids</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Risk of endometrial cancer</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>↑↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>* prevented by concurrent use of progestins</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ESTROGEN USED IN RELIEF OF VASOMOTOR SYMPTOMS OF MENOPAUSE:**

**ORAL**
- Conjugated equine estrogens (Premarin)
  - Mix of estrogens, mainly estrone
- Estradiol hemihydrate (Climara)*
- 17-estradiol (Actuelle, Estrace)*
  - Some preparations also contain a progestin

**TRANSDERMAL**
- 17-estradiol patch (Estradot) applied 2x/week
  - Also available in combo w/ Progestin (Estralis)
- 17-estradiol gel (Estragel 0.06%) applied daily
  - Transdermal route avoids first pass metabolism
  - Some evidence that risk of VTE is lower, but risk of breast cancer is similar, to oral route

**LOCAL ADMIN**
- For relief of vaginal symptoms, such as vaginal dryness, painful intercourse, etc.
  - Vaginal creams: 17-estradiol, conjugated equine estrogens, esterified estrogens – applied daily
  - Vaginal ring: 17-estradiol (Estring) – SR for 90 days
  - Vaginal tablet: Estradiol hemihydrate (Vagifem) – initial daily, then 2x/week for maintenance

**AROMATASE INHIBITORS:**

**TYPES:**
- Type 1: Exemestane – steroidal, irreversible
- Type 2: Anastrozole – non-steroidal, competitive

**USE:**
- As adjunctive txt in early stage breast cancer in post-menopausal women (improve survival compared to other endocrine therapy)
- Advanced breast cancer in post-menopausal women
- Exemestane reduced risk of breast cancer by 65% in healthy post-menopausal women at high risk

**MAJOR ADVERSE EFFECTS:**
- Early: GI disturbances, headache, hot flashes
- Delayed: ↓ bone density ↑ risk of osteoporosis & fracture; polyarthralgia

**ANTI-ESTROGEN (AKA selective estrogen receptor downregulator (SERD))**

**MECHANISM:**
- Binds to the ER; competitively inhibits binding of estrogen and prevents ER dimerization, which leads to its rapid degradation

**FULVESTANT**
- Used in txt of metastatic breast cancer in post-menopausal women who have disease progression following prior endocrine therapy
- AES: nausea, hot flashes, arthralgias
  - Effect on bone density and osteoporotic fracture risk is unclear
- Requires IM administration

**HORMONE REPLACEMENT THERAPY (HRT) IN MENOPAUSE:**

- Vasomotor & GU menopausal symptoms result from low estrogen levels
  - Estrogen replacement is most effective therapy
- Hot flashes generally transient (1-2 years)
  - Local administration may be more effective than other routes for vaginal symptoms

<table>
<thead>
<tr>
<th>Benefits of post-menopausal HRT use</th>
<th>Increased risks associated with post-menopausal HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relief of vasomotor and GU symptoms of menopause</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>Decreased risk of osteoporotic fractures (both vertebral and hip)</td>
<td>Non-fatal ischemic stroke</td>
</tr>
<tr>
<td>Decreased risk of colorectal cancer</td>
<td>Risk increased with longer duration of use and with use of progestin</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>E alone but not E + P</td>
</tr>
<tr>
<td>CHD *</td>
<td>With E + P, but not E alone</td>
</tr>
<tr>
<td>Cognitive decline and dementia*</td>
<td></td>
</tr>
</tbody>
</table>

* current evidence suggests that these risks increased in women starting HRT at > 63 years old & > 10 years past menopause, but not in women aged 50-59
**ANTI-MECHANISM OF ACTION OF PROGESTERONE AND SELECTIVE PROGESTERONE RECEPTOR MODIFIERS:**

**A**

- **Progestosterone**
  - Essential for oocyte release from follicle at ovulation
  - Decreases estrogen-induced endometrial proliferation and promotes secretory changes in the endometrium in preparation for implantation of a fertilized ovum during the luteal phase of the menstrual cycle
  - Influences secretion of gonadotropins during the menstrual cycle
  - Essential for maintenance of pregnancy
    - High levels secreted by corpus luteum and placenta suppresses menstruation and decreases uterine contractility
    - Role in preparing breasts for lactation

**B**

- **Synthetic progestin**
  - Varying degrees of progestin potency
  - Varying amounts of other hormonal activity
  - Therefore, variation between preparations based on both type and dose of progestin

**PROGESTIN PREPARATIONS:**

- **Progestosterone & derivatives**: used mainly in menopausal symptoms
  - Micronized progestosterone
  - Medroxyprogesterone acetate
  - Megestrole acetate
- **Synthetic progestins**: used mainly in contraceptive preparations
  - Varying degrees of progestin potency
  - Varying amounts of other hormonal activity
  - Therefore, variation between preparations based on both type and dose of progestin

**ANTI-PROGESTIN: Mifepristone (RU-486)**

- **MOA**: competitive inhibitor of progestosterone receptors
  - Blocks ovulation if given in follicular phase of menstrual cycle
  - Induces menstrual bleeding if given in luteal phase
  - Results in decidual (endometrial) breakdown in early pregnancy, leading to detachment of the embryo

**USE**: terminate early pregnancy

- Combined with misoprostol to improve efficacy
- Success rate approx. 95% if used within first 49 days

**MIFEGYMISO**: combination of mifepristone (200 mg, PO) plus misoprostol (4 x 200 mcg buccal, 24-48 hours later)

**ADVERSE EFFECTS:**
- Headache, NVD
- Risk of:
  - Infections and sepsis (rare)
  - Prolonged heavy bleeding if incomplete
  - Embryotoxicity if ineffective
- *there is NO delay in return of fertility

**THERAPEUTIC USES:**

**CONTRACTION**

- **Mechanisms of combined estrogen-progestin oral contraceptives**
  1. Negative feedback suppression of gonadotropin secretion (synergistic effect of estrogen and progestin)
     - Decreased production of FSH (to < 70% normal)
     - No LH surge at mid-cycle
     - Minimal follicular development, and NO OVULATION
  2. Abnormal endometrial development
     - Endometrium atrophic → impaired implantation
  3. Abnormal cervical mucus
     - Becomes thicker and more viscous → impairs penetration
  4. Abnormal muscular activity of fallopian tubes and uterine smooth muscle  → impair sperms and ovum transport

**COMBINED WITH ESTROGEN IN HRT OF POST-MENOPAUSAL WOMEN:**

- Oppose effects of estrogen on endometrium, decreasing the risk of endometrial cancer
- May enhance the positive effect of estrogen on bone
- May actually increase the risk of breast cancer*
- Tend to oppose the effects of estrogen on lipoprotein-cholesterol levels *
- * may be affected by the type of progestin used – micronized progesterone may be less likely to have these effects

**OTHER USES:**

- For ovarian suppression (ex/ in dysfunctional uterine bleeding due to relative excess estrogen effect, endometriosis)
- Adjunct or palliative treatment of breast cancer (4th line) and endometrial cancer

**ADVERSE EFFECTS**: edema, weight gain, nausea, menstrual irregularities

**SELECTIVE PROGESTERONE RECEPTOR MODIFIER: Ulipristal acetate**

**MECHANISM**: binds to progestosterone receptor; has partial agonist activity

**TREATMENT OF UTERINE FIBROIDS (MYOMAS):**

- **Myomas**
  - Estrogen-sensitive benign fibrous growths
  - Can cause menorrhagia with anemia & pelvic pain
- **MOA**
  - Reduces proliferation and fibrosis, and increases apoptosis of myoma cells (but not normal myometrial cells)
  - Suppress proliferation of endometrium
- **SEs**
  - Increase in endometrial thickness, but not hyperplasia
  - Amenorrhea, hot flashes, headache
- **Dosage**
  - Fibristal 5 mg tablet

**EMERGENCY CONTRACEPTIVE:**

- **MOA**
  - Major action is anti-ovulatory
  - Inhibits LH release from pituitary as well as LH-induced follicular rupture within the ovary
- **Use**
  - More effective than levonorgestrel (plan B) * – approx. 60%
  - May retain efficacy for up to 5 days
- **SEs**
  - Headache, abdominal discomfort, and slight delay in onset of menstrual bleeding (2-3 days)
- **Dosage**
  - Ella 30 mg tablet (single dose)

* Plan B delays or inhibits the LH peak by -ve feedback, if given before the start of the LH surge