

Topic 24: Estrogens and Female Reproductive Drugs

I. Contraceptives

A. Estrogen-Progestin Contraceptives

1. Examples

- Note – all of these drugs contain one estrogen (listed first) and one progestin
- Drug to know: **ethinyl estradiol/norgestimate** (Ortho Tri-Cyclen®, Ortho Cyclen®)
- Other estrogen-progestin contraceptives: ethinyl estradiol/norethindrone (Ortho-Novum 7/7/7®, Loestrin®), ethinyl estradiol/norgestrel (Triphasil®), ethinyl estradiol/desogestrel (Ortho-Cept®), ethinyl estradiol/levonorgestrel (Tri-Levlen®), drospirenone/ethinyl estradiol (Yasmin 28®), norelgestromin/ethinyl estradiol (Ortho Evra®), desogestrel/ethinyl estradiol (Apri®, Kariva®)

2. Therapeutic Use

- Oral contraceptive that is taken every day
 - **Monophasic** contraceptives: contain the same amount of progestin throughout cycle.
 - **Biphasic** and **triphasic** contraceptives: the amount of progestin increases after the first third of the cycle to mimic the natural estrogen:progesterone ratio changes that occur in the menstrual cycle.
 - Pills containing no hormones are given for 7 days to allow the uterine lining to disintegrate and menstruation to occur.
- High-doses of birth control pills can be used up to 72 hours after intercourse to prevent implantation

3. Mechanism of Action

- Estrogens and progestins inhibit ovulation by inhibiting the release of FSH and LH.
 - Without FSH, the follicle will not grow and release estradiol.
 - Without the LH surge, ovulation will not occur.
- Progestins make the lining of the uterus less hospitable to implantation of the fertilized egg. They also thicken the cervical mucus so that it acts as a barrier to sperm.

4. Adverse Effects

- **Thromboembolytic disease** (deep vein thrombosis, pulmonary embolism, stroke) is increased up to 6-fold in oral contraceptive users. The risk is much higher in **smokers** than nonsmokers, and also increases with **age**.
 - Women with heart disease should not use oral contraceptives.
 - Smokers over age 35 should not use oral contraceptives.
- **Hypertension** may occur – blood pressure should be monitored.
- Oral contraceptives can stimulate **growth of pre-existing reproductive system cancers** (e.g. breast cancer). Women who have or have had these cancers should not take oral contraceptives.
- Oral contraceptives cause **birth defects** and should not be taken by someone who thinks she is pregnant!
- Oral contraceptives can worsen liver and gallbladder disease.

- Oral contraceptives interact with many drugs, some of which make the contraceptives potentially ineffective and pregnancy can occur!
- Oral contraceptives may increase the risk of a woman getting cervical cancer, probably do not increase the risk of breast cancer (if given before menopause), and decrease the risk of endometrial and ovarian cancer.
- Non-life-threatening side effects that usually go away after several months or can be decreased by changing the contraceptive dose/formulation include: cramps, breakthrough bleeding, nausea/vomiting, dizziness, fluid retention, weight gain, loss of appetite, stimulation of appetite, breast enlargement, changes in sex drive, headaches, and fatigue.

B. Progestin-Only Contraceptives

1. Examples

- Drug to know: **levonorgestrel** (Mirena® IUD, Plan B® emergency contraceptive)
- Other progestin-only contraceptives: norethindrone (Norlutin® - “mini pill”), medroxyprogesterone acetate (Depo-Provera® injection)

2. Therapeutic Use

- Long-term contraceptives:
 - Injections (Depo-Provera® - lasts months)
 - Intrauterine devices (Mirena® IUD – lasts 5 years): T-shaped devices, implanted in uterus, which slowly release progesterone.
- Emergency contraception after intercourse (Plan B®)
- Progestin “mini-pills” are used to treat **endometriosis** (overgrowth of the lining of the uterus) but are not routinely used for contraception because they are less effective than estrogen-progestin contraceptives.
 - An exception to this is that progestin mini-pills are sometimes used by women who are breastfeeding because they do not decrease milk supply as much as the estrogen-progestin contraceptives do.

3. Mechanism of Action

- Injected and oral progestins act primarily by suppressing the LH surge that stimulates ovulation. They also make the lining of the uterus less hospitable to implantation and thicken the cervical mucus.
 - This is the same mechanism that progestins have in the estrogen-progestin oral contraceptives!
 - The amount of progestin in the mini-pill is not high enough to consistently inhibit ovulation. This is why it is less effective!
- Progestin-containing IUDs have mainly local effects on the lining of the uterus – they make the lining of the uterus less hospitable to implantation and thicken the cervical mucus. They inhibit ovulation in only a small percentage of women.
- The emergency contraceptive pill acts mainly to inhibit or delay ovulation. Secondary mechanisms include inhibition of fertilization and/or inhibition of embryo transport/implantation. This drug does not cause an implanted embryo to dislodge – it is not the same as an “abortion pill.”

4. Adverse Effects

- For oral and injected progestins, the adverse effects are similar to those of combined estrogen-progestin oral contraceptives:
 - **Elevated risk of thromboembolytic disease**
 - Stimulation of **growth of pre-existing reproductive system tumors**
 - **Birth defects** – do not use if pregnancy is suspected
 - Menstrual irregularity
 - Many other adverse effects are similar to estrgen-progestin contraceptives. Too many to list here.
- For the IUD, the major side effects are rare and are localized at the uterus:
 - Increased risk of **uterine infection** (pelvic inflammatory disease)
 - Increased risk of **ectopic pregnancy** (fertilized egg implants outside the uterus)
- For the “Plan B” emergency contraceptive, the major side effects are:
 - **Nausea/vomiting** and **abdominal pain**
 - Headache, fatigue, and the next period being heavier or lighter can also occur.

C. Post-Implantation Contraceptives

1. Examples

- Drug to know: **mifepristone** (RU-486) (Mifeprex®)

2. Therapeutic Use

- Used as a post-implantation contraceptive “abortion pill” in early pregnancy (up to 7 weeks gestation)

3. Mechanism of Action

- Acts as an antagonist of progesterone receptors.
- Since progesterone stimulates development of the uterine lining, blocking progesterone’s effect causes breakdown of uterine lining and detachment of implanted embryo or fetus.
- Another drug is given 24 hours after mifepristone to stimulate uterine contractions to expel the fetus.

4. Adverse Effects

- **GI upset**: diarrhea, nausea, vomiting,
- **Uterine cramping and pain**
- **Heavy uterine bleeding** for 1 -2 weeks; uterine hemmmhorage occurs in 5%
- Mifepristone can also cause headache, dizziness, and fatigue.

II. Fertility Drugs

A. Examples

- Drug to know: **clomiphene** (Clomid®)
- Other fertility drugs: recombinant FSH (r-FSH) (Gonal-F®, Follistim®), recombinant HCG (r-hCG) (Ovidrel®), leuprolide (Lupron®), nafarelin(Synarel®), cetrotorelix (Cetrotide®), ganirelix (Antagon®)

B. Therapeutic Use

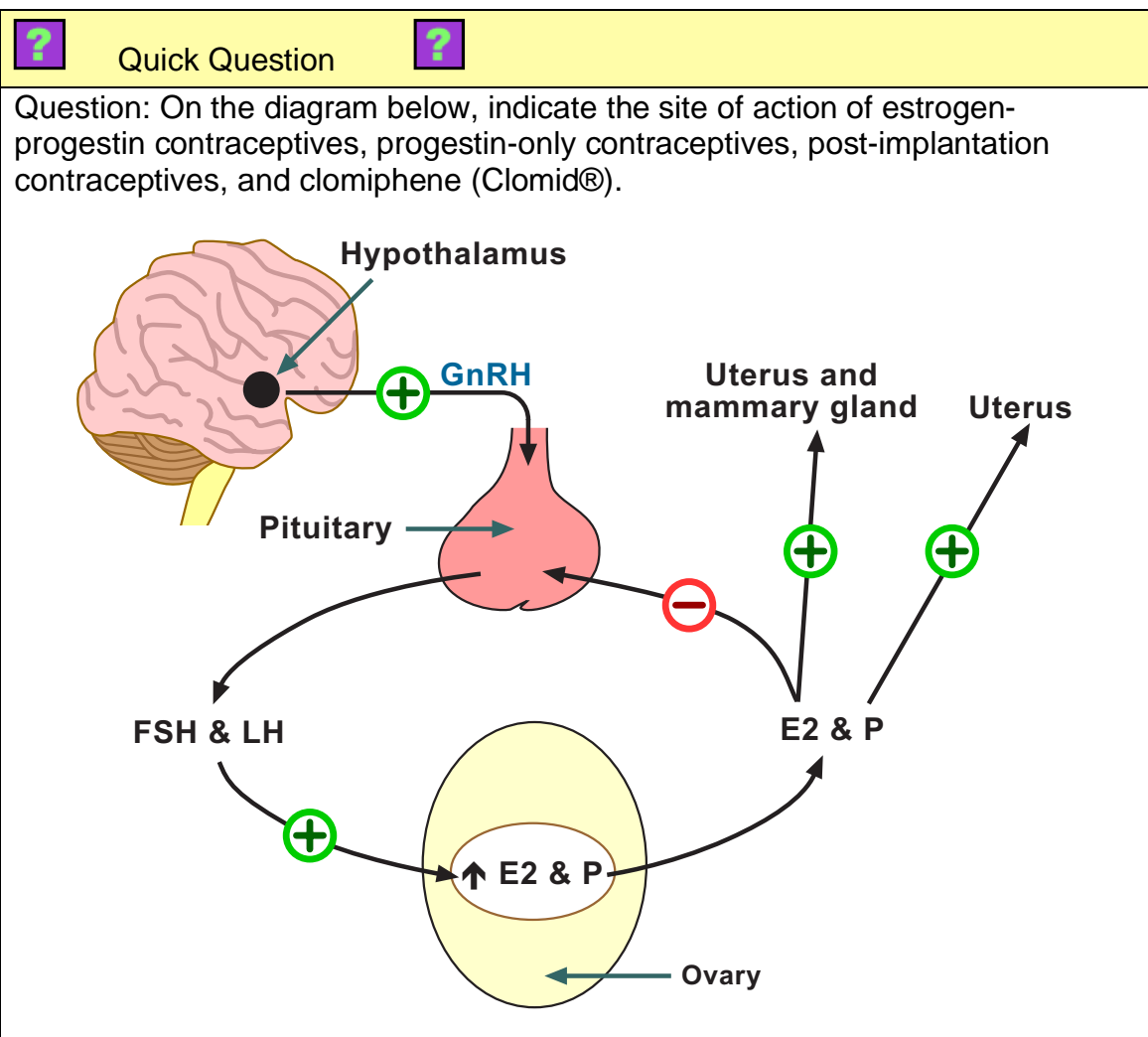
- Clomiphene is used to induce ovulation in women who do not ovulate or ovulate infrequently.
- Depending on the cause of infertility, other infertility drugs may be used

C. Mechanism of Action

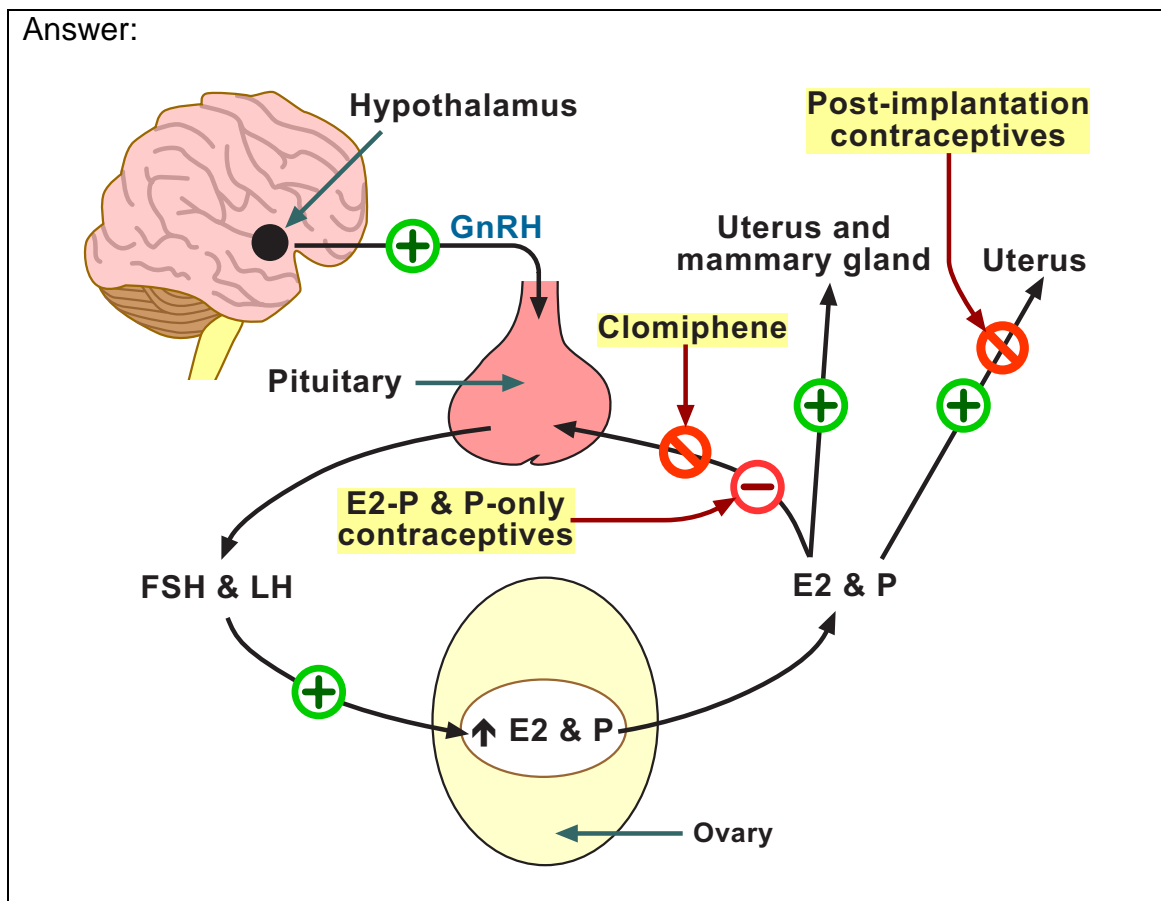
- Clomiphene is an antagonist of the estrogen receptor.
 - Blocking estrogen receptors in the hypothalamus inhibits the negative feedback that estradiol exerts on FSH and LH secretion.
 - Without negative feedback, FSH and LH release increase, leading to the LH surge that stimulates ovulation.
- Other fertility drugs act at other sites in the endocrine and reproductive systems

D. Adverse Effects (clomiphene – note that other fertility drugs have different effects)

- **Multiple births** (3 – 5 times the normal rate of 1%. Usually multiple births are twins)
- **Hot flashes**
- Clomiphene can also cause nausea, pelvic discomfort, vaginal dryness, breast tenderness, dizziness, fatigue, and headache.



Answer:



III. Anticancer Drugs

A. Examples

- Drug to know: **tamoxifen** (Nolvadex®)

B. Therapeutic Use

- Prevention of breast cancer in women at high risk
- Treatment of breast cancer

C. Mechanism of Action

- Tamoxifen is an antagonist of the estrogen receptor
- Blocking the estrogen receptor prevents estradiol from stimulating the growth of breast cancer cells.

D. Adverse Effects

- **Hot flashes**
- Tamoxifen can also cause nausea, vomiting, menstrual irregularities, and vaginal dryness

IV. Treatment of Menopausal Symptoms

A. Menopause

- Symptoms of menopause: hot flashes, heart palpitations, vaginal dryness, emotional disturbances
- Conditions that are more commonly seen in women after menopause: cardiovascular disease, osteoporosis, dementia, urinary tract problems

B. Hormone Replacement Therapy

1. Examples

- Drug to know: **conjugated estrogens** (Premarin®)
- Other hormone replacement therapy drugs: conjugated estrogens/medroxyprogesterone (Prempro®)

2. Therapeutic Use

- Short-term hormone replacement therapy (6 mo – 5 years)
 - Used to provide relief from menopausal symptoms (hot flashes, vaginal dryness, emotional distress)
 - Dose is gradually tapered until hormone replacement therapy is not needed
- Long-term hormone replacement therapy (more than 5 years)
 - Used to provide protection from conditions that are more commonly seen in women after menopause.
 - The actual effectiveness of hormone replacement therapy against cardiovascular disease and dementia is questionable.

3. Mechanism of Action

- Hormone replacement therapy replaces the estradiol and progesterone that are not being made by the ovaries.
- Estrogens relieve menopausal symptoms, but estrogens given alone increase the risk of endometrial (uterine lining) cancer. However, giving progestins along with estrogens greatly decreases this risk.
 - Women who have had a hysterectomy can take estrogens alone since they do not have a uterus and have no chance of uterine cancer.

4. Adverse Effects

- Several recent studies have shown that hormone replacement therapy increases the risk of several conditions. Risk is higher with longer treatment.
 - **Cardiovascular disease** (heart attack, stroke, thromboembolism – the risk is about 25% higher to 2 times higher in women taking hormones)
 - **Breast cancer** and ovarian cancer (the risk is about 25% higher in women who taking hormones)
 - **Dementia**/declining mental function (the risk is about 2 times higher in women taking hormones)
- Estrogens have beneficial effects. They **reduce the risk of**
 - **Osteoporosis** (the risk is decreased by about 30% in women who take hormones)
 - Colon cancer and diabetes (the risk is decreased by about 35% in women who take hormones).
- Hormone replacement therapy can cause adverse effects similar to birth control pills: spotting, bloating, weight gain, breast tenderness

C. Soy

1. Examples

- Food to know: **tofu** (soybean curd)
- Other things containing soy isoflavones: dry soybeans, fresh soybeans (edamame), roasted soybeans (soynuts), tofu, tempeh (fermented soybeans and grains), soymilk, soy flour, miso (fermented soy paste), textured vegetable protein (TVP), and meat substitutes made from soy.
- **Soy isoflavones** are the active ingredients in soybeans and are available in a variety of supplements.

2. Therapeutic Use



- Relief of menopausal symptoms
 - Studies have shown modest effects of soy isoflavones on the prevention of hot flashes. For most women, they are not as effective as hormone replacement therapy.
- Maintenance of bone density, prevention of osteoporosis
 - Limited evidence suggests that large amounts of soy isoflavones may increase bone density
- Maintenance of cardiovascular health
 - Soy protein decreases LDL

3. Mechanism of Action

- Soy isoflavones are weak estrogen agonists.
 - They act like the body's own estrogens, but to a much smaller degree
- Soy isoflavones have a variety of effects that may decrease the risk of reproductive system cancers

4. Adverse Effects

- **Gas** is the most common adverse effect of soy.
- Soy can also cause bloating, nausea, heartburn, and allergic reactions

 Quick Question 
Question: If you were (or are) a woman going through menopause, how would you weigh the risks and benefits of hormone replacement therapy vs. soy supplementation?
Answer: This is a very personalized decision and there is no one correct answer. Overall, hormone replacement therapy carries with it a higher risk of adverse effects but is more potent at reducing symptoms of menopause such as hot flashes and preventing osteoporosis.