PHARMACOLOGY

Female Reproduction

Skye McKennon, PharmD. BCPS, ACSM-GEI

WASHINGTON STATE UNIVERSITY
Elson S. Floyd College of Medicine

DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify the appropriate drugs and drug classes for managing patients who require hormone replacement, termination of pregnancy, and ovulation induction
2. Explain the mechanism of action of drug classes for managing patients who require hormone replacement, termination of pregnancy, and ovulation induction and correlate to underlying pathophysiology
3. Describe adverse effects and contraindications to drug classes for managing patients who require hormone replacement, termination of pregnancy, and ovulation induction
4. Describe the clinically important drug interactions of each drug class for managing patients who require hormone replacement, termination of pregnancy, and ovulation induction

PRACTICE QUESTION

Which of the following is a contraindication to estrogen hormone replacement?

A. Antibiotic use

B. Mood changes

C. Ovulation

D. Venous thromboembolism

ACTIVE LEARNING

A 21-year-old female is undergoing medication abortion. She is prescribed two medications, one of which is dinoprostone. Which of the following is the drug's primary mechanism of action?

A. Aromatase inhibitor that increases estrogen

B. Competitive progesterone antagonist that decreases the effects of progesterone

C. Prostaglandin analog that stimulates uterine contractions

PRACTICE QUESTION

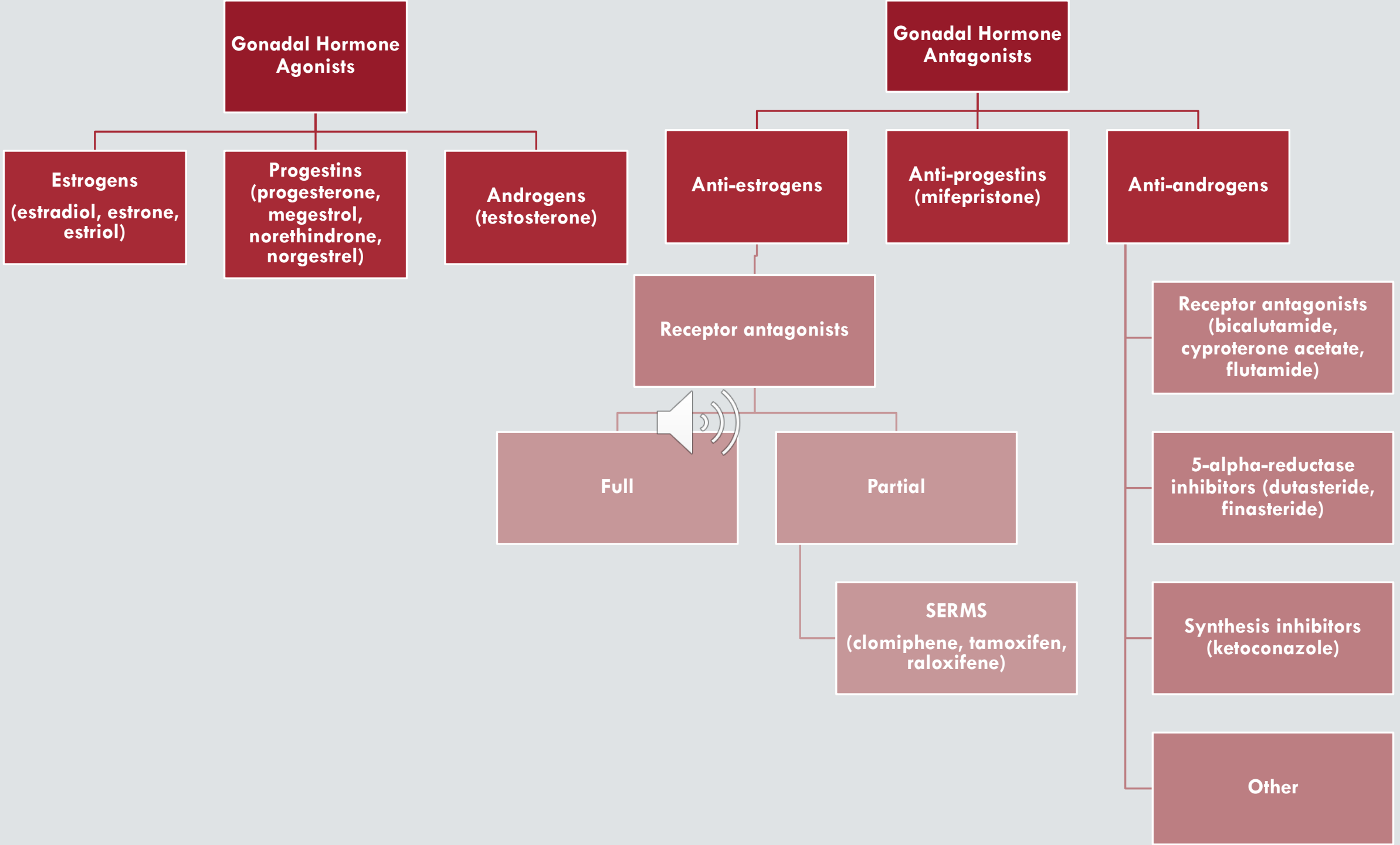
A 31-year-old female is evaluated for infertility. Treatment with appropriate drug therapy is started including letrozole. Which of the following is the primary mechanism of action letrozole?

A. Activation of pituitary dopamine receptors

B. Inhibition of endometrial progesterone receptors

C. Inhibition of aromatase

D. Inhibition of hypothalamic estrogen receptors


Gonadal Hormone Agonists
Estrogens (estradiol, estrone, estriol)
Progestins (progesterone, megestrol, norethindrone, norgestrel)
Androgens (testosterone)
Gonadal Hormone Antagonists
Anti-estrogens
Anti-progestins (mifepristone)
Anti-androgens
Receptor antagonists
Full
Partial
SERMS (clomiphene, tamoxifen, raloxifene)
Receptor antagonists (bicalutamide, cyproterone acetate, flutamide)
5-alpha-reductase inhibitors (dutasteride, finasteride)
Synthesis inhibitors (ketoconazole)
Other

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DRUGS FOR MENOPAUSAL HORMONE THERAPY (MHT)

MENOPAUSE

Permanent cessation of menstrual periods (i.e., for > 12 months)

- From loss of ovarian follicular activity

Estradiol levels decline

- Vasomotor disturbances (hot flashes or flushes)
- Sweating
- Irritability
- Sleep disturbances
- Atrophy of estrogen-dependent tissue
- Increased risk of osteoporosis and bone fractures
- Increased risk of CHD

ACTIVE LEARNING

Complete the missing information from the following table. In the Hormone Replacement column, circle the most appropriate option. In the Rationale column, explain your selection from the Hormone Replacement Therapy column.

Uterus Status	Hormone Replacement Therapy	Rationale
Intact	Estrogen Progestin Both	
Removed	Estrogen Progestin Both	

ACTIVE LEARNING

Uterus Status	Hormone Replacement Therapy	Rationale
Removed	Estrogen Progestin Both	Estrogens treat vasomotor disturbances ("hot flashes") in postmenopausal women. Other important benefits are amelioration of the effects of urogenital atrophy, a decreased incidence of colon cancer, and prevention of bone loss.
Intact	Estrogen Progestin Both	In postmenopausal women with an intact uterus, a progestin is included to prevent endometrial cancer. When the uterus is removed, this is no longer relevant.

ESTROGENS

Estrogens were covered in the context of contraception earlier this week

Highlight MHT uses for estrogen today

ESTROGENS

Relieve hot flashes

Decrease bone resorption (directly regulate osteoblasts, increase osteocyte survival, decrease number of osteoclasts); estrogen *prevents* fractures (rather than restoring bone loss)

Impact lipoprotein profile (reduce total cholesterol, increase HDL, decrease LDL and Lp(a)); promote vasodilation (increase production of nitrous oxide); inhibit the response to vascular injury; reduce atherosclerosis

- Estrogens increase triglycerides
- Estrogens promote coagulation

ESTROGEN RECEPTORS (ERs)

ERα expressed in female reproductive tract (uterus, vagina, and ovaries) + mammary gland, hypothalamus, endothelial cells, and vascular smooth muscle

ERβ expressed most highly in the prostate and ovaries

- Lower expression in lung, brain, bone, vasculature

ERα and ERβ belong to the Nuclear Receptor Structural Family and the Steroid Receptor Functional Family

Cloned G protein–coupled receptor, GPR30, interacts with estrogens in some cell systems

ESTROGENS MOA

Estrogens enter cell via passive diffusion

ER is inactive monomer bound to HSP90 in nucleus

- Estrogens bind to ER → dissociation of HSP90 → dimerization → ↑ affinity and rate of receptor binding to DNA

ER dimer binds to Estrogen Response Element (ERE) – typically in promoter region of target genes

ER/DNA complex recruits cascade of coactivator and other proteins to promoter region of target genes

Initiates transcription

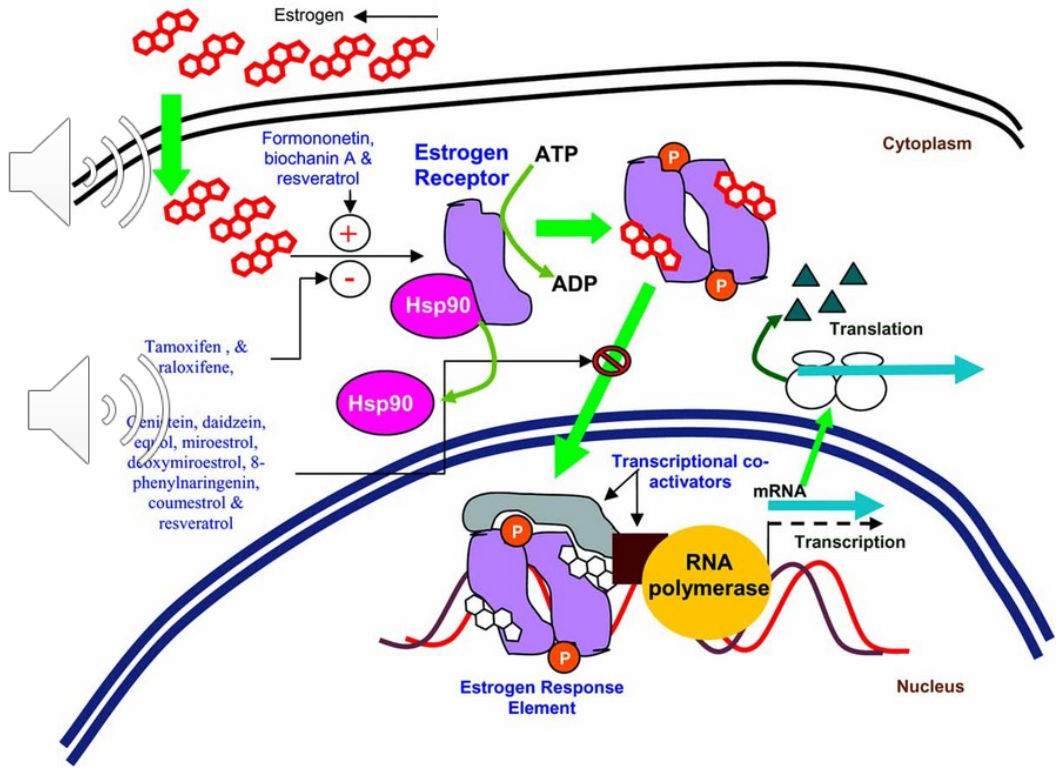


Image credit: https://www.researchgate.net/figure/Fig-2-Estrogen-signaling-mechanism-The-estrogen-receptor-ER-is-a-cytoplasmic_fig1_5630868

ACTIVE LEARNING

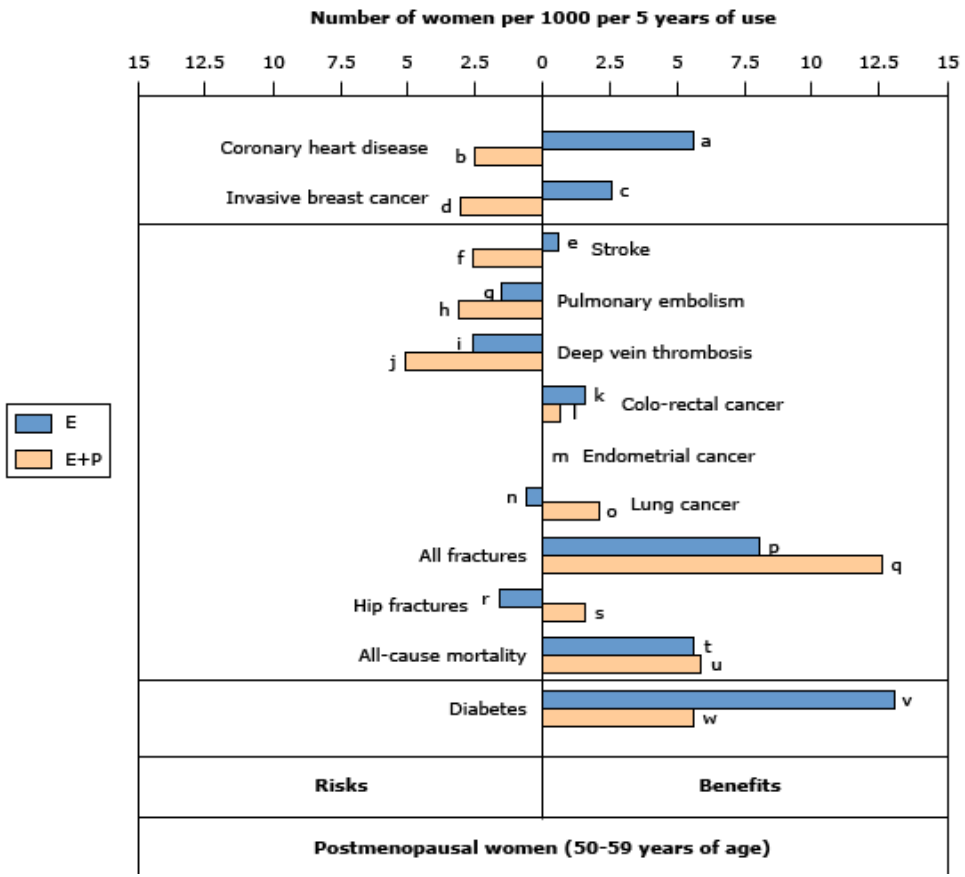
What adverse effects might you expect from exogenous estrogen use?

ACTIVE LEARNING

What adverse effects might you expect from exogenous estrogen use?

- Thromboembolic events
- Unopposed estrogen in postmenopausal women with intact uteri increases the risk of endometrial carcinoma by 5- to 15-fold
- Potential increased risk of breast cancer
- Increased triglycerides

Risks and benefits of menopausal hormone therapy (MHT)



CEE: conjugated equine estrogen; E: estrogen; E+P: estrogen-progestin; HR: hazard ratio; MHT: menopausal hormone therapy; MPA: medroxyprogesterone acetate; WHI: Women's Health Initiative.

Updated summary of the effects of orally administered CEE alone or combined with MPA in women ages 50 to 59 years during intervention phase of WHI. One set of analyses examined the risks and benefits of these agents in women ages 50 to 59 years. This figure plots these data, which are expressed here as excess risks and benefits per 1000 women using MHT for five years. Because women deciding to use MHT are more likely to continue this for a period of years rather than one year, this figure is constructed according to that assumption. WHI studies were not powered for age-related subset analyses, and none of the data presented in the figure are statistically significant. Nonetheless, this figure represents the best estimates that are available at the present time and are likely more reliable than similar estimates based on observational studies as reported previously in The Endocrine Society Scientific Statement.

The HR (95% CI) values for the bars in the figure are listed here with reference to the alphabetical designations shown next to the bars: (a) HR 0.60 (0.35-1.04); (b) HR 1.34 (0.82-2.19); (c) HR 0.82 (0.50-1.34); (d) HR 1.21 (0.81-1.80); (e) HR 0.99 (0.53-1.85); (f) HR 1.51 (0.81-2.82); (g) HR 1.53 (0.63-3.75); (h) HR 2.05 (0.89-4.71); (i) HR 1.66 (0.76-3.67); (j) HR 3.01 (1.36-6.66); (k) HR 0.71 (0.30-1.67); (l) HR 0.79 (0.29-2.18); (m) HR 1.00 (ns-ns); (n) HR 1.12 (0.45-2.75); (o) HR 0.62 (0.30-1.29); (p) HR 0.90 (0.72-1.11); (q) HR 0.82 (0.68-1.00); (r) HR 5.01 (0.59-42.9); (s) HR 0.17 (0.02-1.45); (t) HR 0.70 (0.46-1.09); (u) HR 0.67 (0.43-1.04); (v) HR 0.83 (0.67-1.04); and (w) HR 0.85 (0.66-1.09). (RJ Santen, et al. Competency in menopause management: whither goest the internist? *J Women's Health (Larchmt)* 2014; 23:281, courtesy of Mary Ann Liebert, Inc).

SELECTED ESTROGENS & PROGESTINS FOR MHT

Generic Name (Brand Name)	Contraindications & Cautions	Adverse Effects	Interactions
Estradiol (Estrace) Esterified estrogens (Menest) Conjugated equine estrogens (Premarin) **Oral estrogen-progestin combos**	**Women at high risk for arterial or venous thrombotic diseases** Protein C or S, antithrombin deficiency Undiagnosed genital bleeding Active or h/o arterial thromboembolic disease **Breast cancer or other estrogen- or progestogen-sensitive cancer** Hepatic impairment or disease Pregnancy	**Estrogen:** **VTE, CVA, MI, HTN** Cervical cancer, breast cancer Exacerbation of epilepsy, asthma Endometrial cancer Vaginitis, vulvovaginal candidiasis Enlargement of uterine fibroids Altered bleeding patterns Mood changes Breast changes, tenderness Nausea Bloating, cramps Headache Weight gain?	Antibiotics, St John's wort → potential contraceptive failure Anticonvulsants → reduced contraceptive efficacy Lamotrigine → decreased lamotrigine levels

BOXED WARNING

Boxed warning: Increased risk of endometrial cancer, cardiovascular disorders, breast cancer, and probable dementia.

CLINICAL USE & ADME

Primary ovarian insufficiency

Female hypogonadism

Symptoms associated with menopause, including vulvovaginal atrophy, dyspareunia, hot flashes and night sweats, and prevention of osteoporosis

Oral contraceptive pill (OCP) to prevent pregnancy

Moderate acne vulgaris

Prostate cancer with advanced forms of metastasis

Multiple routes of administration

- Oral
- Estradiol patches, topical gels, sprays, intravaginal rings, vaginal tablets, vaginal creams, depot injections

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DRUGS FOR TERMINATION OF PREGNANCY

ACTIVE LEARNING

What is the role of progesterone in pregnancy?

ACTIVE LEARNING

What is the role of progesterone in pregnancy?

- Sometimes called the “pregnancy hormone”
- Produced by corpus luteum
- Critical to maintenance of early pregnancy until the placenta takes over this function at 7 to 9 weeks
  - Role of progesterone in midpregnancy to late pregnancy is less clear
- Creates a hospitable environment for the ovaries to harbor the fetus by keeping the uterus muscle relaxed and helping the immune system tolerate foreign DNA

ACTIVE LEARNING

How would antagonizing the progesterone receptor impact pregnancy?

ACTIVE LEARNING

How would antagonizing the progesterone receptor impact pregnancy?

- ANTAGONIZING the progesterone receptor would detach the blastocyst, which would decrease hCG production
- This causes decrease in progesterone secretion from the corpus luteum → more decidual breakdown

UNDERLYING PATHOPHYSIOLOGY

Progesterone = "pregnancy hormone"

- Produced by corpus luteum
- Critical to maintenance of early pregnancy until the placenta takes over this function at 7 to 9 weeks
  - ***Progest*** ational st ***er*** oidal ket ***one***
- Role in mid- to late- pregnancy less clear
  - May play role in maintaining uterine quiescence in the latter half of pregnancy
    - Limiting production of stimulatory prostaglandins and inhibiting the expression of contraction-associated protein (CAP) genes (including genes encoding ion channels, oxytocin and prostaglandin receptors, and gap junction proteins) within the myometrium.
    - Plays role in structural reorganization of collagen to allow gradual cervical softening.

ACTIVE LEARNING

Define prostaglandin. Where are prostaglandins synthesized? How to prostaglandin E_1 and E_2 effect the uterus?

ACTIVE LEARNING

Define prostaglandin. Where are prostaglandins synthesized? How do prostaglandin E_1 and E_2 effect the uterus?

- Prostaglandins are a group of endogenously produced compounds that play essential roles in regulating human physiology
- Considered eicosanoids (with leukotrienes)
- All cells with the exception of the red blood cell have the capacity to synthesize prostaglandins
- PGE1 and PGE2 increase uterine contractions

UNDERLYING PATHOPHYSIOLOGY

Pregnancy is maintained, in part, by a mechanism that suppresses **prostaglandin** synthesis, release, and activity

- Uterine tissue contains receptors for naturally occurring prostaglandins; uterine tissue capable of producing prostaglandins
  - PGE_1 and PGE_2 increase uterine contractions

PERTINENT PHYSIOLOGY OF IMPLANTATION

Implantation of a fertilized ovum (embryo) involves complex interactions with the endometrium

Embryo becomes attached to the endometrial epithelium and invades the endometrial stroma on day 6 to 10 after ovulation

- Depends on progesterone, which modifies the transcription of many genes involved in the implantation process
- Progesterone also inhibits myometrial contractions.

Drugs used to terminate pregnancy act by inducing myometrial contractions and antagonizing the action of progesterone

MEDICATION (MEDICAL) ABORTION

Uses medication to induce process similar to miscarriage

- Alternative to other types of abortion (eg, aspiration abortion, surgical abortion).
- Typically utilizes
  - Antiprogestin (such as mifepristone) followed by a prostaglandin (such as misoprostol or dinoprostone)

ANTIPROGESTIN MOA

Acts as **competitive receptor antagonists** for progesterone receptors (PRs)

- When administered in early stages of pregnancy
  - Causes decidual breakdown by blockade of uterine PRs → detachment of the blastocyst, which decreases hCG production → causes decrease in progesterone secretion from the corpus luteum → further accentuates decidual breakdown
- Decreased endogenous progesterone + blockade of PRs in the uterus increases uterine prostaglandin (PG) levels and sensitizes the myometrium to their contractile actions
- Cause cervical softening, which facilitates expulsion of the detached blastocyst

ACTIVE LEARNING

Draw a dose response curve for the agonist progesterone in the presence of an anti-progestin (competitive antagonist).

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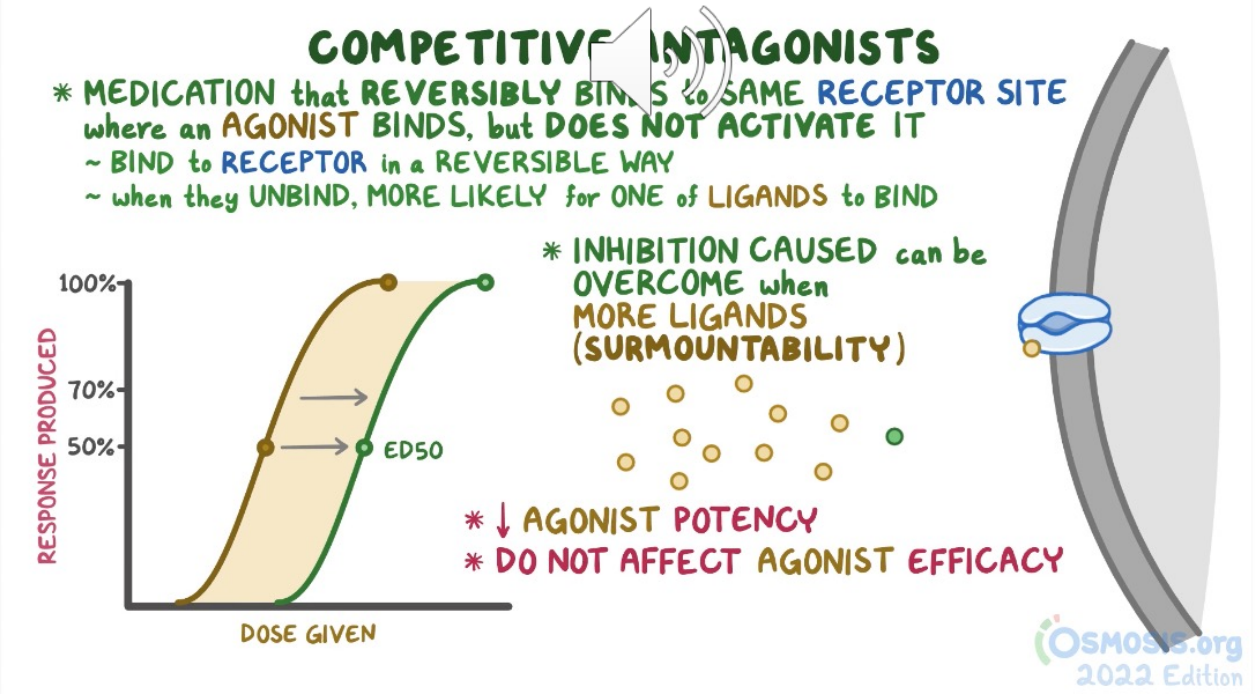
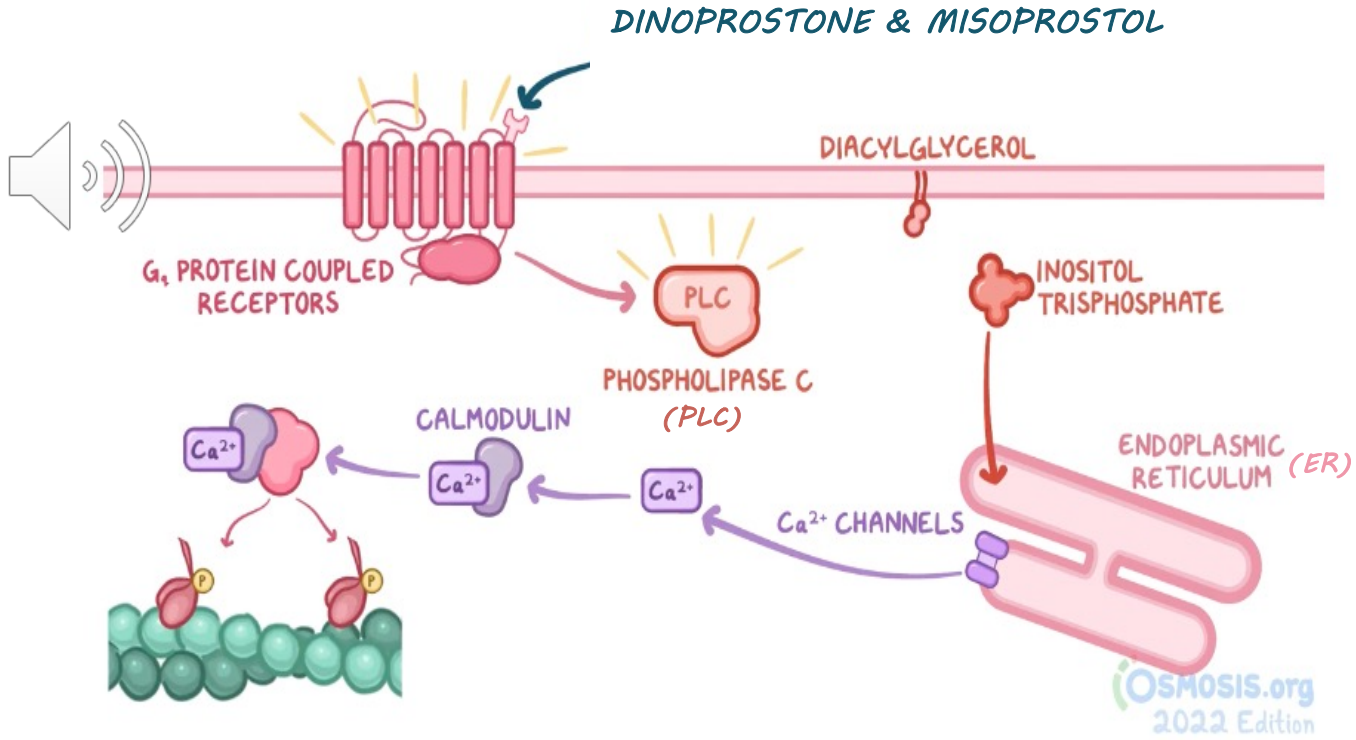


SELECTED ANTIPROGESTIN

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
mifepristone (RU-486)	**C: Serious and sometimes fatal infections**	Vomiting Diarrhea Abdominal/pelvic pain Vaginal bleeding	Moderate, irreversible inhibitor of CYP3A4 (effect lasts ~2 weeks after single dose)

PROSTAGLANDINS MOA

Prostaglandins activate Gq protein coupled receptors → activates PLC → PLC cleaves phosphatidylinositol 4,5-bisphosphate into inositol trisphosphate (IP3) and diacylglycerol (DAG) → IP3 is soluble, diffuses freely through the cytoplasm and into the endoplasmic reticulum where it opens up calcium channels

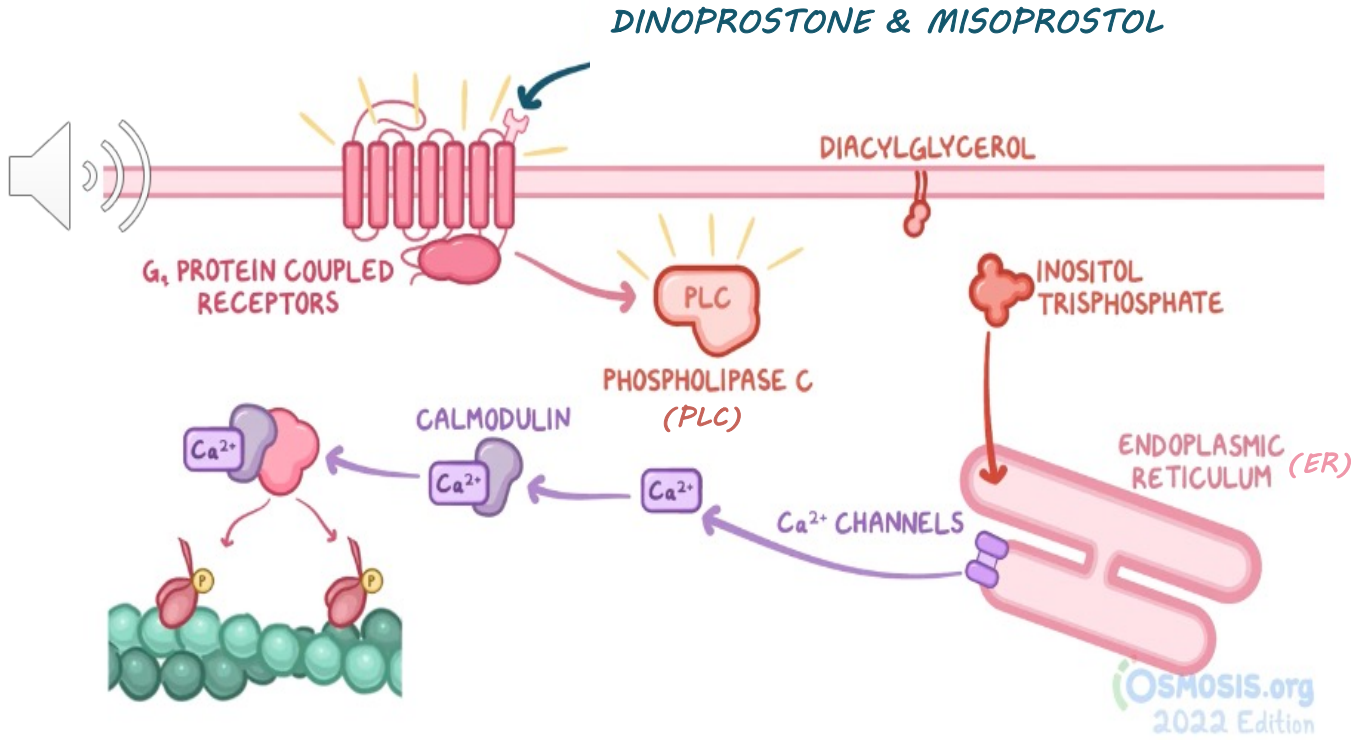


PROSTAGLANDINS MOA

Endoplasmic reticulum has higher calcium concentration than cytoplasm → calcium flows out of the endoplasmic reticulum to the cytoplasm

Calcium ions then bind to calmodulin and activate myosin light-chain kinase → muscle contraction

Prostaglandins are physiological ligands for the Eicosanoid Receptors Functional Family, which belong to the G Protein Coupled Receptor Structural Family



SELECTED PROSTAGLANDINS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Dinoprostone (PGE2 analog) Misoprostol (PGE1 analog)	CI: Suspected/confirmed ectopic pregnancy Gestational trophoblastic disease High risk of uterine rupture Intrauterine device Allergy to prostaglandins Contraindications to medical or surgical uterine evacuations (eg, hemodynamically unstable, coagulopathy)	Uterine hyperstimulation Uterine rupture Diarrhea, nausea, vomiting Fever	Oxytocin Magnesium (eg, antacids)

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DRUGS FOR OVULATION INDUCTION

ACTIVE LEARNING

What is the role of FSH in ovulation? How does estrogen impact FSH levels?

ACTIVE LEARNING

What is the role of FSH in ovulation? How does estrogen impact FSH levels?

- FSH stimulates development of ovarian follicle
- Estrogen lowers FSH levels

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

Mixed estrogen agonists

- Have estrogen agonist effects in some tissues and act as partial agonists or antagonists of estrogen in other tissues
- May be due to recruitment of different regulatory proteins and/or estrogen receptor (ER) dimers (eg, ERα-ERα, ERα-ERβ, ERβ-ERβ)

SERMS: CLOMIPHENE

Clomiphene

Partial agonist at ERs

- Weak estrogen agonist (has less activity than estrogen)
- Occupation of receptors results in effective inhibition
- Selective binding of estrogen receptors in the hypothalamus, ovary, endometrium, cervix
  - Produces estrogenic and anti-estrogenic effects
- Acts as partial estrogen agonist in hypothalamus → inhibits estrogenic negative feedback → increased gonadotropins
  - Increases the secretion of luteinizing hormone (LH) and follicle stimulation hormone (FSH) → stimulation of ovulation

SELECTED ANTI-ESTROGEN: CLOMIPHENE

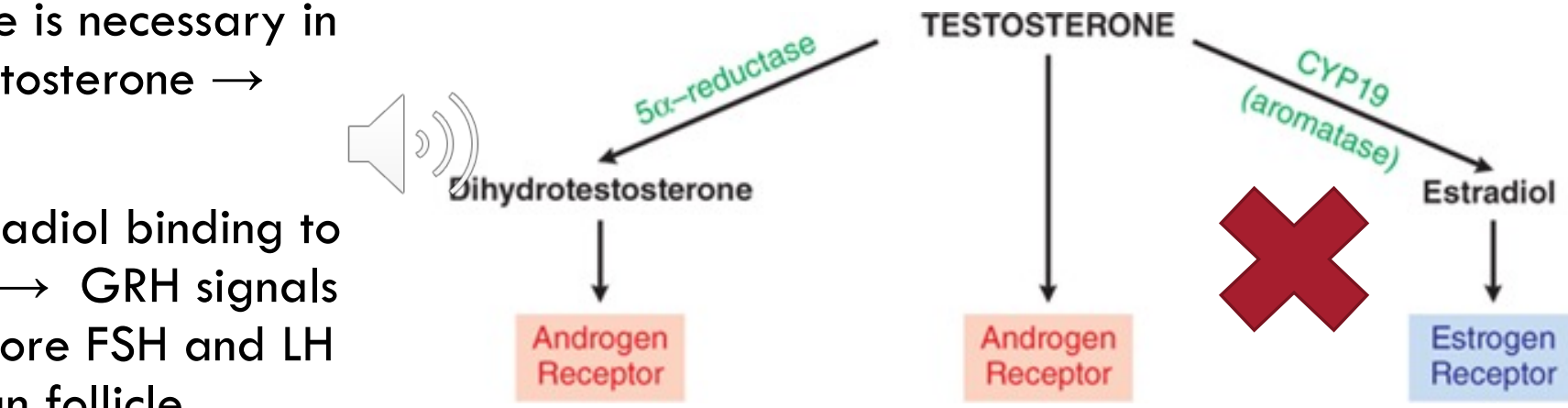
Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
clomiphene	**Contraindications:** Liver disease or hx Abnormal uterine bleeding Ovarian cyst (not d/t PCOS) Uncontrolled thyroid or adrenal dysfunction Organic intracranial lesion (eg, pituitary tumor) Pregnancy **Cautions:** Enlarged ovaries	Hot flashes Abdominal distention/pain Hair loss Breast discomfort Mood swings Visual disturbances Endometrial thinning Multiple pregnancies	Ospemifene (enhance toxic effects of one and other)

*there are additional SERMs, but they have different effects on estrogen receptors

AROMATASE INHIBITORS MOA

Induce follicle development by inhibiting aromatase → aromatase is necessary in estrogen biosynthesis (testosterone → estradiol)

Less estradiol → less estradiol binding to ERs → release of GRH → GRH signals the pituitary to secrete more FSH and LH → FSH develops ovarian follicle



SELECTED AROMATASE INHIBITOR

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
letrozole	**Contraindications:** Pregnancy **Cautions:** Those at risk for osteoporosis, endometrial hyperplasia, and endometrial neoplasia	Hot flashes Arthralgia Arthritis Back pain Bone fracture Osteoporosis Hypercholesterolemia	Methadone (may increase methadone levels) Tamoxifen (may decrease letrozole levels)

CLINICAL USE

Clomiphene

- Treatment of ovulatory dysfunction

Letrozole

- Breast cancer in postmenopausal patients
- Off label: Infertility/Ovulation stimulation in anovulatory patients with polycystic ovary syndrome

PRACTICE QUESTION

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ANY QUESTIONS?

skye_mckennon@wsu.edu