

MEN'S AND WOMEN'S HEALTH

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WEST LAFAYETTE, INDIANA**

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Learning Objectives

1. Recommend appropriate treatment options for patients with menopausal symptoms and osteoporosis.
2. Identify drugs that are considered safe and unsafe during pregnancy and lactation, and differentiate between information resources for pregnancy and lactation.
3. Select the appropriate treatment for infertility or sexual dysfunction on the basis of patient-specific factors.
4. Devise a pharmacotherapeutic plan for appropriate contraceptive use, including assessment of estrogen- and progestin-related adverse effects or drug interactions, contraceptive method mishaps, and use of emergency contraception.
5. Identify common menstrual disorders and sexually transmitted diseases and recommend appropriate pharmacotherapy.

Abbreviations in This Chapter

ACE	Angiotensin-converting enzyme
aPTT	Activated partial thromboplastin time
BMD	Bone mineral density
BUM	Backup method
CHD	Coronary heart disease
COC	Combined oral contraceptive
CYP	Cytochrome P450
CVD	Cardiovascular disease
DMPA	Depot medroxyprogesterone acetate
DVT	Deep venous thrombosis
DXA	Dual-energy x-ray absorptiometry
EC	Emergency contraception
EPT	Estrogen and progestogen therapy
ET	Estrogen only therapy
FRAX	Fracture Risk Assessment Tool
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
GSM	Genitourinary syndrome of menopause
hCG	Human chorionic gonadotropin
HSV	Herpes Simplex Virus
HT	Hormone therapy
IUD	Intrauterine device
IUS	Intrauterine system
LARC	Long-acting reversible contraception
LH	Luteinizing hormone
NSAIDs	Nonsteroidal anti-inflammatory drugs
OC	Oral contraceptive
OTC	Over the counter
PCOS	Polycystic ovary syndrome

PDE	Phosphodiesterase
PID	Pelvic inflammatory disease
POP	Progestin-only pill/minipill
VTE	Venous thromboembolism

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. M.T. is a 72-year-old white man (height 69 inches, weight 68 kg) with a history of hypertension who admits smoking one pack of cigarettes per day and having a poor diet. He states that he walks on his treadmill 30 minutes a day. His bone mineral density (BMD) T-score is -2.1 at the hip and -2.2 at the spine. His fracture history includes a fall at age 68 with an ankle fracture. His Fracture Risk Assessment Tool (FRAX) score (10-year major fracture probability) is 14%, and his probability of hip fracture is 6.7%. Which best describes M.T.'s condition?
 - A. He has low bone mass (osteopenia) of the hip and spine.
 - B. He has osteoporosis of the spine and low bone mass (osteopenia) of the hip.
 - C. He has osteoporosis of the hip and spine.
 - D. He has normal BMD of the hip and spine.
2. Which treatment is best for M.T.?
 - A. Take calcium 1200 mg orally daily, vitamin D 800 international units orally daily, and alendronate 70 mg orally weekly.
 - B. Take calcium 1200 mg orally daily and vitamin D 600 international units orally daily, and begin weight-bearing exercise.
 - C. Take calcium 1200 mg orally daily, vitamin D 600 international units orally daily, and raloxifene 60 mg orally daily.
 - D. Take calcium 1200 mg orally daily, vitamin D 400 international units orally daily, and risedronate 35 mg orally weekly, and begin weight-bearing exercise.
3. A 29-year-old woman (height 65 inches, weight 63 kg) has a history of two deep venous thromboses (DVTs) but is otherwise healthy; she is seeking to become pregnant. She currently takes warfarin

- 3 mg orally daily. Which regimen is the best recommendation for this patient?
- Continue current warfarin dose to prevent clots during pregnancy.
 - Continue warfarin therapy but increase the dose to prevent clots during pregnancy.
 - Discontinue warfarin; start enoxaparin 60 mg subcutaneously every 12 hours until pregnant and continue through pregnancy.
 - Discontinue warfarin; start heparin 5000 units subcutaneously every 8 hours daily until 12 weeks pregnant, and then reinstitute warfarin.
4. J.K. is a 51-year-old postmenopausal woman with severe hot flashes that have not resolved with venlafaxine 75 mg orally daily. She is otherwise healthy, with no history of cancer and no surgical procedures. She is given conjugated estrogen 0.625 mg orally daily. Which treatment is best for J.K.?
- No other drug is needed; estrogen alone is sufficient for hot flashes.
 - No other drug is needed; estrogen should be discontinued, and she should continue on venlafaxine.
 - Venlafaxine should be continued and Medroxyprogesterone acetate should be added to decrease the risk of stroke.
 - Venlafaxine should be discontinued and Medroxyprogesterone acetate should be added to decrease the risk of endometrial cancer.
5. C.S. is a 49-year-old postmenopausal woman experiencing severe hot flashes, vaginal dryness, and pain during sexual intercourse. C.S. has a history of irregular heavy uterine bleeding, which resulted in a total hysterectomy 5 months ago. Her hot flashes are affecting her quality of life. Which treatment is best to recommend for C.S.?
- Estradiol vaginal cream 0.1 mg/g.
 - Conjugated estrogen and medroxyprogesterone acetate 0.625 mg/2.5 mg tablets.
 - Conjugated estrogen 0.3-mg tablets.
 - Ospemifene 60-mg tablets.
6. S.F. is a 20-year-old woman initiated on ethinyl estradiol 30 mcg/drospirenone 3 mg oral tablets 5 months ago for contraception. She was recently prescribed lamotrigine for bipolar disorder. Which best describes the drug interaction that may occur with ethinyl estradiol/drospirenone and lamotrigine in this patient?
- The effectiveness of ethinyl estradiol and drospirenone may be decreased.
 - The effectiveness of lamotrigine may be increased.
 - The effectiveness of lamotrigine may be decreased.
 - The effectiveness of ethinyl estradiol and drospirenone may be increased.
7. A study compares the incidence of herpes simplex genital infections in patients receiving suppressive therapy with acyclovir versus valacyclovir. After 1 year of follow-up, 25% in the acyclovir group and 20% in the valacyclovir group experience a recurrent infection ($p < 0.05$). Which best represents how many patients (in 1 year) would need to be treated with valacyclovir over acyclovir to prevent one recurrent infection?
- 5.
 - 20.
 - 25.
 - There is insufficient information to calculate this number.
8. K.M. is a 28-year-old woman (height 68 inches, weight 98 kg) with a history of migraine with aura who is seeking contraception. Her blood pressure today is 135/82 mm Hg; she denies smoking and alcohol use and states that she would like to have children in a year or so. Which is the best contraceptive agent for K.M.?
- Levonorgestrel intrauterine system.
 - Oral norethindrone tablet.
 - Transdermal ethinyl estradiol/etonogestrel patch.
 - Oral ethinyl estradiol/desogestrel tablet.

9. L.L. is a 38-year-old woman who has been trying to conceive for the past 7 months. Her husband's medical examination is normal; L.L. is not ovulating every month. She has not tried any medications previously to induce ovulation. Which medication is best to initiate in L.L. to induce ovulation?
- A. Human chorionic gonadotropin (hCG).
 - B. Nafarelin/gonadotropin-releasing hormone (GnRH) agonist.
 - C. Human menopausal gonadotropin (hMG).
 - D. Clomiphene.
10. T.G. is a 22-year-old woman who comes to a community pharmacy and asks about emergency contraception (EC). She states that she was out of town for the weekend and was swimming when her contraceptive vaginal ring slipped out. She has been without the ring for 3 days because she did not have a new one with her for replacement. She states she had unprotected intercourse 4 nights ago. She is worried about becoming pregnant. Which is the best recommendation for T.G.?
- A. Recommend that she see her physician for a levonorgestrel 1.5 mg prescription.
 - B. Recommend EC; it may still be effective because she is within the 120-hour time window.
 - C. Do not recommend EC; it may be ineffective because she is beyond the 72-hour time window.
 - D. Do not recommend EC; instead, recommend that she insert a new contraceptive vaginal ring.
11. K.S. is a 45-year-old man who has difficulty maintaining an erection during intercourse. His medical history includes diabetes mellitus and hyperlipidemia. His drugs include aspirin, metformin, and pravastatin. Blood pressure is 130/81 mm Hg, hemoglobin A1C 6.2, total cholesterol 195 mg/dL, low-density lipoprotein cholesterol (LDL) 106 mg/dL, high-density lipoprotein cholesterol (HDL) 54 mg/dL, triglycerides 145 mg/dL, total testosterone concentration 970 ng/dL (reference range 270–1070 ng/dL), and free testosterone concentration 22 ng/dL (reference range 9–30 ng/dL). Which drug is best to initiate for his erectile dysfunction?
- A. Vardenafil.
 - B. Testosterone transdermal patch.
 - C. Yohimbine.
 - D. Fluoxetine.
12. T.M., a 33-year-old man, has a history of intravenous drug abuse and lives in and out of homeless shelters. He is taken to the emergency department by ambulance after experiencing paralysis on the right side of his body. The people at the shelter thought he might be having a stroke. In the emergency department, screening was positive for the Venereal Disease Research Laboratory test (syphilis test) with 10 white blood cells/mm³. T.M. has no known significant medical history (except for treatment of a sexually transmitted disease [STD]), but he is allergic to penicillin (anaphylactic reaction). Assuming serologic testing confirms a diagnosis of syphilis, which therapy is best for T.M.?
- A. Levofloxacin 750 mg intravenously for one dose.
 - B. Penicillin G 4 million units every 4 hours intravenously for 14 days after penicillin desensitization.
 - C. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks after penicillin desensitization.
 - D. Azithromycin 500 mg intravenously or orally daily for 6 weeks.
13. A prospective double-blind study compared the effects of three different antivirals—acyclovir, famciclovir, and valacyclovir—in 360 patients with first-episode genital herpes. Which statistical test is best to compare the mean duration of time until the lesions healed?
- A. Analysis of variance (ANOVA).
 - B. Chi-square test.
 - C. Mann-Whitney U test.
 - D. Student t-test.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain I: Patient-Centered Pharmacotherapy
 - Task 1: Knowledge statements: a-q
 - Task 2: Knowledge statements: a-c
 - Task 3: Knowledge statements: a-d, g
 - Task 4: Knowledge statements: a
2. Domain II: Application of Evidence to Practice and Education
 - Task 1: Knowledge statements: d, f, g
3. Domain III: Healthcare Systems and Population Health
 - Task 1: Knowledge statement: b
 - Task 2: Knowledge statement a-c
 - Task 3: Knowledge statement: b

I. HORMONE THERAPY AND MENOPAUSE

A. Background of Menopause

1. Definition: Cessation of menstrual periods for 1 year, also known as final menstrual period, loss of ovarian follicular function
2. Average age of menopause is 52 years, but age ranges from 40 to 58 years.
3. Common symptoms
 - a. Vasomotor symptoms, also known as hot flashes
 - i. Most common reason for treatment
 - ii. May interrupt sleep and cause insomnia
 - iii. May affect quality of life
 - iv. Occur in 75%–85% of women, usually within 12–24 months after the last menstrual period.
 - v. May cause increased skin temperature, nausea, dizziness, headache, palpitations, diaphoresis, and night sweats.
 - b. Genitourinary syndrome of menopause (GSM): This syndrome includes genital symptoms of dryness, burning, and irritation; urinary symptoms and conditions of dysuria, urgency, and recurrent urinary tract infections (UTIs); and sexual symptoms of pain and dryness. (Menopause 2014; 21:1-6, Menopause 2017;24:1-26, Menopause 2020;27:976-92)
 - i. Decrease in estrogen and other sex steroids causes thinning of hair of the mons and shrinkage of the labia minora; vulvovaginal atrophy (VVA) leads to pruritus and pain.
 - ii. Loss of lubrication leads to dyspareunia (pain during sexual intercourse).
 - iii. Vaginal pH changes and becomes more basic (from 4.5–5 to 6–8), creating a favorable environment for bacterial colonization.
 - iv. Thinning of urethra and bladder lining and decreased muscle tone result in recurrent episodes of urinary frequency, urgency with dysuria, and urinary tract infections.

B. Treatments

1. Individualization of therapy is essential. Need to consider the woman's medical *Treponema pallidum* passive particle agglutination (TP-PA) assay history (cancer history [specifically breast cancer], cardiovascular disease [CVD], stroke, hypertension, quality of life with menopausal symptoms).
2. Hormone therapy (HT) is an all-encompassing term that includes estrogen and progestogen therapy (EPT), estrogen-only therapy (ET), progestogen-only therapy (PT), and estrogen-receptor (ER) agonists or antagonists.
 - a. FDA-Approved indications for various HT: Treatment of moderate to severe vasomotor symptoms (VMS), treatment of moderate to severe GSM because of menopause, prevention of postmenopausal osteoporosis, hypoestrogenism caused by hypogonadism, castration or premature ovarian failure.
 - b. Recommendations for HT
 - i. Menopausal symptom relief
 - (a) Moderate to severe vasomotor symptoms (primary HT indication)
 1. Recommend lowest effective dose.
 2. For women younger than 60 or women who are within 10 years of menopause onset without contraindications or at a high risk of CVD or breast cancer, assess the baseline risk of breast cancer and CVD, and consider risk when making a recommendation.
 - (b) Moderate-to-severe GSM
 1. Moderate to severe vaginal symptoms – Recommend local ET versus systemic therapy if treating vaginal symptoms only AND
 2. Urinary health – Systemic HT may worsen stress incontinence; local ET therapy may help with overactive bladder

- (c) Sexual symptoms – HT not recommended for sole treatment of diminished libido
- (d) Osteoporosis – EPT and ET indication for prevention, ↓ osteoporotic fractures, used only when alternative therapies are not appropriate; ER agonists/antagonists may also be used for osteoporosis. See section below.

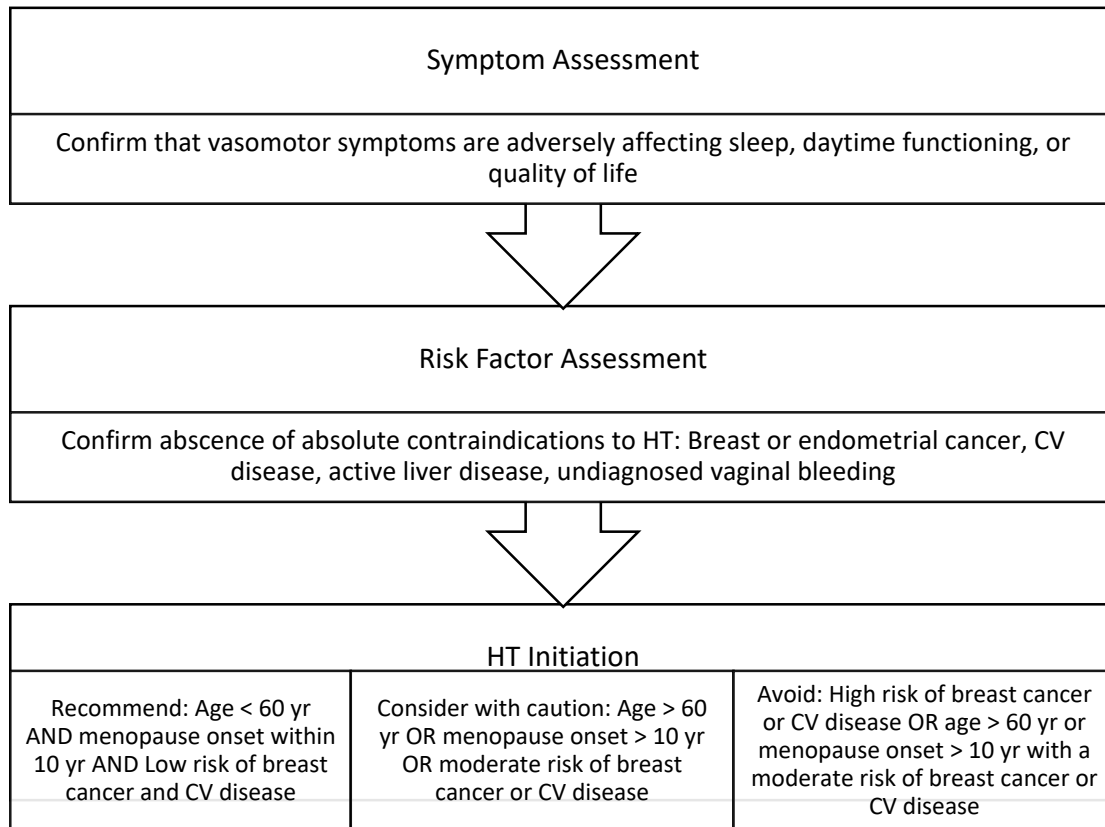


Figure 1. Risk Assessment for Initiating Hormone Therapy

CV = cardiovascular; HT = hormone therapy

Adapted from: Shifren JL, Crandall CJ, Manson JE. Menopausal hormone therapy. JAMA 2019;321:2458-9.

- ii. Risk assessment (J Clin Endocrinol Metab 2015;100:3975-4011)
 - (a) For women with a high risk of VTE who request HT: Nonoral route at lowest effective dose is recommended (if not contraindicated).
 - (b) For women with a high risk or history of breast cancer: Nonhormonal treatment is recommended for symptom relief.
 - (c) For women with a high risk of CVD (known myocardial infarction [MI], cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes mellitus, chronic kidney disease, and 10-year CVD risk greater than 10%: Nonhormonal treatment is recommended for symptom relief.
 - (d) For women with a moderate risk of CVD: Transdermal estradiol with appropriate use of progestogen (individualized) is recommended if HT is needed.
- c. Benefits and risks of estrogen and progestogens
 - i. Benefits of estrogen
 - (a) Relieves genitourinary atrophy (if only symptom, may use estrogen vaginal product locally)
 - (b) Relieves vasomotor instability

- (c) Osteoporosis: Reduction in hip fractures by 25%; reduction in vertebral fractures by 50%. Estrogen reduces the rate of bone resorption but does not reverse bone loss.
- (d) It was once thought to lower LDL and increase HDL; however, it was not shown to lower coronary heart disease (CHD) according to the Heart and Estrogen/Progestin Replacement Study (HERS; JAMA 1998;280:605-13) and the Women's Health Initiative (WHI; JAMA 2002;288:321-33) trials.
- (e) May help improve sleep by decreasing hot flashes
- ii. Risks of estrogen
 - (a) Adverse effects: Bloating, headache, breast tenderness (5%–10%)
 - (b) Endometrial cancer: Risk increases with unopposed estrogen use in women with an intact uterus.
 - (1) Cancer risk increases 8-fold for 10–20 years of estrogen use.
 - (2) Not recommended for use in women with a history of endometrial cancer. Women with early stage, low-risk endometrial cancers (grade 1 and 2 endometrioid subtypes with negative estrogen and progesterone receptors) who used HT may have similar recurrence and death rates but overall recommendation is to avoid HT use in women with endometrial cancer, especially advanced stages (Menopause 2017;24:1-26).
 - (3) A progestogen is recommended in all women with an intact uterus using estrogen (JAMA 1996;275:370-5, Menopause 2017;24:1-26).
 - (c) Breast cancer with unopposed estrogen: Uncertain
 - (1) WHI showed no increased risk and a nonsignificant decrease in risk in women who use estrogen for an average of 7.2 years. May increase relative risk among women who take estrogen for longer than 5 years, though some studies have not shown this risk (Menopause 2017;24:1-26).
 - (2) Not recommended for use in women with a history of breast cancer (Menopause 2017;24:1-26).
 - (3) Risk seems to increase with the addition of the progestogen and be related to the length of use. The risk is small and decreases after discontinuation of use.
 - (d) CHD: Possible increased risk of cardiovascular outcomes; not recommended for coronary protection at any age (see text that follows for further information).
 - (e) Gallbladder effects: Use of oral estrogen may increase risk of gallbladder disease that may result in gallstones, cholecystitis, cholecystectomy. Risk is slightly lower with medroxyprogesterone acetate in combination with estrogen (Menopause 2017;24:1-26).
- iii. Benefits of progestogen (progestogen is an umbrella term for progesterone [natural] and progestins [synthetic]):
 - (a) Decreased risk of estrogen-induced irregular bleeding
 - (b) Decreased risk of endometrial hyperplasia and carcinoma
- iv. Risks of progestogen
 - (a) Adverse effects: Bloating, weight gain, irritability, depression (dose related)
 - (b) Unpredictable endometrial bleeding with continuous estrogen/progestin during first 8–12 months (30%–50%)
- v. Selected outcomes related to EPT and ET
 - (a) Cardiovascular outcomes with conjugated estrogens and medroxyprogesterone acetate (JAMA 1998;280:605-13)
 - (1) A longer duration of use leads to a greater decrease in relative hazards in nonfatal MI and CHD death; however, there was an increased risk of venous thromboembolism (VTE) and gallbladder disease.

- (2) Conclusions of study: HT was not appropriate to initiate for secondary prevention of CHD, but for women already using HT, long-term use might result in a decrease in CHD.
- (3) A follow-up study suggested that older women with CHD who used HT for longer than 6.8 years had a higher risk of VTE and biliary tract surgery (JAMA 2002;288:58-66).
- (b) Other findings related to cardiovascular outcomes from various trials
 - (1) Venous thromboembolism
 - (A) Observational studies indicated increased risk.
 - (B) A randomized controlled trial, the WHI (JAMA 2002;288:321-33), found increased risk in the EPT arm (18 additional VTEs per 10,000 women per year of EPT) and in the estrogen only therapy (ET) arm (7 additional VTEs per 10,000 women per year of ET).
 - (C) In WHI, when EPT and ET were initiated in women 50–59 years of age, the risk of VTE was lower in this age group (11 additional VTEs per 10,000 women per year of EPT and 4 additional VTEs per 10,000 women per year of ET).
 - (2) Stroke
 - (A) Both EPT and ET showed an increased risk of stroke (8 additional strokes per 10,000 women per year of EPT and 11 additional strokes per 10,000 women per year of ET).
 - (B) Women 50–59 years of age had no significant increase in stroke with EPT in the WHI, but in the ET group alone, risk doubled. Nurses' Health Study showed similar results (Cochrane Database Syst Rev 2015;3:CD002229).
 - (3) Coronary heart disease
 - (A) Observational studies indicated therapy may decrease CHD risk, but most women were younger than 55 and had entered menopause within the past 2–3 years.
 - (B) Randomized controlled trials indicated an increased risk of CHD, but women had an average age of 63–64 years and had entered menopause about 10 years earlier. When adjusted for age, the estrogen-only arm of the WHI trial matches observational data, indicating a lower risk of CHD in younger patients.
 - (C) Data show women who begin HT within 10 years of entering menopause may have a lower risk of CHD, whereas older women may have a higher risk of CHD.
 - (D) Coronary artery calcium, a marker associated with atheromatous plaque burden and CHD risk, has been decreased in some observational studies. In the WHI study, estrogen-only arm participants had lower concentrations of coronary artery calcium after 7 years of treatment.
 - (E) Subclinical atherosclerosis, measured as carotid intima-media thickness, is reduced in women who started estrogen therapy with or without a progestogen less than 6 years past the time of menopause compared with placebo. This was not true in women who started hormone therapy 10 years or more after menopause onset (N Engl J Med 2016;374:1221-31).
 - (F) WHI findings (JAMA 2002;288:321-33). The WHI trial included conjugated estrogens and medroxyprogesterone acetate in healthy women 50–79 years of age for primary prevention of CHD. Controversy exists because the average age of women was older; thus, increases in breast cancer or CVD could be caused by age (Table 1).

Table 1. Summary of WHI Outcomes for EPT Use

Risk or Benefit	Relative Risk	Absolute Risk Each Year
Blood clots	2.11, or 111% ↑	18 more cases in 10,000 women
Dementia ^a	2.05, or 105% ↑	23 more cases in 10,000 women > 65
Strokes	1.41, or 41% ↑	8 more cases in 10,000 women
Heart attacks	1.29, or 29% ↑	7 more cases in 10,000 women
Breast cancer	1.26, or 26% ↑	8 more cases in 10,000 women
Hip fractures	0.66, or 33% ↓	5 fewer cases in 10,000 women
Colon cancer	0.63, or 37% ↓	6 fewer cases in 10,000 women

^aWomen's Health Initiative Memory Study.

EPT = estrogen and progestogen therapy; WHI = Women's Health Initiative

- (c) Further information suggests increased risk of ovarian cancer (data conflicting); long-term use greater than 5 years may increase risk, particularly in estrogen-only therapy; overall risk of occurrence considered rare, according to WHI data (JAMA 2009;302:298-305). A more recent meta-analysis showed that hormone therapy, regardless of type or regimen, was associated with an increased risk of ovarian cancer (Menopause 2016;4:417-24, Menopause 2017;24:1-26).
- (d) Lung cancer may be increased in older women with a history of smoking (Lancet 2009;374:1243-51); some data are conflicting. Seems to be more associated with EPT use than with ET use.
- (e) Cumulative 18-year follow-up on WHI trials of conjugated equine estrogens (0.625 mg/day) and medroxyprogesterone acetate (2.5mg/day) used for a median of 5.6 years or conjugated equine estrogens alone for a median of 7.2 years showed no difference in all-cause and cause-specific mortality risk (JAMA 2017;318(10):927-938).
- vi. Formulations
 - (a) Oral: Used for vasomotor symptoms, also covers GSM if concomitant.
 - (b) Transdermal: For women who are intolerant of oral preparations, used for vasomotor symptoms, also covers GSM if concomitant, according to 2015 Endocrine Society clinical practice guideline first-line formulation for women with moderate risk of CVD if estrogen is needed.
 - (c) Vaginal and local preparations: For women with GSM. In general, topical treatment is sufficient and should be tried before oral preparations for patients experiencing no other symptoms (Femring vaginal ring is only vaginal preparation indicated for vasomotor symptoms).
- vii. Hormone regimens
 - (a) Therapy duration: Lowest dose for least amount of time. Check after 3 months to 1 year, and try to discontinue if asymptomatic; if symptoms recur, treat for an additional 3 months; best to limit treatment to less than 5 years.
 - (b) Unopposed estrogen
 - (1) Women with a uterus must have a progestogen and cannot use estrogen alone; use of estrogen alone in women with a uterus causes endometrial hypertrophy and increases the risk of endometrial cancer. (Original reference: JAMA 1996;275:370-5).
 - (2) Estrogen taken daily without interruption is suggested for women with a hysterectomy.
 - (A) Transdermal estradiol patches can be used in women who are intolerant of oral preparations or want nondaily administration

- (c) Estrogen plus cyclic progestogen
 - (1) Continuous estrogen daily
 - (2) Cyclic progestogen such as medroxyprogesterone acetate 5–10 mg/day or the equivalent for 10–14 days/month
 - (3) Similar to female cycle, with a withdrawal bleed each cycle
 - (d) Estrogen plus continuous progestogen
 - (1) Continuous estrogen daily
 - (2) Continuous progestogen such as medroxyprogesterone acetate 1.5–2.5 mg/day or the equivalent without interruption
 - (3) Irregular menstrual cycle for the first 8–12 months of therapy, leading to amenorrhea
 - (e) Intermittent
 - (1) Continuous estrogen daily
 - (2) Three days on progestogen, 3 days off
 - (3) Seldom used
- viii. Monitoring criteria
- (a) Monthly: Breast self-examination
 - (b) Annually: Breast examination by provider, mammography (or biannually per U.S. Preventive Services Task Force), pelvic examination
 - (c) Evaluation of vaginal bleeding
 - (1) Unopposed estrogen: Any episode of vaginal bleeding unless the woman has had a health assessment deemed normal in the past 6 months
 - (2) Estrogen plus cyclic progestogen: If bleeding occurs other than at the time of expected withdrawal bleeding
 - (3) Estrogen plus continuous progestogen: If bleeding is heavier than normal, is prolonged (longer than 10 days at a time), is frequent (more often than monthly), or persists for more than 10 months after beginning therapy
- ix. Products and dosing (Tables 2, 3, 4, 5, and 6)

Table 2. Oral Estrogen Products

Brand Name	Generic Name	Strengths (mg)
Estrace	17 β -Estradiol	0.5, 1, 2
Femtrace	Estradiol acetate	0.45, 0.9, 1.8
Menest	Esterified estrogens	0.3, 0.625, 1.25, 2.5
Various generics	Estropipate	0.75, 1.5, 3, 6
Premarin	Conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25
Cenestin	Conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25
Enjuvia	Conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25

Table 3. Vaginal Estrogen Products

Formulation	Brand Name	Generic Name and Strength	Dose
Vaginal creams	Estrace	Micronized estradiol (0.1 mg/g)	Initial: 2–4 g/day for 1–2 wk; then gradually reduced to half the initial dose for 1–2 wk, followed by maintenance of 1 g/day applied vaginally one to three times weekly
	Premarin	Conjugated estrogens (0.625 mg/g)	Atrophic vaginitis: Use 0.5–2 g/day applied vaginally for 21 days and then 7 days off; may also use twice-weekly regimen of 0.5 g intravaginally for dyspareunia
Vaginal rings	Estring	17 β -Estradiol (2-mg ring that delivers 7.5 mcg/day)	1 ring every 3 mo inserted vaginally
	Femring	Estradiol acetate (0.05 or 0.1 mg/day)	
Vaginal tablet	Vagifem, Yuvaferm	Estradiol hemihydrate (10 or 25 mcg/day)	1 vaginal tablet once daily for 2 wk; then 1 tablet twice weekly
	Imvexxy	Estradiol inserts (4 or 10 mcg)	1 vaginal insert daily for 2 wk; then 1 vaginal insert twice weekly

Table 4. Transdermal Estrogen Products

Brand Name	Formulation	Estrogen Provided (mg/day)	Dose	Unique Traits and Counseling Points
Alora	17 β -Estradiol matrix patch	0.025, 0.05, 0.075, 0.1	1 patch twice weekly	Rotate sites of application to avoid irritation for all patches
Climara		0.025, 0.0375, 0.05, 0.06, 0.075, 0.1	1 patch weekly	
Minivelle		0.025, 0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	
Vivelle-Dot, Dotti		0.025, 0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	Minivelle should be placed on dry skin below umbilicus on abdomen or buttocks
Menostar		0.014	1 patch weekly	
Esclim		0.025, 0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	
Estraderm		0.05, 0.1	1 patch twice weekly	
Divigel 0.1%	17 β -Estradiol transdermal gel	Unknown	0.25, 0.5, 0.75, or 1 g of gel	Apply Divigel to one leg daily, alternate sites daily
Elestrin 0.06%		0.52 (0.0125 absorbed), 1.04 (0.0375 absorbed)	0.25, 0.5, 0.75, or 1 g of gel	Apply Divigel to one leg daily, alternate sites daily
EstroGel 0.06%		0.75 (0.035 absorbed)	0.25, 0.5, 0.75, or 1 g of gel	Apply Divigel to one leg daily, alternate sites daily
Evamist	17 β -Estradiol transdermal spray	1.53 (0.021 absorbed)	Initial 1 spray/day (1.53 mg) increasing to 2 or 3 sprays/day	1 spray on forearm daily, can increase to 2 or 3 sprays on forearm daily

Table 5. Combination Products

Brand Name	Generic Name	Hormone Strengths	Dose
Activella, Amabelz, Mimvey, Lopreeza	17 β -Estradiol/ norethindrone acetate	0.5 mg estrogen, 0.1 mg progestogen (Mimvey unavailable at 0.5/0.1 mg strength); 1 mg estrogen, 0.5 mg progestogen	1 tablet daily
Angeliq	17 β -Estradiol/ drospirenone	1 mg estrogen, 0.5 mg progestogen; 0.5 mg estrogen, 0.25 mg progestogen	1 tablet daily
Climara Pro	17 β -Estradiol/ levonorgestrel	0.045 mg estrogen, 0.015 mg progestogen	1 patch weekly
CombiPatch	17 β -Estradiol/ norethindrone acetate	0.05 mg estrogen, 0.14 mg progestogen 0.05 mg estrogen, 0.25 mg progestogen	1 patch twice weekly
Bijuva	17 β -Estradiol/ progesterone	1 mg estrogen, 100 mg progestogen	1 capsule every evening with food
Femhrt, Jinteli, Fyavolv	Ethinyl estradiol/ norethindrone acetate	0.0025 mg estrogen, 0.5 mg progestogen (Femhrt, Fyavolv) 0.005 mg estrogen, 1 mg progestogen (Jinteli, Fyavolv) 0.002 mg estrogen, 1 mg progestogen 0.003 mg estrogen, 1 mg progestogen	1 tablet daily
Prefest	17 β -Estradiol/ norgestimate	1 mg estrogen, 0.09 mg progestogen	3 days of estrogen tablets only, 3 days of estrogen and progestogen
Premphase	Conjugated estrogens/ medroxyprogesterone acetate	0.625 mg estrogen with 5 mg progestogen	0.625 mg/day for 14 days; then 0.625 mg and 5 mg/day for 14 days
Prempro	Conjugated estrogens/ medroxyprogesterone acetate	0.625 mg estrogen with 2.5 or 5 mg progestogen 0.3 or 0.45 mg estrogen with 1.5 mg progestogen	1 tablet daily

Table 6. Progestogen Products

Brand Name	Generic Name	Dosage Strengths and Formulation
Crinone 4%, 8%	Progesterone gel	45-mg vaginal applicator vaginally, 90-mg vaginal applicator vaginally
Endometrin	Progesterone vaginal suppository	100 mg vaginal suppository
Prometrium	Micronized progesterone in peanut oil	100- and 200-mg oral capsules
Provera	Medroxyprogesterone acetate	2.5-, 5-, and 10-mg oral tablets

- d. Selective estrogen receptor modulators, also known as estrogen receptor agonist/antagonists, indicated for use in menopause symptoms.
 - i. Ospemifene 60-mg oral tablets (Osphena): 1 tablet orally daily
 - (a) Indicated for the treatment of moderate to severe dyspareunia or vaginal dryness caused by vulvar and vaginal atrophy of menopause.

- (b) Agonist on endometrial lining affects uterine endometrium; it is recommended that women with a uterus add a progestin to any agent with estrogenic properties, although clinical studies with ospemifene alone did not find an increased risk of endometrial hyperplasia. No studies are available evaluating the use of ospemifene with a progestin.
 - (c) Adverse reactions (greater than 1%)
 - (1) Hot flashes
 - (2) Muscle cramps
 - (3) Vaginal discharge
 - (4) Hyperhidrosis
 - (d) Contraindications similar to those of estrogen (e.g., history of estrogen-dependent cancer, undiagnosed vaginal bleeding)
 - (1) Pregnancy, nursing, pediatrics
 - (2) History of VTE
 - (3) Severe hepatic impairment (Child-Pugh class C)
 - (e) Drug interactions
 - (1) Rifampin decreases ospemifene exposure by 59%, and they should not be used together.
 - (2) Fluconazole increased ospemifene concentrations 2.7-fold and should not be used concomitantly; ketoconazole increases ospemifene 1.4-fold.
 - (3) Highly protein bound, about 99%; may affect other medications that are protein bound.
 - (4) Should not be given with estrogen products, including other selective estrogen receptor modulators.
- ii. Conjugated estrogens 0.45 mg plus bazedoxifene 20 mg oral tablets (Duavee); 1 tablet orally daily (see Osteoporosis section in text that follows for more information)
 - (a) Indicated for treatment of moderate to severe vasomotor symptoms, prevention of osteoporosis.
 - (b) Selective estrogen receptor modulator used instead of a progestin (estrogen plus selective estrogen receptor modulator is called tissue selective estrogen complex).
 - (c) May be used in people with an intact uterus.
 - (d) May increase risk of DVT; should not be used in women with a history of blood clots; has contraindications similar to those of estrogen.
 - (e) Common adverse effects: Muscle spasms; nausea and vomiting; throat, neck, or upper abdominal pain; and indigestion
- e. Prasterone vaginal insert (Intrarosa)
 - i. Indicated for the treatment of moderate to severe dyspareunia due to vulvar and vaginal atrophy resulting from menopause.
 - ii. Inactive endogenous steroid that is converted into androgens and/or estrogens. Mechanism of action is not fully understood.
 - iii. Administration: Vaginal insert of prasterone 6.5 mg placed vaginally once at bedtime
 - iv. Should not be used in women with current or past history of breast cancer; contraindicated in women with undiagnosed genital bleeding.
 - v. Common adverse effects: Vaginal discharge and abnormal pap smear
 - vi. May be stored in refrigerator or at room temperature.
- f. Other hormone products
 - i. Bioidentical hormones: May still have adverse effects similar to those of conjugated/esterified estrogens and synthetic progestins.

- ii. Androgens: Testosterone may help with sexual dysfunction but not vasomotor symptoms; not approved for use.
 - iii. Phytoestrogens (see text that follows for soy isoflavones): Act similarly to estrogen and carry similar contraindications.
 - iv. Megestrol (progestogen; see earlier section on progestogens)
3. Serotonin reuptake inhibitors: Best for vasomotor symptoms in high-risk women for whom HT is not recommended.
 - a. Paroxetine 7.5 mg orally once daily (Brisdelle marketed product; only selective serotonin reuptake inhibitor with indication for vasomotor symptoms)
 - b. Venlafaxine 75 mg orally once daily
 - c. Fluoxetine 20 mg orally once daily
 - d. Paroxetine 20 mg orally once daily
 - e. Sertraline 100 mg orally once daily
 - f. Escitalopram 10–20 mg orally once daily
 - g. Citalopram 10–20 mg orally once daily
 - h. Desvenlafaxine 100–150 mg orally once daily
 4. Natural products: Some data for effectiveness (no U.S. Food and Drug Administration [FDA] indication)
 - a. Soy isoflavones: May still have adverse effects similar to those of conjugated estrogens.
 - b. Evening primrose oil: No solid evidence for use.
 - c. Black cohosh: Some effectiveness for vasomotor symptoms; reports of liver toxicity.
 5. Others: Used for vasomotor symptoms (no FDA indication) (Int J Womens Health 2012;4:305-19)
 - a. Clonidine
 - b. Gabapentin
 - c. Pregabalin
 - d. Acupuncture
 - e. Hypnosis
 - f. Lifestyle changes

Patient Case

Questions 1 and 2 pertain to the following case:

E.L. is a 50-year-old woman with hot flashes and vaginal irritation. She has tried exercise, diet, and antidepressants to help relieve her hot flashes but has been unsuccessful. She is otherwise healthy with no history of cancer and no surgical procedures. She states that her hot flashes are interfering with her daily activities and wants to try HT.

1. When counseling E.L. on the use of HT and explaining the WHI trial, which has been proven to be statistically significant with conjugated estrogen and medroxyprogesterone acetate?
 - A. Increased risk of VTE
 - B. Decreased risk of stroke
 - C. Decreased risk of MI
 - D. Increased risk of fractures
2. Which treatment is best to recommend to E.L.?
 - A. Estrogen patch 0.025 mg (17 β -estradiol); change patch twice weekly.
 - B. Prasterone 6.5 mg vaginal inserts; insert vaginally once daily.
 - C. Conjugated estrogen 0.3 mg/medroxyprogesterone acetate 1.5 mg; take 1 tablet daily.
 - D. Ospemifene 60 mg; take 1 tablet daily.

II. OSTEOPOROSIS

- A. World Health Organization (WHO) Definitions Based on T-scores (T-score indicates that for every standard deviation [SD] below the mean young adult bone mineral density [BMD], fracture risk increases 2-fold)
1. Normal = BMD within 1 SD of the young adult mean.
 2. Low bone mass (osteopenia) = BMD 1–2.5 SD below the young adult mean (often seen as T-score between -1 and -2.5).
 3. Osteoporosis = BMD at least 2.5 SD below the young adult mean (often seen as T-score of less than -2.5).
 4. Severe or established osteoporosis = BMD 2.5 SD below the young adult mean (often seen as T-score less than -2.5) with a fragility fracture
- B. Guidelines were updated by the North American Menopause Society (NAMS) in 2021 and by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) in 2020. Additional guidelines that influence osteoporosis care include the 2012 American College of Obstetricians and Gynecologists (ACOG) Clinical Management of Osteoporosis, the Clinician's Guide to Prevention and Treatment of Osteoporosis by the National Osteoporosis Foundation (NOF) dated 2014, the Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society (ES) Clinical Guideline dated 2019, Osteoporosis in Men and the American College of Physicians 2017 Clinical Guideline, Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians (ACP).
1. Risk factors for osteoporotic fractures
 - a. Female sex
 - b. White race
 - c. Poor nutrition, long-term low-calorie intake
 - d. Early menopause (before age 45 (before age 40 based on AACE/ACE)) or prolonged premenopausal amenorrhea
 - e. Estrogen deficiency
 - f. Drugs: glucocorticoids, heparin, anticonvulsants, excessive levothyroxine, gonadotropin-releasing hormone (GnRH) agonists, lithium, cancer drugs, proton pump inhibitors, sodium glucose-like transporter-2 inhibitors, selective serotonin-reuptake inhibitors
 - g. Low body mass index (BMI) or low weight
 - h. Family history of osteoporosis
 - i. Low calcium and vitamin D intake
 - j. Sedentary lifestyle, decreased mobility
 - k. Cigarette smoking
 - l. Chronic alcohol use
 - m. Dementia
 - n. Impaired eyesight despite adequate correction
 - o. Previous fractures
 - p. History of falls
 - q. Type 1 and Type 2 diabetes
 - r. Inflammatory bowel disease
 - s. Chronic liver disease
 2. Recommendations
 - a. Advise patient to avoid smoking and to consume only moderate amounts of alcohol.
 - b. Encourage regular weight-bearing and muscle-strengthening exercise.
 - c. Encourage adequate intake of calcium (at least 1000 mg/day) and vitamin D (800–1000 international units/day) according to the NOF guidelines, or 600 international units/day for those younger than 70 years and 800 international units/day for 70 years or older according to the Institute of Medicine (IOM).

- d. Assessment
 - i. Dual-energy x-ray absorptiometry (DXA): Gold standard, measures hip or lumbar spine BMD
 - ii. Quantitative computed tomography (QCT): Measures volumetric BMD of lumbar spine
 - iii. Peripheral DXA (pDXA) and peripheral QCT (pQCT): Not appropriate for monitoring
 - iv. Vertebral imaging: Used to identify vertebral fractures because they are often asymptomatic
 - (a) All women 70 years or older and men 80 years or older with BMD T-score of -1.0 or less at spine, total hip, or femoral neck
 - (b) Women 65–69 years and men 70–79 years if BMD T-score is -1.5 or less at spine, total hip, or femoral neck
 - (c) Postmenopausal women or men 50 and older with the following risk factors:
 - (1) Low-trauma fracture as an adult (age 50)
 - (2) Historical height loss of 1.5 inches (4 cm) or more (since peak in adulthood)
 - (3) Prospective height loss of 0.8 inches (2 cm) or more (measured at medical assessments)
 - (4) Recent or ongoing long-term glucocorticoid treatment
 - (d) Follow-up needed only if new back pain or further height loss is documented
 - v. Clinical screening tools
 - (a) Fracture Risk Assessment Tool (FRAX) score items (www.sheffield.ac.uk/FRAX/tool.jsp)
 - (1) Used to estimate fracture risk
 - (2) Most useful to estimate for patients with low BMD of hip
 - (3) Recommended for postmenopausal women and men 50 years or older
 - (4) Useful to determine whether patients with low bone mass (osteopenia) need pharmacologic treatment
 - (5) Not validated for patients on drug therapy for osteoporosis
 - (6) No data to show benefit in fracture reduction based on use for treatment decisions.
 - (b) Other screening tools
 - (1) Simple Calculated Osteoporosis Risk Estimation (SCORE)
 - (2) Osteoporosis Risk Assessment Instrument (ORAI)
 - (3) Osteoporosis Index of Risk (OSIRIS)
 - (4) Osteoporosis Self-Assessment Tool (OST)
- e. Recommended BMD testing
 - i. All women 65 years and older (NAMS, ACOG, AACE/ACE, NOF), men older than 70 (NOF, ES). The USPSTF recently released a statement on osteoporosis screening for the prevention of fractures and confirmed this recommendation for women but stated that evidence was insufficient for weighing the risk-benefit for screening in men (JAMA 2018;319:2521-31).
 - ii. Men 50–69 years of age with previous fractures or risk factors such as delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, or chronic obstructive pulmonary disease; drugs such as glucocorticoids or GnRH agonists; alcohol abuse or smoking; or other causes of secondary osteoporosis (ES)
 - iii. All postmenopausal women with medical causes of bone loss (NAMS)
 - iv. Postmenopausal women younger than 65 years with at least one of the following:
 - (a) Previous fracture after menopause other than skull, facial bone, ankle, finger, or toe; thinness (body weight less than 127 lb [58 kg] or BMI less than 21 kg/m^2); history of hip fracture in a parent; current smoking; rheumatoid arthritis, alcohol intake of 2 units/day or more (1 unit = 12 oz beer, 4 oz wine, 1 oz liquor) (NAMS)
 - (b) With any risk factor listed in section B1 (ACOG)
 - (c) Previous fracture not caused by severe trauma after age 40–45 (AACE/ACE)
 - (d) Thinness (body weight less than 127 lb [58 kg]), family history of spine or hip fracture (AACE)

- (e) Low bone mass (osteopenia) identified radiographically (AACE/ACE)
- (f) Starting or taking long-term systemic glucocorticoids for 3 months or longer (AACE/ACE, NOF)
- (g) USPSTF statement recommends use of a clinical tool for screening (FRAX, SCORE, OST, ORAI, or OSIRIS) in women to determine whether BMD assessment is necessary (JAMA 2018;319:2521-31).

Table 7. 2020 AACE/ACE Criteria for Diagnosis of Osteoporosis in Postmenopausal Women

T-score -2.5 or below (lumbar spine, femoral neck, total proximal femur, or 1/3 radius)
Low-trauma spine or hip fracture (regardless of bone mineral density)
T-score between -1.0 and -2.5 and a fragility fracture (proximal humerus, pelvis, distal forearm)
T-score between -1.0 and -2.5 and high FRAX fracture probability

FRAX = Fracture Risk Assessment Tool.

- f. Initiation of drug therapy (AACE/ACE, NOF, NAMS, ES)
 - i. If hip or spine fracture
 - ii. If BMD T-score is -2.5 or below at spine, hip, or femoral neck
 - iii. If BMD T-score is between -1.0 and -2.5 at the femoral neck or spine and the 10-year probability of hip fracture is 3% or greater, or the 10-year probability of major osteoporosis-related fracture is 20% or greater, according to the FRAX system
- g. Length of drug therapy: American College of Physicians recommends 5 years of pharmacologic therapy for women with osteoporosis, NAMS recommends a bisphosphonate holiday only in those with low fracture risk who no longer meet criteria for therapy.
- h. Recommendations for follow-up on BMD-DXA vary. The 2021 NAMS position statement suggests repeat BMD testing 1–2 years after beginning treatment or when considering a change in therapy. The 2020 AACE/ACE guidelines discuss using bone turnover markers (BTMs) (e.g., propeptide of type 1 collagen [P1NP] for bone formation; C-terminal telopeptide type 1 collagen [CTX] for bone resorption) to assess treatment adherence and efficacy. A recent fracture can cause a transient elevation in BTM. Most recent ACP guidelines recommend against monitoring BMD while on 5-year osteoporosis therapy. Other recommendations suggest follow up on BMD-DXA every 2 years. Some situations may warrant a follow-up BMD sooner than 2 years. The interval may be longer in patients with T-scores in the normal or upper bone mass range who do not have major risk factors.

C. Osteoporosis Treatments

- 1. Bisphosphonates (Table 8)
 - a. Inhibit normal and abnormal bone resorption
 - b. First-line therapy; Ibandronate is considered second-line therapy
 - c. Efficacy: Reduces vertebral and non-vertebral fractures by 30%–50% (see individual agents; exception: Ibandronate reduces only vertebral fractures)
 - d. Adverse events (not dose-dependent)
 - i. Gastrointestinal (GI): Flatulence, acid regurgitation, esophageal ulcer, dysphasia, abdominal distention, gastritis. To reduce the risk of GI adverse effects, those taking oral bisphosphonates should not lie down for 30–60 minutes after taking the dose.
 - ii. Miscellaneous: Headache, musculoskeletal pain, rash
 - iii. Laboratory values: Decreases in serum calcium concentrations; decreases in serum phosphorus concentrations in the first month.

- iv. Osteonecrosis of jaw: Most are associated with dental procedures. Most cases occur in patients with cancer after prolonged therapy. High-dose intravenous administration (usually for cancer-related issues) has a greater risk than oral therapy.
- v. Atypical fractures and esophageal cancer: The FDA is monitoring these adverse drug reactions; for now, the recommendation is to continue use as directed by physician.
- vi. Atrial fibrillation: Possible increased risk of atrial fibrillation but not of stroke or cardiovascular mortality (Chest 2013;144:1311-22). One meta-analysis showed no increased risk of stroke, myocardial infarction, total cardiovascular events or death (PLoS One 2015;10:e0122646).
- e. Drug holidays are controversial; bone density may decrease 5 years after discontinuation of bisphosphonate therapy, but risk of hip fracture stays the same; however, higher risk of vertebral fracture may occur.
 - i. American Society for Bone and Mineral Research recommends that, after 5 years of oral bisphosphonate use or 3 years of intravenous treatment, women be reassessed for risk.
 - ii. Women at a high risk of fractures should continue oral therapy for up to 10 years and up to 6 years with intravenous therapy with intermittent follow-up (AACE/ACE).
 - iii. Women whose fracture risk decreased after 3–5 years of use should stop treatment for 2–3 years (J Bone Miner Res 2016;31:16-35).
- f. Drug-food interactions: Wait at least 30 minutes after taking bisphosphonate before taking any medications, food, or drinks except for water. Exceptions: oral ibandronate (must wait 60 minutes), risedronate sodium, delayed release (must be taken with food.)
- g. Administration considerations
 - i. Alendronate: 10 mg/day or 70 mg/week. Alendronate (daily dose regimen) was shown to decrease vertebral fractures by 47% and hip fractures by 51% (Fracture Intervention Trial [FIT]) in women with previous fractures.
 - ii. Alendronate with vitamin D: 70 mg/week with 2800 international units of vitamin D₃ or 70 mg/week with 5600 international units of vitamin D₃
 - iii. Alendronate 70-mg effervescent tablet/week (Binosto): Dissolve tablet in 4 oz water, wait for about 5 minutes for effervescence to stop, stir for 10 seconds, and drink contents. Has similar recommendations of waiting 30 minutes before eating or drinking and staying upright for 30 minutes after administration.
 - iv. Risedronate: 5 mg/day or 35 mg/week or 150 mg once monthly. Decreases non-vertebral fracture risk by 33%–39% and vertebral fracture by 41%–49%
 - v. Ibandronate: 150 mg once monthly orally, waiting at least 60 minutes before eating, drinking, or taking another drug, or 3 mg intravenously every 3 months. Increases BMD at spine and hip; however, studies show only a decreased risk of vertebral fractures.
 - vi. Zoledronic acid: 5 mg intravenously annually for treatment and every 2 years for prevention (infuse over a minimum of 15 minutes); reduces non-vertebral fracture risk by 25%, hip fracture by 40%, and vertebral fracture risk by 70%. Lack of GI adverse effects; higher risk of atrial fibrillation with zoledronic acid than with placebo (1.3% vs. 0.4%); hypocalcemia may occur; patient must take calcium and vitamin D supplements. Infusion reactions occur, necessitating pretreatment with acetaminophen. Shown to decrease mortality in high-risk patients who have had a hip fracture (only bisphosphonate shown to decrease mortality)

- h. Dose adjustments may be necessary in renal impairment (see Table 8).

Table 8. Bisphosphonates

Drug	Indications	Osteoporosis Dosing and Routes
Alendronate (Fosamax, Binosto) Alendronate + vitamin D ₃ (Fosamax Plus D)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget disease	10 mg PO daily 70 mg PO weekly, 70-mg effervescent tablet PO weekly 70 mg PO weekly + vitamin D ₃ 2800 international units/wk or 5600 international units/wk 5 mg PO daily for prevention 35 mg PO weekly for prevention Not recommended for CrCl < 35 mL/min
Risedronate (Actonel) Risedronate delayed release (Atelvia)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget disease	5 mg PO daily 35 mg PO weekly (delayed release available also) 150 mg PO monthly Not recommended for CrCl < 30 mL/min
Ibandronate (Boniva)	Prevention and treatment of osteoporosis in women	2.5 mg PO daily 150 mg PO monthly 3 mg IV every 3 mo Not recommended for CrCl < 30 mL/min
Zoledronic acid (Reclast)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget disease	5 mg IV yearly 5 mg IV every 2 yr (prevention in women) Not recommended for CrCl < 35 mL/min

BMD = bone mineral density; CrCl = creatinine clearance; IV = intravenously; PO = by mouth

2. Denosumab (Prolia): Approved for postmenopausal women with osteoporosis at high risk of fracture, for increasing bone mass in men with osteoporosis, for treatment of glucocorticoid-induced osteoporosis, and for men and women with bone loss associated with prostate or breast cancer.
 - a. Inhibits osteoclast-mediated bone resorption; monoclonal antibody against receptor activator of nuclear factor κ β ligand (RANKL) (cytokine essential for formation, function, survival of osteoclasts)
 - b. Considered alternative first-line therapy by NAMS, AACE and ACP guidelines.
 - c. Administered as 60 mg subcutaneously every 6 months
 - d. Not contraindicated with renal dysfunction.
 - e. Efficacy
 - i. Increased hip (6%) and spine (9%) BMD
 - ii. Reduced spinal fracture risk by 68%, hip fracture risk by 40%
 - f. Safety issues
 - i. Possible opportunistic infections, skin infections such as cellulitis
 - ii. Hypocalcemia: Patients should take calcium and vitamin D together with denosumab. Those with impaired renal function are more likely to have hypocalcemia.
 - iii. The FDA has Risk Evaluation and Mitigation Strategies (REMS) requirements for this drug (Medication Guide).

3. Calcium

- a. Recommended for all patients with osteoporosis to maintain normal calcium concentrations and to prevent hypocalcemia associated with other drug treatments for osteoporosis
- b. Elemental calcium intake: Avoid doses higher than 2500 mg/day; NOF recommends no more than 1200–1500 mg/day. Higher doses may increase risk of constipation, contribute to kidney stones, and inhibit absorption of zinc or iron (Table 9).
- c. Most common forms: Calcium carbonate (take with food), calcium citrate (take with or without food, may be good option for patients taking antacids or acid-suppressive therapy or for patients with achlorhydria)
- d. Recent systematic reviews and meta-analyses have raised concerns about the potential association between calcium supplements and an increased risk of cardiovascular disease (Nutrients 2021;13:368).

Table 9. Recommended Daily Calcium Intake

Age Group	Recommended Daily Calcium Intake (mg)
19–50 yr: Women 51–70 yr: Men	1000
≥ 51 yr: Women ≥ 71 yr: Men	1200

4. Vitamin D

- a. Recommended for all patients with osteoporosis; promotes calcium reabsorption.
- b. Minimum dose is 800 international units/day for those older than 70 years, 600 international units/day 70 years of age and younger (IOM recommendations 2010); NOF recommendations are 800–1000 international units/day for those 50 and older.
- c. Higher doses of vitamin D may be necessary for those with vitamin D concentrations less than 30 ng/mL.
- d. Goal: 30 ng/mL in adults (NOF), although the IOM states that concentrations of 20 ng/mL may be adequate for most of the population.

5. Selective estrogen receptor modulators

- a. Raloxifene (Evista)
 - i. Indication: Prevention and treatment of osteoporosis in postmenopausal women
 - ii. Mechanism: Selective estrogen receptor modulator
 - (a) Reduction in resorption of bone.
 - (b) Decrease in overall bone turnover.
 - (c) Data suggest estrogen antagonist in uterine and breast tissue.
 - (d) Consider use for primary prevention in women with low BMD and a 5-year risk of developing invasive breast cancer greater than 3% (Ann Intern Med 2013;158:604).
 - iii. Efficacy
 - (a) Reduces the risk of vertebral fractures; (30%–50%); has not been shown to decrease hip fractures.
 - (b) Lowers total cholesterol by 7% and LDL by 11%; does not reduce risk of CHD.
 - iv. Adverse reactions
 - (a) Hot flashes: 6%–25%
 - (b) Leg cramps: 6%
 - (c) VTE: About 1% (hazard ratio 2.4; 95% confidence interval, 1.2–4.5; two- to threefold increased risk compared to placebo)
 - v. Dose: 60 mg/day orally

- vi. Contraindications
 - (a) Pregnancy, nursing, pediatrics
 - (b) History of VTE events; greatest risk of VTE events occurs during first 4 months.
- vii. Drug interactions
 - (a) Bile acid resins decrease raloxifene absorption by 60%.
 - (b) Warfarin: Prothrombin time is decreased by 10%.
 - (c) Thyroid hormones: Separate administration by 12 hours.
- b. Conjugated estrogens and bazedoxifene (Duavee)
 - i. Indication: Prevention of osteoporosis in postmenopausal women
 - ii. Mechanism: Selective estrogen receptor modulator plus estrogen (tissue-selective estrogen complex [TSEC])
 - iii. Efficacy
 - (a) Significantly increased total hip BMD at 24 months by 1.96% compared with placebo in women who had been postmenopausal for 1–5 years and by 1.73% in women who had been postmenopausal for more than 5 years.
 - (b) Significantly increased mean lumbar spine BMD (by 1.51%) compared with placebo at 12 months in women who had been postmenopausal for 1–5 years.
 - iv. Adverse reactions (5% or more)
 - (a) Hot flashes
 - (b) Muscle cramps
 - (c) Throat, neck, and muscle pain
 - (d) Dizziness
 - (e) Nausea and vomiting
 - v. Dose: Conjugated estrogen 0.45 mg and bazedoxifene 20 mg/day orally
 - vi. Contraindications
 - (a) Pregnancy, nursing, pediatrics
 - (b) History of VTE events or coagulopathy
 - (c) Hepatic impairment
 - (d) Similar to estrogen contraindications
 - vii. Drug interactions: Metabolized by cytochrome P450 (CYP) 3A4; inducers or inhibitors of CYP3A4 may affect estrogen concentrations.
- 6. Human parathyroid hormone related peptide analogs
 - a. Teriparatide (Forteo)
 - i. Recombinant human parathyroid hormone regulates bone metabolism, intestinal calcium absorption, and renal tubular calcium and phosphate reabsorption.
 - ii. Indications: Treatment of postmenopausal women with osteoporosis that have a high risk of fracture, increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
 - iii. Efficacy
 - (a) Reserved for treating women at high risk of fracture, including those with very low BMD (T-score lower than –3.0) and a previous vertebral fracture.
 - (b) Decreases vertebral fractures by 65% and non-vertebral fractures by 53%; not shown to decrease hip fractures.
 - iv. Contraindications: Hypercalcemia, bone metastases, disorders that predispose women to bone tumors such as Paget disease, and alkaline phosphatase elevation (unexplained)
 - v. Adverse effects: Nausea, orthostatic hypotension
 - vi. Carcinogenicity: Osteosarcoma in rats; should not be used longer than 2 years.
 - vii. Drug interactions: Increases calcium concentrations and may increase risk of digoxin toxicity.
 - viii. Dosage: 20 mcg/day subcutaneously

- b. Abaloparatide (Tymlos)
 - i. Regulates bone metabolism, intestinal calcium absorption, and renal tubular calcium and phosphate reabsorption.
 - ii. Indication: Treatment of postmenopausal women with osteoporosis that have a high risk of fracture.
 - iii. Efficacy
 - (a) Reserved for treating women at high risk of fracture, including those with very low BMD (T-score lower than -3.0) and a previous vertebral fracture.
 - (b) Decreases vertebral fractures by 86% and non-vertebral fractures 43%; not shown to decrease hip fractures.
 - iv. Contraindications: None
 - v. Precautions (1) Orthostatic hypotension: patient should be instructed to sit or lay down if symptoms occur post dose administration (2) Hyperkalemia: avoid in patients at risk for hypercalcemia (3) Hypercalciuria and urolithiasis: monitor urine calcium if patient experiences symptoms.
 - vi. Adverse effects: Nausea, dizziness, headache, palpitations, hypercalciuria, upper abdominal pain, and vertigo
 - vii. Carcinogenicity: Osteosarcoma in rats; should not be used longer than 2 years.
 - viii. Drug interactions: Increases calcium concentration and may increase risk of digoxin toxicity.
 - ix. Dosage: 80 mcg/day subcutaneously; patients should also take supplemental calcium and vitamin D if dietary intake is not enough.
- 7. Romosozumab-aqqg (Evenity)
 - a. Sclerostin inhibitor, a factor in bone regulation, helps build bone and decreases bone resorption.
 - b. Indication: Treatment of osteoporosis in postmenopausal women who are at high risk of fracture (defined as a history of osteoporotic fracture or several risk factors for fracture) or for those whose other osteoporosis treatments have failed
 - c. Efficacy: In a study of more than 7000 women, romosozumab decreased the absolute risk of new vertebral fracture by 1.3% at 12 months (fracture risk in placebo group 1.8% vs. 0.5% in treatment group, $p \leq 0.001$) and by 1.9% at 24 months (fracture risk in placebo group 2.5% vs. 0.6% in treatment group, $p < 0.001$); increased BMD by 12.7% at lumbar spine, 5.8% at total hip, 5.2% at femoral neck
 - d. Contraindications: Hypocalcemia, sensitivity to romosozumab
 - e. Precautions: Major adverse cardiac events (MI, stroke); hypocalcemia; hypersensitivity (e.g., allergic reaction, angioedema); osteonecrosis of the jaw and atypical femoral fracture
 - i. Should not be initiated in patients who have had an MI or stroke within the previous year.
 - ii. Consider risk-benefit of therapy in patients with other CV risk factors.
 - f. Adverse effects: Joint pain and headache
 - g. Carcinogenicity: None reported
 - h. Dosages: Dose of 210 mg injected subcutaneously once a month for 12 months. May be injected in abdomen, thighs, or upper arm. Need to have 2 injections to achieve the dose of 210 mg (give one after the other). Patients should also take supplemental calcium and vitamin D if dietary intake is not enough. No dosage adjustments for renal impairment; however, in patients receiving dialysis or who have a creatinine clearance (CrCl) less than 29 mL/minute, may increase the risk of hypocalcemia
- 8. Calcitonin-salmon (Miacalcin)
 - a. Inhibition of bone resorption
 - b. Not a first-line drug; useful for bone pain caused by vertebral compression fractures, no longer used frequently for osteoporosis therapy.
 - c. Efficacy: Nasal calcitonin reduces the incidence of new vertebral fractures by 36%.

- d. Adverse effects
 - i. Nasal (10%–12%): Rhinitis, epistaxis, irritation, nasal sores, dryness, tenderness
 - ii. Other (3%–5%): Backache, arthralgia, headache
- e. Drug interactions: None
- f. Dosage: 200 international units/day in one nostril, alternating nostrils daily
- g. FDA labeling changes regarding safety in 2014: Malignancies reported to be higher in those treated with calcitonin than in those treated with placebo. Benefits for patient should be discussed with patient and carefully considered.
- 9. Menopausal estrogen therapy or menopausal estrogen and progestogen therapy; (see Hormone Therapy and Menopause section earlier)
- 10. Lifestyle modifications
 - a. Weight-bearing exercise (e.g.; walking, tai chi, dancing, and tennis); recommend 30–40 minutes per session most days of the week.
 - b. Smoking cessation: Smokers tend to have lower BMD scores than nonsmokers and may reach menopause earlier.
 - c. Limiting alcohol intake: Affects fall risk; 2 or more units of alcohol per day associated with 20% of falls at home, according to one study. No more than 2 units/day or 7 units/week is recommended.
 - d. Fall prevention

Table 10. Postmenopausal Osteoporosis Treatment

High Risk/No Prior Fractures			
First Line	Alternative First Line	Increasing or Stable BMD and No Fractures	Progression of Bone Loss or Recurrent Fractures
Alendronate, denosumab, risedronate, zoledronate	Ibandronate, raloxifene	Drug holiday (after 5 yr of PO or 3 yr of IV therapy) Resume therapy with a fracture, BMD declines, BTM rises to pretreatment value	Assess adherence Change to injectable antiresorptive (if on PO) If on injectable or at very high risk, change to abaloparatide, romosozumab, or teriparatide
Very High Risk/Prior Fractures			
First Line			Alternative First Line
Denosumab – continue until no longer high risk; transition to another antiresorptive agent Romosozumab × 1 yr – sequential therapy with PO or injectable antiresorptive agent Abaloparatide or teriparatide × 2 yr – sequential therapy with PO or injectable antiresorptive agent Zoledronate × 6 yr (if stable) – if progressive bone loss or recurrent fractures, change to abaloparatide, teriparatide, or romosozumab			Alendronate, risedronate

BMD = bone mineral density; BTM = bone turnover marker.

Patient Case

Questions 3 and 4 pertain to the following case:

R.K. is a 71-year-old woman (height 63 inches, weight 64 kg) with a history of rheumatoid arthritis who smokes ½ pack/day. She is lactose intolerant and has minimal intake of dairy products. She takes calcium 1200 mg orally per day in divided doses and vitamin D 600 international units/day orally. Her calculated CrCl is 60–70 mL/minute. Her BMD T-score is -2.6 at the hip and -2.1 at the spine. Her FRAX score indicates she has a 10-year probability of a major osteoporotic fracture of 22% and a 10-year probability of a hip fracture of 11%.

3. Which statement best describes the correct diagnosis for R.K.?
 - A. She has normal BMD of the spine.
 - B. She has low bone mass (osteopenia) of the hip.
 - C. She has osteoporosis of the hip.
 - D. She has severe osteoporosis of the spine.
4. Which is the best therapy for R.K.?
 - A. No further treatment is needed; continue calcium 1200 mg/vitamin D 600 international units/day orally.
 - B. Give abaloparatide 80 mcg subcutaneously daily, and continue calcium 1200 mg/vitamin D 600 international units/day orally.
 - C. Give romosozumab 210 mg subcutaneously every month, continue calcium 1200 mg/day orally, and increase vitamin D to 800 international units/day orally.
 - D. Give risedronate 35 mg orally every week; continue calcium 1200 mg orally per day, and increase vitamin D to 800 international units/day orally.

III. DRUGS IN PREGNANCY

- A. Definitions and Overview
 1. Teratogen: Drug or environmental agent with the potential to cause abnormal fetal growth and development
 2. Teratogenicity: Capability of producing congenital abnormalities, major or minor malformations
- B. Causes of Defects
 1. Genetic predisposition 25%
 2. Drug 2%–3%
 3. Unknown 72%–73%
- C. Factors That Influence Risk of Medication Use in Pregnancy
 1. Genotypes of mother and fetus
 2. Embryonic stage at exposure
 3. Medication dose
 4. Simultaneous exposure to other drugs that may increase or decrease medication concentrations

5. Timing of exposure
 - a. 1 month before conception: Folic acid 0.4 mg or more taken daily to prevent neural tube defects
 - b. Around time of conception and implantation
 - c. First 12–15 days after conception: If one cell is damaged, another can assume its function.
 - d. First 3 months: Physical malformations
 - e. Throughout pregnancy: Functional and behavioral defects because brain development occurs throughout pregnancy.
 6. Factors for placental transport
 - a. Molecular weight of drug less than 400–600 Da crosses placenta; most drugs weigh 250–400 Da.
 - b. Degree of protein binding; lower in fetus, so more free-drug concentration.
 - c. Maternal and fetal blood flow usually equivalent; simple diffusion allows fetal drug concentration to be 50%–100% of maternal.
 - d. Metabolic activity of the placenta; excretion of medications by the fetus occurs in liver and placenta.
- D. Risk Factor Categories
1. In 1979, the FDA introduced risk categories for drugs used during pregnancy.
 2. The previous FDA pregnancy risk categories appear in Box 1.

Box 1. Previous FDA Pregnancy Risk Categories

A: Controlled studies of women fail to show risk.
B: Animal studies indicate no risk, or animal studies show a risk that has not been shown in human studies.
C: No available studies of women or animals, or animal studies have shown a risk.
D: Positive evidence of fetal risk.
X: Definite fetal risk in animals or women.

3. The FDA decided current pregnancy risk categories were inadequate; therefore, in 2008 the FDA recommended a new labeling system that became effective June 30, 2015 that includes the following:
 - a. Pregnancy (includes labor and delivery)
 - i. Fetal risk summary
 - ii. Clinical considerations
 - iii. Data section
 - iv. Information for exposure registries
 - b. Lactation
 - c. Females and males of reproductive potential
- E. Factors to Consider When Initiating Medications in Pregnant Women (Boxes 2, 3, 4, and 5)
1. Risk-benefit ratio
 2. Is drug necessary?
 3. Most effective agent with least risk
 4. Lowest effective dosage for shortest possible duration
 5. Health of mother without drug

Box 2. Selected Known Teratogens

Alcohol	Mercury
Androgens	Methimazole
Angiotensin-converting enzyme inhibitors	Methotrexate
Angiotensin II receptor blockers	Paroxetine
Anticonvulsants	Penicillamine
Antineoplastics	Statins
Cocaine	Tetracyclines
Diethylstilbestrol	Thalidomide
Fluconazole (high doses)	Vitamin A (higher than recommended daily doses)
Iodides	Warfarin
Isotretinoin	
Lead	
Lithium	

Box 3. Examples of Drugs Used in Pregnancy (if benefit outweighs risk)

Acetaminophen
Cephalosporins
Cetirizine
Erythromycin
Penicillin
Pyridoxine/doxylamine

Box 4. Some Drugs with Known Pregnancy Risks: Should Be Used with Caution

Aminoglycosides	Diuretics
Antithyroid drugs	Isoniazid
Aspirin	Narcotic analgesics (chronic)
Barbiturates	Nicotine
Benzodiazepines	NSAIDs
Caffeine	Oral hypoglycemics
Chloramphenicol	β-Blockers

NSAIDs = nonsteroidal anti-inflammatory drugs

Box 5. Types of Adverse Effects After Fetal Drug Exposure

Cancer	Renal dysfunction
Developmental delay or deficiency	Seizures
Fetal death	Sexual or reproductive dysfunction
Growth retardation	Teratogenic abnormalities
Hematologic abnormalities	Thyroid dysfunction
Low birth weight for gestational age	Withdrawal
Metabolic abnormalities	

F. Resources for Medication Use During Pregnancy

1. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Philadelphia: Wolters Kluwer, 2021.
 - a. Available as a textbook or online by subscription to Facts & Comparisons eAnswers online and Lexi-Comp.
 - b. Provides information about medication use during pregnancy and lactation.
2. TERIS (Teratogen Information System, <http://depts.washington.edu/terisdb/>) and Shepard's Database
 - a. Available on its own by subscription or by a subscription to Micromedex Solutions.
 - b. Provides access to the Clinical Teratology Web (<http://depts.washington.edu/terisdb/terisweb/index.html>) and has a list of several textbook references and websites not all listed here.
3. Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians. Bethesda, MD: American Society of Health-System Pharmacists, 2009.
 - a. Available as a textbook.
 - b. Provides information on chronic disease management in pregnancy.
4. Organization of Teratology Information Specialists (OTIS): MotherToBaby (<http://mothertobaby.org/>)
 - a. Available online by subscription.
 - b. Has some resources available to public and providers such as information sheets.
 - c. Free hotline for questions (866-626-6847) or e-mail an expert.
5. Micromedex Solutions: REPROTEXT and REPROTOX
 - a. Available by purchase.
 - b. Provides information about pregnancy, teratogenicity, and lactation and medication use.

IV. DRUGS IN LACTATION**A. Drugs That Decrease Milk Supply (Box 6)****Box 6. Selected Drugs That Decrease Milk Supply**

Androgens	Monoamine oxidase inhibitors (MAOIs)
Bromocriptine	Nicotine
Ergot alkaloids	Pyridoxine
Estrogen	Sympathomimetics
Levodopa	

B. Drugs That Increase Milk Production (Galactagogues) (Box 7)**Box 7. Selected Drugs That Increase Milk Production (Galactagogues) (may or may not be safe in breastfeeding)**

Amoxapine	Methyldopa
Antipsychotics	Metoclopramide
Cimetidine	Reserpine

C. Ways to Minimize Effects of Drugs During Breastfeeding

1. Choose drugs with short half-lives.
2. Administer drug immediately after a feeding or before a long sleep period.
3. Consider whether the drug is given to neonates.
4. Consider age and health status of the infant (e.g., concomitant medical conditions, preterm birth).
5. Short-term drug: Mother can pump and discard milk ("pump and dump").

D. Safe and Unsafe Drugs in Breastfeeding (Boxes 8 and 9)**Box 8. Some Drugs Contraindicated in Breastfeeding According to the American Academy of Pediatrics**

Amphetamines	Pain medications
Antineoplastics	(common ones include
Benzodiazepines	oxycodone, pentazocine,
Bromocriptine	and meperidine)
Cocaine	Yohimbe
Drugs of abuse	Herbs that lack safety data
Ergotamine	(chamomile, black cohosh,
Kava	blue cohosh, chaste tree,
Lithium	echinacea, ginseng, ginkgo,
Nicotine	St. John's wort, valerian)

Box 9. Relatively Safe Agents During Lactation

Analgesics (ibuprofen, acetaminophen) Antibiotics (penicillins, cephalosporins, erythromycins) Caffeine (in moderation [1 or 2 cups/day]) Insulin
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E. Specific Resources for Drug Information Regarding Lactation

1. LactMed (<http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>)
 - a. Available through the U.S. National Library of Medicine.
 - b. Available without purchase or subscription, although specific database is being phased out with information incorporated in other databases.
 - c. Provides information about safety of medication use during lactation and provides alternative recommendations.
2. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Philadelphia: Wolters Kluwer, 2021.
 - a. Available as a textbook or by subscription to Facts & Comparisons eAnswers online.
 - b. Provides information about medication use during pregnancy and lactation.
3. Hale T. Medications and Mothers' Milk
 - a. Available by purchase; online site: www.halesmeds.com
 - b. Provides information on medication use in lactation with a scoring system of safety.
 - i. L1: Safest. Drug has been taken by many breastfeeding mothers with no observed increase in adverse effects in the infant
 - ii. L2: Safer. Drug has been studied in a limited number of breastfeeding women with no increase in adverse effects in the infant
 - iii. L3: Moderately safe. No controlled studies in breastfeeding women; however, adverse effects in the infant are possible
 - iv. L4: Possibly hazardous. Positive evidence of risk to a breastfed infant or to breast milk production
 - v. L5: Contraindicated. Studies of breastfeeding mothers have shown that there is risk to the infant, or there is a high risk of causing significant harm to the infant.
4. Micromedex solutions: REPROTEXT and REPROTOX
 - a. Available by purchase.
 - b. Provides information about pregnancy, teratogenicity, and lactation and medication use.
5. Organization of Teratology Information Specialists OTIS: MotherToBaby (<http://mothertobaby.org/>)
 - a. Available online by subscription.
 - b. Has some resources available to public and providers such as information sheets.
 - c. Free hotline for questions (866-626-6847) or e-mail an expert.

V. COMPLICATIONS IN PREGNANCY

A. Conditions in Pregnancy

1. Morning sickness
2. Heartburn
3. Constipation
4. Hemorrhoids
5. Headache
6. Coagulation disorders
7. Gestational diabetes mellitus
8. Pregnancy-induced hypertension
9. Preterm labor
10. Induction of labor

B. Morning Sickness

1. Nausea and vomiting associated with pregnancy
2. Usually during first trimester, but can last throughout pregnancy.
3. Usually occurs upon rising and diminishes as day progresses
4. Cause: Unknown, although various theories have been proposed
5. Hyperemesis gravidarum: Severe nausea and vomiting lead to dehydration and malnutrition.
6. Nonmedical treatment: First line
 - a. Eat saltine crackers.
 - b. Keep stomach from becoming completely empty.
 - c. Eat small, dry meals.
 - d. Avoid spicy and odorous foods.
7. Symptomatic treatment
 - a. Doxylamine and pyridoxine (Diclegis: doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg; dosage 2 tablets orally at bedtime daily. Maximum dosage: One tablet in the morning, one mid-afternoon, and two at bedtime. Bonjesta: doxylamine succinate extended release 20 mg and pyridoxine hydrochloride 20 mg; maximum dosage: 1 tablet in the morning, 1 tablet at bedtime) – considered first-line treatment after nonpharmacologic treatment.
 - i. Diclegis and Bonjesta are the only FDA-approved medications for nausea and vomiting in pregnancy. Diclegis is a delayed-release formulation and Bonjesta is an extended-release formulation. Because of the cost or insurance coverage, physicians and patients have attempted off-label use of over-the-counter 12.5 mg doxylamine plus 10–25 mg pyridoxine; however, the efficacy of treatment appears diminished.
 - b. Pyridoxine: Considered first-line treatment after nonpharmacologic treatment (with or without doxylamine).
 - c. Dimenhydrinate
 - d. Diphenhydramine
 - e. Ondansetron: Only if nausea and vomiting not controlled with first-line agents; possibility of a slight increase in cardiac birth defects, mainly septal defects, according to two studies; best to avoid, especially during first 10 weeks of gestation, if possible (Obstet Gynecol 2018;131:e15-e30).
 - f. Metoclopramide – Only if nausea and vomiting not controlled with first-line agents.
 - g. Phenothiazines – Only if nausea and vomiting not controlled with first-line agents.

C. Heartburn

1. Occurs in latter half of pregnancy.
2. Cause: Enlarged uterus puts pressure on stomach, and esophageal sphincter relaxes.

3. Nonmedical treatment
 - a. Smaller, more frequent meals
 - b. Avoid food and liquids 3 hours before bed.
 - c. Elevate head of bed with blocks.
 4. Symptomatic relief
 - a. Antacids
 - i. Magnesium hydroxide
 - ii. Aluminum hydroxide (overuse may lead to neurotoxicity)
 - iii. Calcium carbonate
 - b. Sucralfate: Not absorbed in GI tract.
 - c. Second line: Famotidine proton pump inhibitors
- D. Constipation
1. Cause: Decreased peristalsis
 2. Nonmedical treatment
 - a. Increase high-fiber foods.
 - b. Increase fluid intake to eight 8-oz glasses of water a day.
 - c. Increase exercise.
 3. Symptomatic relief
 - a. Stool softeners (check that prenatal vitamin does not already contain docusate)
 - b. Bulk laxatives: Not absorbed.
 - c. Stimulants: Not recommended as first-line therapy.
 - d. Avoid mineral oil: Impairs vitamin K absorption and could cause hypoprothrombinemia.
- E. Hemorrhoids
1. Caused by constipation and increased venous pressure below uterus
 2. Correct constipation with stool softeners, appropriate hydration, and dietary fiber.
 3. Sitz baths
 4. Avoid topical anesthetics and steroids, not well studied. If medication therapy is required, topical anesthetics and steroids may be used short-term under a physician's direction (Can Fam Physician 2008;54:189-90).
- F. Headache
1. Cause: Hormone fluctuations
 2. Therapy
 - a. Rest, ice packs
 - b. Acetaminophen
 3. Drugs to avoid
 - a. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)
 - b. Triptans, ergotamine
- G. Coagulation Disorders
1. Anticoagulation necessary
 - a. History of VTE
 - b. Prosthetic heart valve
 - c. Deficiencies of clotting factors
 - d. Antiphospholipid antibodies
 2. Therapy
 - a. Avoid warfarin.

- b. Heparin or low-molecular-weight heparin (monitor for osteoporosis if heparin is used long term)
- c. Low-molecular-weight heparin preferred to heparin (Obstet Gynecol 2018;132:e18-34; Chest 2012; 141: e691S-736S).
- d. Dosing
 - i. Prophylactic
 - (a) Enoxaparin 40 mg subcutaneously daily
 - (b) Dalteparin 5000 units subcutaneously daily
 - (c) Tinzaparin 4500 units subcutaneously daily
 - (d) Heparin 5000–7500 units subcutaneously every 12 hours for first trimester, 7500–10,000 units subcutaneously every 12 hours for second trimester, and 10,000 units subcutaneously every 12 hours for third trimester unless activated partial thromboplastin time (aPTT) is elevated
 - ii. Therapeutic
 - (a) Enoxaparin 1 mg/kg subcutaneously every 12 hours
 - (b) Dalteparin 200 units/kg subcutaneously daily or 100 units/kg subcutaneously every 12 hours
 - (c) Tinzaparin 175 units/kg subcutaneously daily
 - (d) Heparin 10,000 units subcutaneously every 12 hours with target activated partial thromboplastin time (aPTT) range (1.5–2.5) 6 hours after injection or adjusted-dose unfractionated heparin subcutaneously every 12 hours, with mid-interval aPTT target of 2 times the control
- e. May consider switching LMWH to heparin at 36 weeks of gestation to permit induction of anesthesia during labor and delivery because of the lower risk of an epidural or spinal hematoma with regional anesthesia and a greater ease of heparin reversal by protamine sulfate.
- f. Prophylaxis with LMWH or UFH should be discontinued 12 hours before cesarean section or vaginal delivery. Therapeutic doses should be discontinued 24 hours before cesarean section or vaginal delivery.
- g. Consider timing of catheter placement for anesthesia as well.
- h. Continue anticoagulation for 6 weeks postpartum.
- i. For women experiencing heparin-induced thrombocytopenia, consider fondaparinux; limited data and crosses placenta.

H. Gestational Diabetes Mellitus (GDM)

1. Diagnostic approaches (Table 11)

Table 11. GDM Diagnostic Approaches

Approach	Criteria	Organizations	Comments
Two-step approach	50-g oral glucose test Plasma measured 1 hr after If ≥ 130 mg/dL or 140 mg/dL, give 100-g, 3-hr glucose test	ACOG, NIH	Given at 24–28 weeks' gestation; may be earlier in those with risk factors
One-step approach	Obtain A1C at initial prenatal visit; if elevated, patient has overt diabetes; no further testing 75-g oral glucose test Plasma measured at fasting, 1 and 2 hr	IADPSG, ADA	Given at 24–28 weeks' gestation

ADA = American Diabetes Association; GDM = gestational diabetes mellitus; IADPSG = International Association of the Diabetes and Pregnancy Study Groups; NIH = National Institutes of Health

2. Diagnostic criteria

- a. Two-step approach: 100-g 3-hour oral glucose test (OGTT) used after initial screening; if greater than or equal to values at two or more points, consider GDM (Table 12).

Table 12. 3-Hr Oral Glucose Test Reference Range

Time	Plasma Glucose Concentration (mg/dL) Carpenter-Coustan	Plasma Glucose Concentration (mg/dL) National Diabetes Data Group
Fasting	95	105
1 hr	180	190
2 hr	155	165
3 hr	140	145

- b. One-step approach: Based on 75-g 2-hour oral glucose test (Table 13)

Table 13. Glucose Reference Range for 2-Hr Oral Glucose Test

Time	Plasma Glucose
Fasting	92 mg/dL
1 hr	≥ 180 mg/dL
2 hr	≥ 153 mg/dL

3. Insulin (first line): None of the currently available human insulin preparations have been shown to cross the placenta. No specific insulin regimen has been recommended over another for treatment of GDM in pregnancy.
 4. Sulfonylureas (glyburide) in patients unable to use insulin injections; however, recent evidence shows they may be inferior to insulin and metformin because of increased risk of hypoglycemia and macrosomia in the infant. In addition, they have been shown to cross the placenta (Diabetes Care 2019;42(suppl 1):S165-S172). ACOG recommends against use as first-line therapy stating that glyburide does not yield similar outcomes as insulin (Obstet Gynecol 2018;131:e49-64).
 5. Metformin may have advantage over glyburide; studies are ongoing, (not first line), associated with some risk of premature birth and also may cross the placenta; may emerge as possible treatment, according to ACOG (Diabetes Care 2019;42(suppl 1):S165-S172; Obstet Gynecol 2018;131:e49-64).
 6. Insulin is considered the preferred treatment when pharmacologic treatment of GDM is indicated. In women who decline insulin or who the obstetrician believes that are unable to safely administer insulin, metformin is a reasonable alternative. Previous meta-analyses have noted increased risks of macrosomia and hypoglycemia with glyburide compared with insulin. Observational studies have reported higher rates of preeclampsia, hyperbilirubinemia, and stillbirth with the use of glyburide as compared with insulin (BMJ 2015;350:h102. Am J Obstet Gynecol 2005;193:118-24).
- I. Pregnancy-Induced Hypertension: Hypertension occurring after 20 weeks' gestation
1. Gestational hypertension: 140/90 mm Hg or more, occurring at least 4 hours apart on two different occasions in women with previously normal blood pressure without proteinuria or pathologic edema
 2. Preeclampsia: Hypertension plus proteinuria (300 mg/dL or more every 24 hours, or protein/creatinine ratio of 3.0 mg/dL or more, or dipstick reading of 2+), any other severe features of preeclampsia such as systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 110 mm Hg at least 4 hours apart and on two occasions (unless antihypertensive treatment was started before this time), thrombocytopenia (platelet count less than 100,000/mm³), impaired liver function (increased levels of liver function enzymes to twice normal or severe right upper quadrant pain or epigastric pain refractory to medication and not accounted for by other diagnoses), new development of renal

- insufficiency (serum creatinine greater than 1.1 mg/dL or a doubling of the serum creatinine without evidence of other renal disease), pulmonary edema, new development of headache that does not respond to therapy and has no known cause, or visual changes (ACOG Chronic Hypertension in Pregnancy. *Obstet Gynecol* 2019;133:e26-e50; ACOG Gestational Hypertension and Preeclampsia. *Obstet Gynecol* 2019;133:e1-e25).
3. Eclampsia: Includes the features of preeclampsia with the addition of tonic-clonic seizures
 4. Chronic hypertension: Preexisting hypertension before 20 weeks' gestation
 5. Chronic hypertension with superimposed preeclampsia: New-onset proteinuria after 20 weeks, sudden 2- to 3-fold increase in proteinuria, sudden increase in blood pressure, increased aspartate transaminase–alanine transaminase, thrombocytopenia
 6. Prevention: Women at high risk of preeclampsia development may take aspirin 81–162 mg beginning in late first trimester; a study showed lower incidence of preeclampsia development in women who were administered 150 mg of aspirin from 11 to 14 weeks of gestation to 36 weeks. For women at high risk of preeclampsia, low-dose aspirin should be initiated between 12–28 weeks gestation (optimally before 16 weeks) and continued daily until delivery.
 7. Risk of preeclampsia and aspirin use
 - a. Recommend low-dose aspirin if the patient has one or more of these high-risk factors (history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or 2 diabetes, renal disease, or autoimmune disease)
 - b. Consider low-dose aspirin if the patient has more than one of these moderate-risk factors. (nulliparity, BMI greater than 30 kg/m², family history of preeclampsia in mother or sister, sociodemographic characteristics [Black/African American, low socioeconomic status], older than 35 years, personal history of adverse pregnancy outcomes, more than a 10-year pregnancy interval)
 - c. No aspirin needed if has had a previously uncomplicated full-term pregnancy (*Obstet Gynecol* 2019;133:e1-e25; *NEJM* 2017;377:613-22).
 8. Treatment
 - a. Delivery if at term
 - b. If not at term, get bed rest and monitor blood pressure.
 - c. Severe preeclamptic, parenteral magnesium sulfate to prevent seizures
 - d. Labetalol (oral), nifedipine (oral, extended release) are first-line therapies.
 - e. Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period: Labetalol (intravenous), hydralazine (intravenous), nifedipine (oral, immediate release; concern for serious adverse effects when used simultaneously with magnesium)
 - f. Medications to avoid: Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists
- J. Preterm Labor
1. Definitions
 - a. Term labor: Weeks 37–40
 - b. Preterm labor: Uterine contractions with cervical changes before week 37
 2. Nonpharmacologic treatment
 - a. Inhibition of labor not usually tried before week 20.
 - b. Bed rest, hydration, and sedation
 3. Prophylaxis at 16–36 weeks for patients with a history of preterm labor: 17-hydroxyprogesterone caproate 250 mg intramuscularly every week
 4. Tocolytic drugs (inhibit uterine contractions), especially if cervix dilated less than 4 cm and membranes intact; short term use only
 - a. β -Agonists
 - i. Terbutaline: Often used (unlabeled) intravenously, subcutaneously

- ii. Adverse effects: Hypotension, tachycardia, hypokalemia, tremor, nervousness, angina, headache, hypoglycemia in patients with diabetes mellitus
- iii. FDA warning for intravenous use beyond 48 hours because of severe adverse effects in the mother such as elevated heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Warning also against use of oral terbutaline for preterm labor because of lack of efficacy.
- b. Magnesium sulfate
 - i. Inhibits uterine activity by antagonism of calcium.
 - ii. Anticonvulsant in eclampsia.
 - iii. Serum magnesium concentrations 5–8 mEq/L
 - iv. May be drug of choice in patients with diabetes.
- c. Prostaglandin synthetase inhibitors (NSAIDs)
 - i. Prostaglandins are in amniotic fluid during labor and delivery but not during pregnancy.
 - ii. Indomethacin: Oral or rectal
 - iii. Adverse effects: Premature closure of ductus arteriosus, necrotizing enterocolitis, intracranial hemorrhage, renal dysfunction
 - iv. Limit use to 72 hours.
- d. Calcium channel blockers
 - i. Calcium necessary for muscle contraction; limit use to 48 hours, should be used with caution in combination with magnesium sulfate due to a risk of reduced heart rate, contractility, and left ventricular systolic pressure.
 - ii. Nifedipine: Typically used; use caution when administered near administration of magnesium, may result in hypotension.
 - iii. Verapamil: Large doses needed that mother usually cannot tolerate.

K. Induction of Labor

- 1. Induction indicated when:
 - a. Severe maternal infection
 - b. Uterine bleeding
 - c. Preeclampsia or eclampsia
 - d. Diabetes mellitus
 - e. Macrosomia
 - f. Maternal renal insufficiency
 - g. Premature rupture of membranes after week 36
 - h. Evidence of placental insufficiency
 - i. Postdatism (more than 42 weeks)
- 2. Inducing agents
 - a. Oxytocin
 - i. Drug of choice for labor induction
 - ii. Intravenous administration
 - iii. Adverse effects: Uterine rupture, uteroplacental hypoperfusion, fetal distress from hypoxia
 - b. Ergot alkaloids
 - i. Not used to induce labor at term or late in pregnancy.
 - ii. Violent, sustained uterine contractions
 - iii. Decrease postpartum or postabortion bleeding
 - iv. Oral and parenteral
 - c. Prostaglandins: Used primarily for cervical ripening
 - i. Dinoprostone also known as PGE₂ (prostaglandin E₂)
 - (a) Vaginal gel or insert, sometimes compounded suppositories

- (b) Applied to cervix
 - (c) Adverse effects: Headache, nausea, vomiting, diarrhea, abdominal pain, and uterine hyperstimulation
- ii. Misoprostol (off-label use), also known as PGE₁ (prostaglandin E₁)
 - (a) Available orally and vaginally
 - (b) Adverse effects: Headache, nausea, vomiting, diarrhea, abdominal pain, and uterine hyperstimulation

Patient Case

5. S.E. is a 28-year-old woman who would like to get pregnant soon. Her medical history includes hypertension and allergies. Her medications include lisinopril, nasal saline spray, and folic acid. Which option is best to treat her hypertension while she is pregnant or trying to conceive?
- A. Continue lisinopril and add hydrochlorothiazide.
 - B. Discontinue lisinopril and all other medications.
 - C. Discontinue lisinopril and start labetalol.
 - D. Continue lisinopril and add atenolol.

VI. OVERVIEW OF CONTRACEPTION**A. Epidemiology**

- 1. About 45% of pregnancies are unintended in the United States, with about 42% of those resulting in abortions (according to 2011 data, N Engl J Med 2016;374:843-52).
- 2. Among female contraceptive users in 2016, 21% were using pills and 13% were using an intrauterine device (IUD) (<https://www.guttmacher.org/fact-sheet/contraceptive-method-use-united-states>).

B. Physiology Review: Menstrual Cycle

- 1. Follicular phase: GnRH stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH); FSH stimulates estradiol secretion and stimulates follicles to develop; one in particular will become the dominant follicle; occurs in first half of cycle; later in follicular phase; LH causes an increase in androgen values.
- 2. Ovulation: Typically occurs midcycle; mature follicle ruptures; a surge in LH occurs just before ovulation.
- 3. Luteal phase: Progesterone is the more dominant hormone in the second half of cycle.
- 4. Menses: Hormones have decreased, and withdrawal bleeding occurs if a woman does not become pregnant.

C. Factors in Selecting Contraception

- 1. Effectiveness
 - a. Theoretical: Method failure if patient uses method perfectly (e.g., combined oral contraceptive [pills] [COCs] have 99% theoretical effectiveness in preventing pregnancy)
 - b. Actual: Combines method failure plus patient failure (e.g., COCs have 93% actual effectiveness when average patient use is considered). Sometimes referred to as “typical use” rates.
- 2. Importance of not being pregnant
- 3. Likelihood and ability to adhere
- 4. Frequency of intercourse: Frequent versus infrequent
- 5. Age may affect adherence or adverse effect risks.
- 6. Cost and ability to pay

7. Adverse effects
8. Perceptions, misperceptions, risk-benefit
9. Concomitant drug use
10. Health status and habits
11. Patient preference
12. Cultural preferences
13. Religious influences

D. Methods of Birth Control

1. Abstinence
2. Male or female sterilization
3. Natural family planning
4. Spermicides
5. Barrier methods
 - a. Diaphragm or cervical cap
 - b. Condom
 - c. Female condom
 - d. Sponge
6. Hormonal contraception
 - a. Combined contraceptives
 - i. Combined oral contraceptive (COC) pills
 - ii. Transdermal patch
 - iii. Vaginal ring
 - b. Progestin-only
 - i. Progestin-only pill (POP or minipill)
 - ii. Progestin-only injectable
 - iii. Implanted rod
7. Intrauterine device (IUD) or intrauterine system (IUS)
 - a. Copper IUD
 - b. Progestin-containing IUD or IUS
8. Lactic acid, citric acid, and potassium bitartrate vaginal gel (PHEXXI)
9. Emergency contraception

VII. COMBINED HORMONAL CONTRACEPTIVES, CONTAINING BOTH AN ESTROGEN AND A PROGESTIN HORMONE

A. Indications

1. FDA label approved
 - a. Prevent pregnancy
 - b. Acne (Estrostep Fe, Ortho Tri-Cyclen, YAZ, Beyaz)
 - c. Premenstrual dysphoric disorder (YAZ, Beyaz)
2. Off-label use
 - a. Hirsutism
 - b. Cycle control
 - c. Headaches
 - d. Premenstrual syndrome
 - e. Iron-deficiency anemia
 - f. Relief of menstrual cramps

B. Components**1. Estrogen**

- a. Type of estrogens available in products in the United States
 - i. Ethinyl estradiol (in almost all products), estradiol valerate (Natazia only), estetrol (Nexstellis only)
 - ii. Mestranol (not used often)
- b. Pharmacologic actions of estrogen in contraceptives
 - i. Feeds back to the pituitary, inhibiting FSH and ovulation.
 - ii. Increases aldosterone concentrations, results in increased sodium and water retention.
 - iii. Increases sex hormone-binding globulin, which is produced in the liver and binds free androgens; this may result in clearing up hormone-mediated acne and unwanted facial hair or hirsutism in women.
- c. Adverse effects attributed to estrogen
 - i. Nausea, vomiting
 - ii. Bloating, edema
 - iii. Irritability
 - iv. Cyclic weight gain
 - v. Cyclic headache
 - vi. Hypertension
 - vii. Breast fullness, tenderness

2. Progestin

- a. Types of progestins available in products in the United States
 - i. Norethindrone
 - ii. Norethindrone acetate
 - iii. Ethynodiol diacetate
 - iv. Norgestrel
 - v. Levonorgestrel
 - vi. Desogestrel
 - vii. Norgestimate
 - viii. Etonogestrel
 - ix. Drospirenone
 - x. Dienogest
 - xi. Segesterone acetate
- b. Pharmacologic actions of progestins in contraceptives
 - i. Feeds back to pituitary and helps inhibit ovulation.
 - ii. Causes endometrial atrophy (thinning of uterus lining).
 - iii. Thickens cervical mucus (inhibits sperm from traveling).
- c. Adverse effects caused by progestin
 - i. Headaches
 - ii. Increased appetite
 - iii. Increased weight gain
 - iv. Depression, fatigue
 - v. Changes in libido
 - vi. Androgenic adverse effects
 - (a) Hair loss, hirsutism
 - (b) Acne, oily skin

C. Contraindications for Combined Hormonal Contraceptives

1. The Centers for Disease Control and Prevention (CDC) medical eligibility criteria are separated into four categories:
 - a. Category 1: A condition for which there is no restriction on the use of contraceptive method
 - b. Category 2: A condition in which the advantages of using the method generally outweigh the theoretical or proven risks
 - c. Category 3: A condition in which the theoretical or proven risks usually outweigh the advantages of using the method
 - d. Category 4: A condition that represents an unacceptable health risk if the contraceptive method is used
2. Examples of category 4 contraindications for combined hormonal contraceptives
 - a. Less than 21 days postpartum for women with no risk factors for DVT (regardless of breastfeeding status),
 - b. Smoker (15 cigarettes or more per day) and/or 35 and older, though conservatively, any smoking can be a risk factor
 - c. Blood pressure greater than 160/100 mm Hg
 - d. Vascular disease
 - e. Current DVT or pulmonary embolism or history of DVT or pulmonary embolism
 - f. Complicated diabetes showing nephropathy, neuropathy, or retinopathy
 - g. Major surgery with prolonged immobilization
 - h. Known thrombogenic mutations
 - i. Current or history of ischemic heart disease
 - j. Stroke (history of cerebrovascular accident)
 - k. Migraine headache with aura
 - l. Current breast cancer
 - m. Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies

D. Adverse Effects (see Estrogen and Progestin sections earlier for specific hormone-causing adverse effects)

1. Discontinuation of contraceptives was due to:
 - a. Bleeding irregularities: 32%
 - b. Nausea: 19%
 - c. Weight gain: 14%
 - d. Mood swings: 14%
 - e. Breast tenderness: 11%
 - f. Headache: 11%
2. Management of adverse effects
 - a. Breakthrough bleeding
 - i. Consider new product after trying the product for 3 months, assess adherence.
 - ii. Select new birth control according to when bleeding occurs.
 - iii. If early in the cycle, there is probably not enough estrogen; select a regimen with higher estrogen activity.
 - iv. If late in the cycle, there is probably not enough progestin; select a regimen with higher progestin activity.
 - v. In general, if breakthrough bleeding occurs, it is best to select a regimen with higher estrogen and progestin activities.
 - b. Nausea
 - i. More likely to be related to estrogen component.
 - ii. Suggest the patient take the pill at night before bed.
 - iii. Take the pill with food.
 - iv. If possible, try the product for 3 months; nausea may subside.

- c. Acne
 - i. More likely to be related to the androgenic properties of progestin.
 - ii. Select a product with lower androgenic activity.
 - iii. Alternatively, select a product with higher estrogen activity.
- 3. Serious adverse effects (ACHES)
 - a. **A:** Abdominal pain; could signal liver problems or gallbladder.
 - b. **C:** Chest pain, shortness of breath, coughing up blood; could signal myocardial infarction or blood clot in lung.
 - c. **H:** Headaches (severe); could signal stroke, blood clot.
 - d. **E:** Eye problems (blurred vision, flashing lights, blindness); could signal optic neuritis, stroke, clots.
 - e. **S:** Severe leg pain with or without swelling; could signal DVT.

Patient Case

6. A 22-year-old woman started taking levonorgestrel 0.1 mg/ethinyl estradiol 20 mcg tablet daily 4 months ago for contraception. She has breakthrough bleeding at the start of her active pills that lasts a few days before resolving. As a pharmacist working under a collaborative practice agreement, which OC on her formulary is best to prescribe?

Name of OC	Estrogen Property	Progestin Property	Androgen Property
Levonorgestrel 0.1 mg/ethinyl estradiol 20 mcg	Low	Low	Low
Desogestrel 0.15 mg/ethinyl estradiol 30 mcg	Intermediate	High	Low
Norethindrone 0.5 mg/ethinyl estradiol 35 mcg	Low	Low	Low
Norethindrone acetate 1.5 mg/ethinyl estradiol 30 mcg	Low	High	High

- A. Continue levonorgestrel 0.1 mg/ethinyl estradiol 20 mcg for another 3 months.
- B. Change to desogestrel 0.15 mg/ethinyl estradiol 30 mcg.
- C. Change to norethindrone acetate 1.5 mg/ethinyl estradiol 30 mcg.
- D. Change to norethindrone 0.5 mg/ethinyl estradiol 35 mcg.

E. Common Drug Interactions (list not all-inclusive)

Table 14. Common Drug Interactions with Hormonal Contraception

Increase Effect of HC	Decrease Effect of HC	Drugs that Are Increased or Decreased by HC
Acetaminophen	Amprenavir	Acetaminophen
Ascorbic acid	Aprepitant	Antidepressants, tricyclic
Atazanavir	Barbiturates	Aspirin
Atorvastatin	Bexarotene	Benzodiazepines
Ginseng	Bosentan	β -Blockers
Indinavir	Carbamazepine	Caffeine
Red clover (may increase or decrease effect of combined HCs)	Darunavir	Clofibrate
Rosuvastatin	Efavirenz	Corticosteroids
Tranexamic acid	Felbamate	Cyclosporine

Table 14. Common Drug Interactions with Hormonal Contraception (*Cont'd*)

Increase Effect of HC	Decrease Effect of HC	Drugs that Are Increased or Decreased by HC
Voriconazole	Griseofulvin	Fosamprenavir
	Lopinavir	Lamotrigine
	Modafinil	Levothyroxine
	Mycophenolate mofetil	Morphine
	Nelfinavir	Paclitaxel
	Nevirapine	Salicylic acid
	Oxcarbazepine	Selegiline
	Phenobarbital	Tacrine
	Phenytoin/fosphenytoin	Tacrolimus
	Pioglitazone	Theophyllines
	Primidone	Tizanidine
	Red clover (may increase or decrease effect of combined HCs)	Valproic acid
	Rifamycins	
	Ritonavir	
	Rufinamide	
	Saquinavir	
	St. John's wort	
	Tipranavir	

HC = hormonal contraceptives.

- Questionable effects that hormonal contraceptives may have on other drugs
 - Anticoagulants: Hormonal contraceptives may increase certain clotting factors and reduce anti-thrombin III, so it is questionable whether hormonal contraceptives interfere with anticoagulants.
 - Lamotrigine and fosamprenavir concentrations may be decreased by hormonal contraceptives.
- Simplified list of drug-drug interactions according to the U.S. Medical Eligibility Criteria for Contraceptive Use 2016 (www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6503.pdf)
 - Nucleoside reverse transcriptase inhibitors, maraviroc, HIV integrase strand transfer inhibitors (category 1: before treating any patients, recommend to check specific product information)
 - Nonnucleoside reverse transcriptase inhibitors (category 1 or 2: before treating any patients, recommend to check specific product information)
 - Ritonavir-boosted protease inhibitors (category 2; exception: ritonavir-boosted lopinavir)
 - Protease inhibitors without ritonavir (category 1: indinavir; category 2: – nelfinavir and atazanavir; category 3: fosamprenavir)
 - Antiepileptics (category 3)
 - Rifampin or rifabutin (category 3)
 - St. John's wort (category 2)
 - Broad-spectrum antibiotics, antifungals, antiparasitics (category 1); U.S. Medical Eligibility Criteria for Contraceptive Use 2016 suggest that no alternative form of contraception is necessary with broad-spectrum antibiotics, but other antibiotics may require an alternative form of contraception (see text that follows)

- i. Reported antibiotic cases in the literature: Tetracycline, minocycline, erythromycin, penicillins, and cephalosporins; pharmacokinetic studies have not shown decreased OC steroid concentrations with tetracycline, doxycycline, ampicillin, metronidazole, quinolones, or fluconazole.
 - i. Proposed mechanisms of drug interactions
 - (a) Interference of absorption: Ethinyl estradiol is conjugated in the liver, excreted in bile, hydrolyzed by intestinal bacteria, and reabsorbed as an active drug; non–liver enzyme-inducing antibiotics temporarily decrease colonic bacteria and inhibit enterohepatic circulation of ethinyl estradiol. Gut flora have recovered 3 weeks after the introduction of antibiotics.
 - (b) Liver enzyme induction (rifampin and griseofulvin): The metabolism of progesterone and estrogen is accelerated.
 - ii. Use a backup method (BUM) for the length of antibiotic therapy plus 7 days after discontinuing antibiotic.
- F. Types of Hormonal Contraceptives
- 1. Oral
 - a. COC regimens
 - i. Monophasic: Same amount of hormone in pill every day except in placebo pills
 - ii. Biphasic: Amount of hormone may change halfway through cycle.
 - iii. Triphasic: Amount of hormone changes every week.
 - (a) Traditional: Progestin usually changes and estrogen stays the same.
 - (b) Estrophasic: Estrogen changes.
 - iv. Quadriphasic: Estrogen changes and progestin changes; four varying amounts throughout monthly pack
 - b. Dosing
 - i. High-dose estrogen: Higher than 35 mcg (up to 50 mcg)
 - ii. Low-dose estrogen: Less than 35 mcg (generally 20–35 mcg)
 - iii. Very low-dose estrogen: Less than 10 mcg
 - c. Effectiveness: When taken every day at the same time, 99.7% (perfect use), typical use (about 93%) (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
 - d. Adherence: 68% continue after 1 year
 - e. Start methods
 - i. Same-day start: Start taking an active pill the first day of menses.
 - ii. Sunday start: Start taking an active pill the first Sunday after menses begins (use a BUM for at least 7 days, most conservative for 1 month).
 - iii. Quick start: Start taking an active pill at the physician's office or first day of prescription, regardless of menstrual cycle day. Use a BUM for at least 7 days. Most conservative; use a BUM for 1 month. Menses will not begin until all the active pills have been taken.
 - iv. When changing pills from brand to brand, start the new pack of pills after finishing the placebo pills from the old pack.
 - f. Counseling
 - i. Proper use: Take 1 tablet once daily at the same time every day.
 - ii. Adverse effects
 - (a) See previous text.
 - (b) Adverse effects usually subside after 3 months; general recommendation is to stay on a brand for at least 3 months if adverse effects are not excessively bothersome.

- iii. Missed doses: Missed COC pill means more than 24 hours between doses. Recommendations differ on what to do about missed doses.
 - (a) Recommendations for missed combined oral contraceptives (MMWR 2016;65 (RR4):1-66)
 - (1) Missed 1 pill: Take missed dose as soon as possible, continue taking the remaining doses at the usual time even if it means taking 2 tablets in one day, no BUM needed; generally EC is not necessary but may be considered (except ulipristal) if the patient missed doses earlier in the cycle or in the last week of the previous pack.
 - (2) Missed 2 or more pills: If two or more doses are missed, more than 48 hours since scheduled administration time, may recommend the following:
 - (A) Take most recent doses as soon as possible.
 - (B) Continue taking remaining doses at the usual time even if it means taking 2 tablets in one day.
 - (C) Use a BUM or avoid intercourse until 7 active tablets have been taken for 7 consecutive days.
 - (D) Use EC (except for ulipristal) if unprotected intercourse occurred in the previous 5 days.
- g. Unique formulations (other AB-rated products may be available that are not listed here)
 - i. Natazia (estradiol valerate/dienogest), four-phase OC: 2 days, 3 mg of estradiol valerate; 5 days, 2 mg of estradiol valerate/2 mg of dienogest; 17 days, 2 mg of estradiol valerate/3 mg of dienogest; 2 days, 1 mg of estradiol valerate; 2 days, placebo
 - ii. Mircette, Azurette, Bekyree, Kariva, Kimidess, Pimtree, Violele (ethinyl estradiol/desogestrel): 2 days of placebo and 5 days of estrogen only (10 mcg), instead of 7 days of placebo
 - iii. Femcon Fe, Nexesta Fe, Wymzya FE, Zenchent FE (ethinyl estradiol 35 mcg/norethindrone 0.4 mg): Chewable tablets with iron tablets instead of placebo
 - iv. Lo Loestrin Fe (ethinyl estradiol 10 mcg/norethindrone acetate 1 mg): Lowest oral estrogen COC tablet; contains 24 active tablets, 2 tablets of ethinyl estradiol 10 mcg, and 2 tablets of ferrous fumarate 75 mg
 - v. Generess Fe, Layolis Fe, Kaitlib Fe (ethinyl estradiol 25 mcg/norethindrone 0.8 mg): 24 chewable active tablets and 4 tablets of ferrous fumarate 75 mg
 - vi. Drospirenone progestin-containing contraceptives
 - (a) Drospirenone: Analog of spironolactone, similar to spironolactone 25 mg
 - (b) Exercise caution with drugs that increase potassium such as high doses of NSAIDs, heparin, ACE inhibitors, and potassium-sparing diuretics.
 - (c) No diuretic effect, has antimineralocorticoid effects, decreases bloating effect of ethinyl estradiol.
 - (d) Antiandrogenic: Best for acne, hirsutism, or male pattern balding in women
 - (e) Possible increased risk of DVT, FDA safety communication, April 2012
 - (f) Products (other AB-rated products may be available)
 - (1) Yasmin (ethinyl estradiol 30 mcg/drospirenone 3 mg): 21 active tablets, 7 placebo
 - (2) Yaz (ethinyl estradiol 20 mcg/drospirenone 3 mg): 24 active tablets with 4 days of placebo, approved use for premenstrual dysphoric disorder, acne.
 - (3) Safyral (ethinyl estradiol 30 mcg/drospirenone 3 mg and 0.451 mg of levomefolate calcium) and 4 tablets of 0.451 mg of levomefolate calcium
 - (4) Beyaz: 24 active tablets of ethinyl estradiol 20 mcg, drospirenone 3 mg, and 0.451 mg of levomefolate calcium (folic acid) and 4 tablets of 0.451 mg of levomefolate calcium, approved use for premenstrual dysphoric disorder and acne.
 - (5) Nextstellis (estetrol 14.2 mg/drospirenone 3 mg): 24 active tablets, 4 placebo tablets; may be less effective in those with a BMI greater than 30 kg/m².

h. Advantages and disadvantages (Table 15)

Table 15. Advantages and Disadvantages of COCs

Advantages	Disadvantages
Effective	No HIV or STI protection
Easy to use	Patient adherence
Reversible	Expensive
Regular menstrual cycle	Adverse effects
Reduction of several cancers	Circulatory complications
Decreased risk of benign breast tumors	Menstrual cycle changes
Improves acne	Sexual and psychological effects
Sexual enjoyment	Hepatocellular adenoma
Emergency contraception	Gallbladder disease
Transition therapy for perimenopause	Drug interactions

COC = combined oral contraceptive (tablet); HIV = human immunodeficiency virus; STI = sexually transmitted infection

2. Transdermal patch (Xulane, Twirla)

- a. Patch placed on skin; Xulane delivers 150 mcg of norelgestromin/35 mcg ethinyl estradiol (provides 60% more estrogen exposure than 35-mcg oral tablet of ethinyl estradiol); Twirla delivers 120 mcg of levonorgestrel/30 mcg of ethinyl estradiol.
- b. Effectiveness
 - i. Similar to pills (7% failure rate for typical use, 0.3% for perfect use)
 - ii. Less effective in women weighing more than 198 lb (90 kg); should not be used (Twirla is contraindicated if BMI is 30 kg/m² or greater)
- c. Adherence: Better adherence rates than pill, especially in teens
- d. Counseling
 - i. Proper use
 - (a) Place patch on a dry, hairless area of upper arm, shoulder, abdomen, or buttocks. Should not be placed on the breast. Rotate site of patch each week.
 - (b) One patch per week for 3 weeks; week 4 is patch free (menses will occur then)
 - ii. Adverse effects
 - (a) Higher incidence of blood clots
 - (b) Site irritation from the patch
 - (c) See adverse effects mentioned earlier in text.
 - iii. Missed doses
 - (a) If patch is off for less than 24 hours, reapply patch; no BUM needed.
 - (b) If patch is off for more than 24 hours, open a new patch, new day 1; must use a BUM for first week of the new cycle.
 - iv. Alternative recommendations for missed contraceptive patch application (MMWR 2016;65 (RR4):1-66)
 - (a) Missed dose = delayed patch application of less than 48 hours or recommended time for application.
 - (1) Apply new contraceptive patch as soon as possible (if less than 24 hours, may replace same patch).
 - (2) Keep contraceptive patch on until scheduled patch change day.
 - (3) No BUM needed
 - (4) In general, EC is unnecessary but may be considered (except for ulipristal) if the patient missed doses earlier in the cycle or in the last week of the cycle.

- (b) If delayed application is more than 48 hours from scheduled administration time, may recommend the following:
 - (1) Apply new patch as soon as possible.
 - (2) Keep patch on until scheduled patch change day.
 - (3) Use a BUM or avoid intercourse until contraceptive patch has been in place for 7 consecutive days.
 - (4) If doses missed were during days 15–21 of a 28-day cycle (e.g., 3 weeks active hormone, 1 week placebo); then omit the patch-free week and apply a new contraceptive patch.
 - (5) If unable to apply a new patch immediately, use a BUM or avoid intercourse until new patch has been applied for 7 consecutive days.
- (c) Use EC (except for ulipristal) if active hormone was missed in the first week of the cycle or unprotected intercourse occurred in the previous 5 days.
- e. Advantages and disadvantages (Table 16)

Table 16. Advantages and Disadvantages of Transdermal Contraception Patch

Advantages	Disadvantages
Efficacy Adherence User controlled Readily reversible	Site reactions Patch detachment Appearance, less privacy Breast discomfort Dysmenorrhea Headache Nausea Should not be used in women > 90 kg Questionable increased risk of blood clots

3. Vaginal rings

- a. NuvaRing; EluRyng (other AB-rated products may be available)
 - i. Product inserted vaginally; delivers 15 mcg ethinyl estradiol and 120 mcg etonogestrel (active form of desogestrel) daily.
 - ii. Effectiveness: Similar to pills (7% failure rate for typical use, 0.3% for perfect use) (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
 - iii. Adherence
 - (a) One study found that 92.4% of women using a vaginal ring were adherent versus 75.4% using the COC pill.
 - (b) Users were 96% satisfied; 97% would recommend the ring.
 - iv. Counseling
 - (a) Proper use
 - (1) Insert vaginal ring into vagina and leave for 3 weeks. Week 4, remove ring and menses will occur.
 - (2) Should not be removed during intercourse.
 - (3) May be worn with tampon if there is breakthrough bleeding.
 - (b) Missed doses: Inadvertent removal, expulsion, or prolonged ring-free interval
 - (1) If 3 hours or less, rinse with cool to lukewarm water and reinsert as soon as possible.
 - (2) If more than 3 hours, reinsert and use a BUM until ring has been used continuously for 7 days.

- (c) Alternative recommendations for missed vaginal ring insertion (MMWR 2016;65(RR4):1-66)
 - (1) Missed dose = delayed insertion of less than 48 hours or recommended time for insertion
 - (A) Insert new vaginal ring as soon as possible.
 - (B) Keep ring in until scheduled ring removal day.
 - (C) No BUM needed.
 - (D) In general, EC is unnecessary but may be considered (except for ulipristal) if the patient missed doses earlier in the cycle or in the last week of the cycle.
 - (2) If delayed insertion is more than 48 hours from scheduled administration time, may recommend the following:
 - (A) Insert ring as soon as possible.
 - (B) Keep ring in until scheduled ring removal day.
 - (C) Use a BUM or avoid intercourse until vaginal ring has been in place for 7 consecutive days.
 - If doses missed were during days 15–21 of a 28-day cycle (e.g., 3 weeks active hormone, 1 week placebo); then omit the ring-free week and insert a new vaginal ring.
 - If unable to insert a new ring immediately, use a BUM or avoid intercourse until new ring has been inserted for 7 consecutive days.
 - (D) Use EC (except for ulipristal) if active hormone was missed in the first week of the cycle or unprotected intercourse occurred in the previous 5 days.
 - (d) Adverse effects
 - (1) Decreased libido (8%)
 - (2) Breast tenderness (4%)
 - (3) Device-related events (2.5%–5%)
 - (4) Vaginal discomfort and secretions (2.5%)
 - (5) Irregular bleeding (1.5%–5%)
 - v. Advantages and disadvantages (Table 17)
- b. Annovera
- i. Product inserted vaginally, delivers 0.15 mg/day of segesterone and 13 mcg/day of ethinyl estradiol
 - ii. Effectiveness: 96%–98% effective in preventing pregnancy, has not been studied in women with a BMI greater than 29 kg/m²
 - iii. Counseling:
 - (a) Proper use
 - (1) Insert vaginal ring into vagina and leave for 3 weeks. Week 4, remove ring and menses will occur. Ring is stored and reinserted after 7 days.
 - (2) Should not be removed during intercourse
 - (3) The same vaginal ring is used for 13 cycles (1 year)
 - (4) Does not need to be stored in the refrigerator
 - (b) Missed doses:
 - (1) If out 2 hours or less, rinse with warm water and reinsert as soon as possible
 - (2) If out 2 hours or more at one time or out for a time that adds up to more than 2 hours over the 21 days, a backup contraceptive method should be used until the ring has been in place continuously for 7 days
 - (c) Adverse effects (greater than 5%)
 - (1) Headache/migraine
 - (2) Nausea/vomiting/diarrhea

- (3) Abdominal pain
- (4) Yeast infections
- (5) Dysmenorrhea
- (6) Vaginal discharge
- (7) Breast tenderness
- (8) Menstrual irregularities
- (9) Urinary tract infections
- (10) Genital itching
- (d) Drug interactions
 - (1) Similar to those with combined hormonal contraceptives
 - (2) Increased exposure to hormones occurs with oil-based suppositories such as miconazole 1- or 3-day treatments. Only water-based suppositories should be used concurrently with this vaginal ring.
- (e) Contraindications – Similar to combined hormonal contraceptives

Table 17. Advantages and Disadvantages of Contraceptive Vaginal Ring

Advantages	Disadvantages
Efficacy Adherence User controlled Cycle control Readily reversible Privacy	Adverse effects similar to other combined regimens Vaginal discomfort Potential partner awareness of ring

- 4. Extended regimens (other AB-rated products may be available that are not listed here)
 - a. 3 months: Using active form of combined hormonal contraception for 3 months (results in menses every 3 months instead of once a month)
 - i. Ethinyl estradiol 30 mcg/levonorgestrel 150 mcg, ethinyl estradiol 10-mcg tablets instead of placebo pills (Seasonique, Amethia, Ashlyna, Daysee, Camrese)
 - ii. Ethinyl estradiol 20 mcg/levonorgestrel 100 mcg, ethinyl estradiol 10-mcg tablets instead of placebo pills (LoSeasonique, Amethia Lo, Camrese Lo)
 - iii. 42 tablets of ethinyl estradiol 20 mcg and levonorgestrel 0.15 mg, 21 tablets of ethinyl estradiol 20 mcg and levonorgestrel 0.15 mg, 21 tablets of ethinyl estradiol 30 mcg and levonorgestrel 0.15 mg, and 7 tablets of ethinyl estradiol 10 mcg instead of placebo pills (Quartette)
 - iv. 84 tablets levonorgestrel 0.15 mg and ethinyl estradiol 30 mcg (Jolessa, Quasense, Introvale)
 - b. 1 year: Using active form of combined hormonal contraception for 1 year; product: ethinyl estradiol 20 mcg/levonorgestrel 90 mcg (Amethyst)

VIII. PROGESTIN-ONLY CONTRACEPTIVES, CONTAINING ONLY A PROGESTIN AGENT WITH NO ESTROGEN

- A. Indications: Those who cannot use or tolerate combined hormonal contraceptives (see list) or those seeking long-term contraception
 - 1. History of or current MI, stroke, DVT, CVD
 - 2. Atrial fibrillation
 - 3. Blood pressure 160/100 mm Hg
 - 4. Smoker age 35 or older

5. Active, symptomatic liver disease
 6. Migraine headache with neurologic impairment or aura
 7. Retinopathy or neuropathy because of diabetes
 8. Surgery within the past 4 weeks
 9. Breastfeeding (estrogen may decrease breastmilk production)
- B. Components: One of the following progestins
1. Norethindrone 0.35 mg
 2. Drospirenone 4 mg
 3. Depot medroxyprogesterone acetate (DMPA)
- C. Mechanisms of Action
1. Thickens cervical mucus, prevents sperm movement.
 2. Thins uterus lining.
 3. Suppresses midcycle peak of LH and FSH, inhibits ovulation (minimal with oral progestin pills).
- D. Contraindications
1. Suspected or demonstrated pregnancy
 2. Active hepatitis, hepatic failure, jaundice
 3. Inability to absorb sex steroids from GI tract (i.e., active colitis)
 4. Concurrently taking medications that increase hepatic clearance (CYP inducers). Note: Medroxy-progesterone acetate okay to use with CYP inducers.
 5. Taking an antibiotic such as rifampin or rifabutin (category 3), broad-spectrum antibiotics (category 1).
- E. Adverse Effects: See progestin adverse effects in Combined Hormonal Contraceptives section earlier in text.
- F. Types
1. Oral
 - a. Norethindrone 0.35 mg ("mini-pill")
 - i. Effectiveness: 7% failure rate (typical), 0.3% failure (perfect use) (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
 - ii. Start methods: May start on any day or on first day of period. There are no hormone-free days with the POPs.
 - iii. Adverse effects: Progestin related (see earlier text)
 - iv. Missed doses: Doses of POPs must be at the SAME time every day; a missed dose of POPs means more than 3 hours late to take a dose. If a missed dose occurs, must use a BUM for 48 hours.
 - v. Advantages
 - (a) Efficacy
 - (b) Decreased menstrual blood loss, cramps, pain
 - (c) Readily reversible
 - (d) Preferable in lactating women
 - vi. Disadvantages
 - (a) Progestin-related adverse effects (e.g., weight gain, acne)
 - (b) Irregular menses
 - (c) Adherence: Short time window for a missed pill
 - (d) Low-dose progestin; patient may ovulate
 - (e) Fewer noncontraceptive benefits

- b. Drospirenone 4 mg
 - i. Effectiveness: 98% effective in preventing pregnancy
 - ii. Start methods: Start active tablet on the first day of menses. There are 24 active tablets and 4 inactive tablets.
 - iii. Adverse effects: Acne, metrorrhagia, headache, breast pain or tenderness, weight gain, dysmenorrhea, nausea, vaginal hemorrhage, decreased libido, and irregular bleeding
 - iv. Missed doses: If 1 active tablet is missed, take as soon as possible and finish the pill pack as instructed. If 2 active tablets are missed, take the last missed tablet as soon as possible. Continue taking 1 tablet a day as instructed. Use an additional BUM for 7 days.
 - v. Advantages: Dosing is not as sensitive to timing as for traditional POPs.
 - vi. Disadvantages
 - (a) Progestin-related adverse effects
 - (b) Irregular menses
 - (c) Monitoring of thromboembolism, hyperkalemia, bone loss
- 2. Depot medroxyprogesterone acetate (DMPA) intramuscular (IM) injection
 - a. A 1-mL crystalline suspension of 150 mg of DMPA injected intramuscularly into deltoid or gluteus maximus muscle every 11–13 weeks
 - b. Effectiveness: Perfect use failure rate: 0.3%; typical use failure rate: 4% (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
 - c. Start methods
 - i. Preferred start: First 5 days of menses. No BUM needed.
 - ii. Alternative start: Any time in cycle if not pregnant. Use BUM for 7 days.
 - iii. Postpartum: May give injection before hospital discharge.
 - iv. Breastfeeding: May start immediately or wait 4–6 weeks.
 - v. Switching methods: Any time patient not known to be pregnant. Use BUM if necessary.
 - d. Adverse effects
 - i. Progestin related (see earlier text)
 - ii. Progressive significant weight gain
 - iii. Severe depression (rare)
 - iv. Boxed warning: Loss of bone; women who used DMPA for at least 5 years have significantly reduced BMD of lumbar spine and femoral neck, particularly after 15 years of use and if initiated before age 20.
 - (a) The effect is almost completely reversible, even after 4 years or more of DMPA use.
 - (b) All women placed on DMPA should be taking sufficient calcium and exercising regularly.
 - e. Missed dose: More than 13 weeks between injections
 - f. Patient counseling
 - i. Wait a few hours before massaging area where shot was given.
 - ii. Irregular bleeding or spotting in the beginning that should decrease over time.
 - iii. Take calcium if not achieving 1000–1200 mg/day through diet.
 - iv. Return in 11–13 weeks for next injection. Use BUM if ever more than 13 weeks.
 - v. If ever changing from DMPA to another method, start method when next injection is due.
 - vi. May have delayed return to fertility for up to 18 months. Use with caution in women 35 years or older who express interest in future conception.
- 3. DMPA subcutaneously: Subcutaneous injection of 104 mg DMPA, information similar to that stated earlier but, in addition, has FDA indication for endometriosis.

IX. INTRAUTERINE DEVICES (IUDs) AND SYSTEMS (IUSs)

- A. Indications: To prevent pregnancy long term; levonorgestrel IUS is also indicated for heavy menses in women who elect to use an IUD for contraception.
- B. Recommended for Women Who:
1. Have no history of pelvic inflammatory disease (PID) or ectopic pregnancy
 2. Have heavy menses, cramps, anemia, or dysfunctional uterine bleeding
 3. Are seeking long-term (2 years or more) pregnancy protection
 4. Do not want to use estrogen-containing products
- C. Types
1. Copper (ParaGard T 380A)
 - a. Copper IUD inserted into the uterus by a health care professional
 - b. Mechanism of action
 - i. Primary action: Spermicidal
 - ii. Copper ions inhibit sperm motility and acrosomal enzyme activation so that sperm seldom reach fallopian tube and are unable to fertilize the ovum.
 - iii. A sterile inflammatory reaction created in endometrium phagocytizes sperm.
 - iv. Does not interfere with ovulation and is not an abortifacient.
 - c. Effectiveness: Perfect use failure rate: 0.6%; typical use failure rate: 0.8% (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
 - d. Contraindications specific to copper IUD
 - i. Pregnancy
 - ii. Women with current or recent (within 3 months) sexually transmitted infection (STI) or woman at risk of STI
 - iii. Uterus less than 6 cm or greater than 9 cm
 - iv. Undiagnosed abnormal vaginal bleeding
 - v. Active cervicitis or active pelvic infection
 - vi. Known symptomatic actinomyces
 - vii. Recent endometritis (past 3 months)
 - viii. Allergy to copper; Wilson's disease
 - ix. Uterine distortion or pathology affecting placement
 - x. Known or suspected uterine or cervical cancer
 - xi. Unresolved abnormal Papanicolaou (Pap) test
 - xii. Severe anemia (relative contraindication)
 - e. Advantages and disadvantages (Table 18)

Table 18. Advantages and Disadvantages of Copper IUD

Advantages	Disadvantages
Efficacy (long term, 10 yr)	Monthly blood loss increased about 35%
Adherence	Dysmenorrhea
Spontaneous sexual activity	Spotting and cramping
Readily reversible	Expulsion
Cost-effective	Foreign body
Patient satisfaction	Increased risk of infection for 20 days after insertion

IUD = intrauterine device

2. Progestin (levonorgestrel)
 - a. Kyleena: Inserted into uterus by health care professional, stays in for up to 5 years, releases 17.5 mcg levonorgestrel per day, indicated for contraception.
 - b. Liletta: Inserted into uterus by a health care professional; stays in for up to 5 years; releases 18.6 mcg/day initially and declines steadily to 16.3 mcg/day at 1 year, 14.3 mcg/day at 2 years, and 12.6 mcg/day at 3 years; indicated for contraception.
 - c. Mirena: Inserted into uterus by health care professional, stays in for up to 6 years, releases 20 mcg levonorgestrel per day, indicated for contraception and menorrhagia.
 - d. Skyla: Inserted into uterus by a health care professional; stays in for up to 3 years; releases 14 mcg levonorgestrel per day after 24 days, decreasing to 10 mcg/day after 60 days and then to less than 5 mcg after 3 years; indicated for contraception.
 - e. Mechanism of action
 - i. Foreign object in uterus, prevents implantation
 - ii. Progestin thickens cervical mucus, thins endometrium, and inhibits sperm motion.
 - iii. Effectiveness: 99% effective in preventing pregnancy
 - f. Contraindications (package insert)
 - i. Pregnancy or suspicion of pregnancy
 - ii. Congenital or acquired uterine anomaly
 - iii. Acute or history of PID
 - iv. Postpartum endometritis or infected abortion in the past 3 months
 - v. Known or suspected uterine or cervical neoplasia
 - vi. Unresolved abnormal Papanicolaou (Pap) test
 - vii. Genital bleeding of unknown etiology
 - viii. Untreated acute cervicitis or vaginitis
 - ix. Acute liver disease or liver tumor (benign or malignant)
 - x. Woman or partner with several sexual partners
 - xi. Conditions associated with increased susceptibility to infections with microorganisms (e.g., leukemia, acquired immunodeficiency syndrome, intravenous drug abuse)
 - xii. Genital actinomycosis
 - xiii. A previously inserted IUD that has not been removed
 - xiv. Hypersensitivity to any component of this product
 - xv. Known or suspected carcinoma of the breast
 - xvi. History of ectopic pregnancy or condition that would predispose to ectopic pregnancy
 - g. Advantages and disadvantages (Table 19)

Table 19. Advantages and Disadvantages of Progestin IUS

Advantages	Disadvantages
Efficacy (long term, 3–6 yr)	Progestin-related adverse effects
Adherence	Irregular menses (generally for the first 6 mo; then possibly amenorrhea)
Menorrhagia improves	Expulsion
Spontaneous sexual activity	Increased risk of infection first 20 days after insertion
Readily reversible	Foreign body

IUS = intrauterine system

- D. Contraceptive CHOICE Project (Clin Obstet Gynecol 2014;5:635-43; and N Engl J Med 2014;371:1316-23)
1. Study looked at the use of long-acting reversible contraception (LARC) that included IUDs and implants, followed for 3 years.
 2. Women were provided contraceptive of choice at no cost. Women had the choice of pill, patch, vaginal ring, levonorgestrel IUD, copper IUD, or progestin implant.
 3. Findings
 - a. LARC methods chosen by 75% of women
 - b. Continuation rates for LARC (implants and IUDs) were higher than for short-acting methods (86% vs. 55% at 12 months and 77% vs. 41% at 24 months).
 - c. Sexual behaviors did not change; 71% of participants reported no change in partners at 6 and 12 months.
 - d. Failure rates for pill, patch, and ring users were higher (4.8%–9.4%) than for LARC users (less than 1%) over the 3 years.
 - e. Those who used shorter-acting birth control methods compared with LARC were 22 times more likely to have an unintended pregnancy.
 - f. Showed safety of LARC use among teens (15–19 years of age).
- E. Patient Counseling
1. Strings of IUD will be outside the cervix. Patient will be instructed on how and when to check the strings to verify IUD is still inserted correctly.
 2. Adverse effects: PAINS
 - a. **P:** Period late; abnormal spotting or bleeding
 - b. **A:** Abdominal pain, pain with intercourse
 - c. **I:** Infection exposure (STI); abnormal vaginal discharge
 - d. **N:** Not feeling well, fever, chills
 - e. **S:** String missing, shorter, or longer

Patient Case

7. L.M., a 37-year-old woman (height 67 inches, weight 95 kg), states that she wants to begin contraception for now; however, she would like to have children in a year or so. Her medical history includes hypertension for 2 years and gastroesophageal reflux disease; she drinks 2 glasses of wine a week and smokes ½ pack of cigarettes/day. Her medications include hydrochlorothiazide 25 mg orally daily, amlodipine 5 mg /benazepril 20 mg orally daily, omeprazole 20 mg orally daily, and occasional ibuprofen. Which contraceptive product is best to recommend for L.M.?
- A. Transdermal contraceptive patch
 - B. Oral tablet ethinyl estradiol/drospirenone
 - C. Oral tablet norethindrone
 - D. DMPA IM injection

X. IMPLANT (NEXPLANON)

- A. Indication: Long-term prevention of pregnancy
- B. Components: Etonogestrel, releases 60–70 mcg/day during weeks 5–6 and then decreases to 35–45 mcg/day by the end of the first year, 30–40 mcg/day after the second year, and 25–30 mcg/day at the end of 3 years. Of note: etonogestrel (Implanon) has been discontinued; only etonogestrel (Nexplanon) is being manufactured and distributed currently.

- C. Mechanism of Action: A rod inserted in upper arm, 99% effective for up to 3 years, releases progestin etonogestrel, which acts similarly to other progestin-only contraceptives; not tested in women weighing more than 130% of their ideal body weight; may be less effective in overweight women; return to fertility within 1–3 months; Nexplanon is radio-opaque so it is visible on radiograph.
- D. Adverse Effects
 - 1. Similar to progestin-related adverse effects.
 - 2. Bleeding irregularities
 - 3. Site reactions, inflammation, hematoma, pain, redness at site (3.6%)
 - 4. Difficulty removing rod after 3 years, rod breaks, fibrosis (1.7%)
- E. Studies (see Contraceptive CHOICE Project under IUD section)

XI. LACTIC ACID, CITRIC ACID, AND POTASSIUM BITARTRATE VAGINAL GEL (PHEXXI)

- A. Single use applicator inserted into the vagina before sex
- B. Lowers pH of the vagina and decreases the motility or mobility of the sperm. It is not a spermicide.
- C. Must be used before each session of sex (“1 dose, 1 hour, 1 act”).
- D. 86–93% effective
- E. Can be used in combination with other methods, except for the vaginal ring.
- F. Benefits: Hormone free, potential for increased sexual satisfaction
- G. Adverse effects: Vaginal irritation (increased risk with increased frequency of use)

XII. EMERGENCY CONTRACEPTION

- A. Definition: “A therapy used to prevent pregnancy after an unprotected or inadequately protected act of sexual intercourse.” ACOG definition (ACOG Practice Bulletin 152. Obstet Gynecol 2015;126(3):e1-11.)
- B. Mechanism of Hormonal Methods
 - 1. Inhibits ovulation
 - 2. Prevents fertilization
 - 3. Increases thickness of cervical mucus
 - 4. Prevents implantation (controversial; most recent data suggest this does not occur)
 - 5. Not considered an abortifacient by medical standards; does not disrupt an implanted, fertilized egg.
- C. Indications
 - 1. Condom broke
 - 2. Misused contraceptive method (e.g., missed a pill, contraceptive patch fell off)
 - 3. Sexual assault
 - 4. Exposure to teratogen
 - 5. Unprotected vaginal intercourse

- D. Timing: Within 120 hours after unprotected intercourse; package insert for marketed products (levonorgestrel products) states 72 hours, but studies show up to 120 hours may still prevent pregnancy.
- E. Effectiveness: 57%–85%
- F. Methods
1. Yuzpe method (not frequently utilized clinically)
 - a. High-dose estrogen plus progestin with dosing obtained using available COC products.
 - b. Adverse effects
 - i. Nausea: 30%–60%; vomiting: 33% with estrogen-containing EC (if vomiting within 2 hours of dose, repeat dose; may take with food or meclizine 50 mg prophylactically 30–60 minutes before each dose)
 - ii. May notice changes in menstrual cycle
 - iii. Breast tenderness, headache
 2. Progestin-only method
 - a. Products: Levonorgestrel 1.5 mg (1 tablet)
 - i. Available over the counter (OTC) for all ages; anyone may purchase.
 - b. Adverse effects
 - i. Nausea: 18%; vomiting: 4%
 - ii. May notice changes in menstrual cycle
 - c. Special populations
 - i. BMI greater than 25 kg/m²
 - (a) Progestin-only emergency contraceptive pills are not as effective for those with a BMI of 25 kg/m² or greater. Either ulipristal acetate (ella) or the copper IUD (Paragard T380A) is recommended for these patients. CDC Medical Eligibility criteria state that hormonal methods of EC may lose effectiveness at a BMI of 30 kg/m² and higher.
 - (b) Controversial: FDA asking for more data and not recommending package labeling changes for levonorgestrel at this time for increased BMI and decreased effectiveness (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109775.htm)
 - (c) The copper IUD is recommended for those with a BMI greater than 35 kg/m².
 - ii. Breastfeeding women: All EC methods are category 1 for use according to the CDC Medical Eligibility Criteria; exception: breastfeeding not recommended within 24 hours of taking ulipristal because of high concentrations of ulipristal in milk during first 24 hours, with the highest peak 1–3 hours after administration (breast milk for first 24 hours after administration should be discarded)
 3. Ulipristal acetate
 - a. Prescription only
 - b. Progesterone receptor modulator: Binds to progesterone receptor
 - c. Indicated for EC within 120 hours of unprotected intercourse; reported to have 42% more effectiveness in preventing pregnancy than levonorgestrel at 72 hours postcoitus
 - d. Dose = 30 mg orally within 120 hours of unprotected intercourse
 - e. Adverse effects: Headache, nausea, abdominal pain, dysmenorrhea, menstrual changes
 - f. Not approved for use during breastfeeding
 - g. Not recommended for women with a BMI greater than 35 kg/m², category 2 for women with a BMI of greater than 30 kg/m²; copper IUD is recommended instead
 - h. Use BUM for 7 days after taking ulipristal if using hormonal contraception because ulipristal blocks progesterone receptors.

- i. Recommended to wait 5 days before initiating or resuming hormonal contraception after taking ulipristal. Starting hormonal contraception before waiting 5 days might alter the effect of ulipristal as well as the effect of hormonal contraception.
- 4. Copper IUD: May be used within 5 days of unprotected intercourse; requires in-office visit.
- 5. Levonorgestrel IUD: Shown to be noninferior to copper IUD at preventing pregnancy when inserted within 120 hours of unprotected vaginal intercourse (NEJM 2021;384:335-44).

XIII. MENSTRUAL DISORDERS (Independent Study)

A. Amenorrhea

- 1. Definitions
 - a. Primary: Absence of menarche by age 16 years with presence of secondary development or age 14 years with absence of secondary development and absence of menarche
 - b. Secondary: Absence of menses for 6 months or three cycles (more common than primary)
- 2. Causes
 - a. Rule out pregnancy.
 - b. Excessive exercise or low BMI
 - c. Hyperprolactinemia
 - d. Polycystic ovary syndrome (PCOS)
 - e. Unknown
- 3. Treatment
 - a. Excessive exercise or low BMI
 - i. Decrease exercise and encourage weight gain.
 - ii. Combined hormonal contraceptives
 - iii. Estrogen therapy
 - (a) Conjugated estrogens 0.625 to 1.25 mg orally daily on cycle days 1–25
 - (b) Transdermal estrogen patch, ethinyl estradiol 50 mcg/day patch
 - b. Hyperprolactinemia
 - i. Bromocriptine 2.5 mg orally daily
 - ii. Cabergoline 0.25 mg orally twice weekly; then increase as needed.
 - c. PCOS (see Endocrine and Metabolic Disorders chapter)
 - d. Unknown primary
 - i. Combined hormonal contraceptives
 - ii. Estrogen therapy
 - (a) Conjugated estrogens 0.625 to 1.25 mg orally daily on cycle days 1–25
 - (b) Transdermal estrogen patch, ethinyl estradiol 50 mcg/day patch
 - e. Unknown secondary
 - i. Progestins
 - (a) Micronized progesterone 400 mg orally daily for 10 sequential days to induce menses
 - (b) Medroxyprogesterone acetate 5 to 10 mg orally daily on days 14–25 to induce menses
 - ii. Combined hormonal contraceptives

B. Abnormal Uterine Bleeding

- 1. Definition: “Bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration in the absence of pregnancy.” ACOG Committee Opinion No. 557 April 2013

2. Causes
 - a. Structural: "PALM"
 - i. Polyp
 - ii. Adenomyosis
 - iii. Leiomyoma
 - iv. Malignancy and hyperplasia
 - b. Nonstructural: "COEIN"
 - i. Coagulopathy
 - ii. Ovulatory dysfunction
 - iii. Endometrial
 - iv. Iatrogenic
 - v. Not yet classified
3. Assessment
 - a. Initial laboratory testing
 - i. Complete blood cell count
 - ii. Blood type and cross-match
 - iii. Pregnancy test
 - b. Check for disorders of hemostasis
 - i. PTT, PT, aPTT
 - ii. Fibrinogen
 - iii. Markers for von Willebrand disease
 - c. Other laboratory tests
 - i. Thyroid-stimulating hormone
 - ii. Iron concentrations
 - iii. Liver function tests
 - iv. *Chlamydia trachomatis*
4. Treatment: Goal is to control current episode of heavy bleeding and reduce menstrual loss in subsequent cycles.
 - a. Acute
 - i. Hormonal therapy: First line
 - (a) Progestins: Medroxyprogesterone acetate 20 mg orally three times daily for 7 days (for acute bleeding)
 - (b) Estrogens: Intravenous conjugated equine estrogens
 - (c) Combined hormonal contraceptives: Best if at least 35 mcg of ethinyl estradiol and monophasic; Estradiol valerate and dienogest (Natazia) has approved indication for heavy menstrual bleeding.
 - ii. Tranexamic acid
 - iii. Desmopressin (use with caution; may help for those with von Willebrand disease)
 - iv. Surgery
 - (a) Hysterectomy
 - (b) Endometrial ablation (not recommended as primary therapy)
 - b. Chronic
 - i. Hormonal therapy: First line
 - (a) Progestins
 - (1) Medroxyprogesterone acetate 5–10 mg orally for 5–10 days starting on day 16 or day 21 of a 28-day cycle
 - (2) Levonorgestrel IUD
 - (b) Combined hormonal contraceptives: Low dose may be option.

- ii. Surgery
 - (a) Hysterectomy
 - (b) Endometrial ablation (not recommended as primary therapy)
- C. Dysmenorrhea
 - 1. Definition: Painful menses, usually cramping right before or during menses
 - 2. Causes
 - a. Primary: Caused by menstrual period, mediated by prostaglandins
 - b. Secondary: Caused by disorder in reproductive system (endometriosis, fibroids, adenomyosis), usually starts later in life.
 - 3. Treatment
 - a. NSAIDs: Begin 1–2 days before menses
 - b. Hormonal contraceptives: Combined hormonal contraceptives or levonorgestrel IUD
 - c. Nonpharmacologic approaches (exercise, heat therapy, self-acupressure, acupuncture)
- D. Endometriosis
 - 1. Definition: Chronic disorder that may result in chronic pain and infertility, endometrial tissue found outside the uterus
 - 2. Treatment
 - a. Hormonal contraceptives
 - i. Combined hormonal contraceptives (not FDA-approved use)
 - ii. Depot medroxyprogesterone acetate (subcutaneous formulation, FDA-approved use)
 - iii. Levonorgestrel IUS (not FDA-approved use)
 - b. Gonadotropin-releasing hormone (GnRH) agonists: Goserelin, leuprolide, nafarelin, triptorelin
 - i. Consider adverse effects such as osteopenia, hot flashes, vaginal dryness.
 - ii. Recommend calcium 1000 mg orally daily while taking GnRH agonist.
 - iii. May use add-back therapy with norethindrone with or without low-dose conjugated estrogen; transdermal patch with estradiol and medroxyprogesterone acetate may also be used if norethindrone is not well tolerated.
 - iv. See GnRH analog drug information in the Infertility section that follows.
 - c. GnRH antagonists: Elagolix (Orilissa) - Approved for the treatment of moderate to severe pain associated with endometriosis and endometriosis with dyspareunia (NEJM 2017;377:28-40)
 - i. Endometriosis dose - 150 mg orally once daily, maximum use 24 months
 - ii. Endometriosis with dyspareunia - 200 mg orally twice daily, maximum use 6 months
 - iii. For moderate hepatic impairment, the dose is 150 mg orally once daily for a maximum of 6 months.
 - iv. Adverse effects: Bone loss, mood changes, elevated liver function enzymes
 - v. Contraindications: Pregnancy, severe osteoporosis, severe hepatic impairment, use of strong organic anion transporting polypeptide 1B1 inhibitors; may decrease effect of estrogen-containing contraceptives (best to use non-hormonal method of contraception during treatment as well as for 7 days after treatment with elagolix)
 - d. Danazol
 - i. Androgenic agent
 - ii. Adverse effects: Acne, hirsutism, myalgias
 - e. Aromatase inhibitors: Anastrozole or letrozole, need hormonal contraceptive in addition to minimize risk of ovarian stimulation.
 - f. NSAIDs
 - i. Used to help decrease pain
 - ii. Ibuprofen and naproxen
 - g. Surgery

- E. PCOS (see Chapter, “Endocrine and Metabolic Disorders”)

XIV. INFERTILITY

A. Background

1. Using no birth control method, women have an 85% chance of pregnancy over 1 year.
2. About 20% of women have their first baby after age 35.
3. Probability of having a baby decreases 3%–5% every year after age 30; faster after age 40.
4. Miscarriages: 12%–15% for those in their 20s, 50% after age 40

B. Things That Can Increase Fertility

1. Diet
 - a. Protein, fruits, and vegetables
 - b. Men need zinc.
2. Exercise, although too much may stop ovulation.
3. Fertility improves with BMI of 20–25 kg/m² or within 15% of ideal body weight; fertility decreased in those less than 95% of ideal body weight or in those greater than 125% of ideal body weight.

C. Definition

1. Couples who have had unprotected intercourse for 1 year who have not conceived
2. Couples in which the woman is 35 years or older, the couple is having unprotected intercourse, and the couple has not conceived within 6 months

D. Risk Factors

1. Age older than 35 years
2. Tobacco use
3. Alcohol use
4. Caffeine use (more than 500 mg/day)
5. Vitamin D deficiency
6. Excessive exercise
7. BMI less than 19 kg/m² or more than 25 kg/m² for women

E. Causes of Infertility

1. Male factor
 - a. Endocrine: Spermatogenesis, hypogonadism
 - b. Anatomic: Blockage, abnormal anatomy
 - c. Sexual dysfunction: Ejaculation or erection difficulties
 - d. Often treated with sperm extraction and assisted reproductive technologies
2. Female factor
 - a. Ovulatory
 - i. WHO group I: Hypogonadotropic hypogonadal anovulation
 - (a) About 5%–10% of anovulatory women
 - (b) Low estrogen, low FSH
 - ii. WHO group II: Eugonadotropic anovulation (normogonadotropic normoestrogenic anovulation)
 - (a) About 75%–85% of anovulatory women
 - (b) Normal FSH concentrations
 - (c) Women with PCOS generally fall into this classification.

- iii. WHO group III: Hypergonadotropic anovulation
 - (a) About 10%–20% of anovulatory women
 - (b) Elevated FSH concentrations
 - (c) Premature ovarian failure or advanced age fall into this classification.
 - iv. Hyperprolactinemic anovulation
 - (a) About 5%–10% of anovulatory women
 - (b) May have hyperprolactinemia.
 - (c) Laboratory values may appear similar to those in WHO group I.
 - b. Cervical
 - i. Abnormality
 - ii. Blockage
 - iii. Thickened cervical mucus
 - c. Pelvic
 - i. Fibroids
 - ii. Endometriosis
 - iii. Fallopian tube damage or blockage
 - iv. Uterine abnormality
 - v. Pelvic adhesions
- F. Medical Conditions in Women
- 1. PCOS
 - 2. Endometriosis
 - 3. Pelvic inflammatory disease
 - 4. Uterine fibroids
 - 5. Idiopathic
- G. Fertility Agents
- 1. Clomiphene citrate
 - a. Used to stimulate or induce ovulation (used off-label to increase sperm production in men)
 - b. Administered for 5 days starting on days 2, 3, 4, or 5 of cycle
 - c. Taken by mouth usually 50–150 mg/day
 - d. First-line agent
 - e. Selective estrogen receptor modulator that works by blocking estrogen receptors; body perceives hypoestrogenic state and increases the release of GnRH, which increases concentrations of FSH and LH.
 - f. Adverse effects: Hot flashes, abdominal and breast tenderness, mood swings, visual alterations
 - 2. Aromatase inhibitors (off-label use): letrozole, anastrozole
 - a. Increase GnRH and gonadotropins
 - b. Help induce ovulation with less risk of multiple follicles stimulated (less risk of multiple births).
 - c. Adverse effects: Headache, GI complaints, joint pain, bone pain, edema, sweating, and flushing
 - 3. Human menopausal gonadotropin (hMG)
 - a. Class known as menotropins, both FSH and LH
 - b. Derived from the urine of postmenopausal women
 - c. Given on day 2 or 3 of cycle and continued for 7–10 days, or as determined by estradiol concentrations and ultrasound monitoring of follicle development.
 - d. Regimens may vary for in vitro protocols.
 - e. Adverse effects: Flu-like symptoms, muscle aches, malaise, headaches, dizziness, pain at site

4. Follicle-stimulating hormone (FSH)
 - a. Naturally occurring (urine source): Bravelle urofollitropin
 - b. Recombinant: follitropin alpha, follitropin beta
 - c. Injection form
 - d. Highly purified
 - e. Helps stimulate development of follicle in ovary; given in the first half of the cycle.
 - f. Adverse effects: Mood swings, depression, breast tenderness and swelling, pain at site
5. Human chorionic gonadotropin (hCG)
 - a. Recombinant: Ovidrel injection subcutaneously
 - b. Naturally occurring: Derived from urine of pregnant women, Pregnyl or Novarel, injection intramuscularly
 - c. Similar to LH.
 - d. Helps stimulate release of egg; given 36 hours before insemination or harvest.
 - e. Adverse effects: Irritation at site of injection, edema, headache, mood changes, thromboembolic disorder, allergic reactions
6. GnRH analogs
 - a. Used to prevent LH surge that occurs right before ovulation, which helps with timing of ovulation.
 - b. Helps optimize the effectiveness of hMG or FSH.
 - c. Administered by nasal spray, injection, or capsule
 - d. Also used to treat endometriosis.
 - e. Induces “menopause” state; may cause osteoporosis in women who use agents for long periods; not usually the case in infertility treatment, but more so for endometriosis.
 - f. Agonists versus antagonists
 - i. GnRH agonists
 - (a) Leuprolide, nafarelin
 - (b) Adverse effects: Hot flashes, headache, mood swings, insomnia, vaginal dryness, decreased breast size, bone loss
 - ii. GnRH antagonists
 - (a) Ganirelix and cetrorelix
 - (b) More recently investigated for infertility protocols versus traditional use of GnRH agonists.
 - (c) Said to have fewer complications.
 - (d) Faster onset of action than agonists
7. Metformin
 - a. Sometimes used in conjunction with clomiphene to help ovulation in women with PCOS.
 - b. Increases insulin sensitivity and decreases hyperinsulinemia, thus reducing circulating androgens.
 - c. Weight loss may also occur, leading to better outcomes for ovulation.

H. Other Fertility Agents

1. Progesterone: Used for luteal phase support or patients with frequent miscarriages
 - a. Capsules (micronized): Orally, vaginally
 - b. Injectables
 - c. Vaginal suppositories
2. Bromocriptine: Decreases prolactin concentrations; prolactin lowers progesterone concentrations, may prevent ovulation.
3. Sildenafil: Aids in increasing the thickness of uterus lining (off-label use).
4. Guaifenesin: May help thin the cervical mucus to aid in conception (off-label use).
5. Aspirin: Can be used before fertility procedures for uterine blood flow and decreased risk of ovarian hyperstimulation syndrome.

I. Complications: Ovarian Hyperstimulation Syndrome

1. Etiology
 - a. Life-threatening complication of assisted conception
 - b. Occurs in less than 4% of cycles for ovulation induction.
 - c. About 1%–10% for in vitro fertilization
 - d. Usually occurs in postovulatory stage.
2. Pathophysiology
 - a. Ovary enlargement
 - b. Capillary permeability increase
 - c. Protein-rich fluid escaping from the intravascular space to the extravascular space
 - d. Patient may start to feel bloated; shortness of breath may occur; lethargy, nausea, vomiting, and diarrhea.
3. Clinical signs
 - a. Rapid weight gain
 - b. Ascites
 - c. Pleural and pericardial effusions
 - d. Oliguria or anuria
 - e. Hemoconcentration
 - f. Leukocytosis
 - g. Hypovolemia, hyponatremia, hyperkalemia
 - h. Adult respiratory distress syndrome
 - i. Hypercoagulability
 - j. Multiple organ failure
4. Risk factors
 - a. Young age
 - b. Low body weight
 - c. High estradiol concentrations or rapidly increasing
 - d. Size and number of follicles stimulated
 - e. Number of eggs retrieved
 - f. History of PCOS
5. Outpatient management
 - a. Light physical activity
 - b. Drink 1 L of fluid a day.
 - c. Possibly withhold hCG injection to prevent it.
6. Hospital management
 - a. Fluid management
 - b. Thrombosis prophylaxis

Patient Case

8. L.L. is a 26-year-old woman (height 61 inches, weight 78 kg) who has been trying to conceive for 13 months without success. She and her male partner would like to conceive in the next year or so. Her BMI is 32 kg/m², and she has moderate acne and hirsutism. Her menstrual cycle is fairly regular at 26–27 days. Her partner's physical examination and semen analysis are normal. Her pelvic ultrasonography reveals polycystic ovaries, and she is given a diagnosis of PCOS. Which is the best first-line agent to recommend to L.L. to help her conceive?
- A. Consider weight loss and start clomiphene tablets.
 - B. Continue trying to conceive; make no recommendations at this time.
 - C. Start FSH injections.
 - D. Start hCG injections.

XV. SEXUALLY TRANSMITTED INFECTIONS INCLUDING PELVIC INFLAMMATORY DISEASE, GYNECOLOGIC INFECTIONS**A. Herpes Simplex Virus (HSV) Infection****1. Characteristics**

- a. Types: HSV-1 and HSV-2 can cause genital herpes, with most cases of recurrent genital herpes caused by HSV-2.
- b. Diagnosed in at least 50 million people in the United States, with 11.9% of persons aged 14–49 years estimated to be infected.
- c. Treatment can partly control symptoms but does not affect the risk, frequency, or severity of recurrences after it is discontinued.
- d. Symptoms include itching, genital burning, vesicle formation, and ulcer formation. Most persons infected with HSV-2 have mild or unrecognized infections but shed virus intermittently in the anogenital area.
- e. After the primary infection, the virus is latent in the sacral dorsal root ganglia.
- f. From 50% to 80% of patients have recurrent infections (generally less severe and of shorter duration).

2. Diagnosis

- a. Culture and polymerase chain reaction: Preferred
- b. Serologic testing

3. Therapy**a. Initial HSV infection**

- i. Acyclovir 400 mg orally three times daily for 7–10 days
- ii. Famciclovir 250 mg orally three times daily for 7–10 days
- iii. Valacyclovir 1 g orally twice daily for 7–10 days
- iv. Treatment can be extended if healing is incomplete after 10 days of therapy.

b. Recurrent HSV infection

- i. The regimens listed in recurrent and suppressive section are primarily for HSV-2 type, not for HSV-1. No data are available regarding the efficacy of suppressive therapy for preventing transmission among persons with HSV-1.
- ii. If treatment is initiated within 1 day of lesion onset, patients with recurrent infections may benefit.
 - (a) Acyclovir 800 mg orally three times daily for 2 days
 - (b) Acyclovir 800 mg orally twice daily for 5 days
 - (c) Famciclovir 125 mg orally twice daily for 5 days
 - (d) Famciclovir 500 mg orally for 1 day; then 250 mg orally twice daily for 2 days
 - (e) Famciclovir 1000 mg orally twice daily for 1 day
 - (f) Valacyclovir 500 mg orally twice daily for 3 days
 - (g) Valacyclovir 1000 mg orally once daily for 5 days
- iii. Daily suppressive therapy recommended in patients with six or more episodes yearly (reassess annually the need for suppressive therapy)
 - (a) Acyclovir 400 mg orally twice daily
 - (b) Famciclovir 250 mg orally twice daily
 - (c) Valacyclovir 500 mg/day orally (may be less effective in those who have frequent recurrences [10+ episodes/year])
 - (d) Valacyclovir 1000 mg/day orally

c. Severe disease (e.g. disseminated infection, pneumonitis, or hepatitis)

- i. Should be hospitalized.
- ii. Treatment: Acyclovir intravenously 5–10 mg/kg every 8 hours for 2–7 days, followed by oral antiviral therapy for at least 10 days of total therapy

4. Herpes encephalitis
 - a. Characteristics
 - i. Caused primarily by HSV-1
 - ii. Spreads through neural routes during primary or recurrent infection
 - iii. Primarily temporal lobe involvement with eventual hemorrhagic encephalitis
 - iv. Frequent neurologic sequelae, and high mortality if untreated
 - b. Diagnosis
 - i. Signs and symptoms (nonspecific)
 - (a) Headache
 - (b) Fever
 - (c) Speech disorders and behavioral changes
 - (d) Focal seizures
 - ii. Cerebrospinal fluid analysis
 - (a) Moderate pleocytosis (generally lymphocytosis)
 - (b) Normal glucose and moderately elevated protein
 - iii. Brain biopsy (rarely performed)
 - c. Therapy: Treatment should be intravenous acyclovir for 21 days.
 - d. According to the 2021 STI guidelines, HSV-2 meningitis is also a rare complication of HSV-2 genital herpes infection. The clinical characteristics and diagnosis are similar to herpes encephalitis; however, the treatment regimen is intravenous acyclovir until clinical improvement followed by high-dose oral antiviral therapy to complete 10–14 days course of therapy.

Patient Case

Questions 9 and 10 pertain to the following case:

D.H. is a 21-year-old woman who presents to the clinic with genital itching and vesicles on her vulva. She is sexually active with one partner who has a history of herpes. Her partner does not always use a condom when they have sex. She is initiated on acyclovir for this initial HSV infection.

9. Which statement is best to mention to D.H. regarding the treatment of her herpes infection?
 - A. Treatment of the initial infection will prevent recurrent herpes infections.
 - B. Treatment will shorten the duration of symptoms and infectivity of the initial infection.
 - C. Treatment of the initial infection will decrease the severity of recurrent herpes infections.
 - D. Treatment of the initial infection will prevent the virus from remaining latent in the dorsal root ganglia.
10. D.H. returns to the clinic 10 months after her initial herpes infection. She is troubled by all the recurrences she is having (seven to date). Which therapy is best to recommend?
 - A. Valacyclovir 500 mg orally twice daily to be used for 5 days whenever she notices a recurrence beginning.
 - B. Acyclovir 400 mg orally three times daily to be used for 10 days whenever she notices a recurrence beginning.
 - C. Suppressive therapy with famciclovir 250 mg orally three times daily.
 - D. Suppressive therapy with valacyclovir 500 mg daily orally.

B. Syphilis (*T. pallidum*)

1. Diagnosis
 - a. Dark-field examination and direct fluorescent antibody stains of exudate for spirochetes
 - b. Nontreponemal (Venereal Disease Research Laboratory and Rapid Plasma Reagin); detect serum concentrations of antibody to cardiolipin.
 - c. Treponemal (fluorescent treponemal antibodies and *T. pallidum* particle agglutination test): Detect antibodies to *T. pallidum*.
 - d. Two testing algorithms may be used
 - i. Traditional testing algorithm: Nontreponemal test, confirm with the treponemal test.
 - ii. Reverse testing algorithm: Treponemal test; if positive, followed by quantitative nontreponemal, then confirm with treponemal test if nontreponemal is negative.
2. Primary syphilis
 - a. From 10 to 90 days after exposure (mean 21 days)
 - b. The primary symptom is the development of a chancre.
 - c. The chancre resolves spontaneously in 2–6 weeks, even without treatment.
 - d. Recommended treatment
 - i. Benzathine penicillin G 2.4 million units intramuscularly in a single dose (adults)
 - ii. If penicillin allergy: Doxycycline 100 mg orally twice daily or tetracycline 500 mg four times daily for 2 weeks
3. Secondary syphilis or early latent syphilis (<1 year)
 - a. 4–10 weeks after exposure
 - b. Skin lesions: Characteristically on the palms and soles
 - c. Latent phase begins when all symptoms have resolved.
 - d. Recommended treatment
 - i. Benzathine penicillin G 2.4 million units intramuscularly in a single dose
 - ii. If penicillin allergy: Doxycycline 100 mg orally twice daily or tetracycline 500 mg four times daily for 28 days
4. Late latent syphilis
 - a. More than 1 year in duration or unknown duration
 - b. Recommended treatment
 - i. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks
 - ii. If penicillin allergy: Doxycycline 100 mg twice daily or tetracycline 500 mg four times daily for 4 weeks
5. Tertiary syphilis
 - a. Infectious granulomas and cardiovascular effects: Aortic insufficiency and aortitis
 - b. Recommended treatment
 - i. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks
 - ii. If penicillin allergy: Treat in consultation with an infectious disease specialist.
6. Neurosyphilis
 - a. Recommended treatment: Aqueous crystalline penicillin G 3–4 million units intravenously every 4 hours or continuous infusion (total of 18–24 million units per day) for 10–14 days
 - b. Alternative regimen
 - i. Procaine penicillin 2.4 million units/day intramuscularly plus probenecid 500 mg four times daily for 10–14 days
 - ii. If penicillin allergy: Ceftriaxone 2 g/day intramuscularly/intravenously for 10–14 days, or patients should be desensitized and given penicillin (see CDC recommendations for skin testing and desensitization).

7. Treatment of sexual partners
 - a. Sexual partners should be presumptively treated if exposed within 90 days preceding the diagnosis in their partner.
 - b. If exposure occurred more than 90 days prior, sexual partners should be tested and monitored closely or treated presumptively if serologic test results are not available immediately.
- C. Chlamydial Infection
 1. Can lead to PID, ectopic pregnancy, and infertility
 2. Less dysuria and penile discharge in men compared with gonococcal infection
 3. Diagnosis
 - a. Nucleic acid amplification testing (NAAT)
 - i. Preferred method
 - ii. Allows for a wide variety of FDA-cleared specimen types such as vaginal swabs, urethral swabs, endocervical, and urine
 - b. Culture
 - i. Requires endocervical swab (women)
 - ii. Requires urethral swab (men)
 4. Treatment
 - a. Doxycycline 100 mg twice daily for 7 days
 - b. Alternatives: Azithromycin 1 g orally for one dose or levofloxacin 500 mg/day orally for 7 days
 - c. Abstain from sexual intercourse for at least 7 days and until sexual partners are adequately treated.
 - d. All sexual partners within the past 60 days should be assessed and treated. Expedited partner therapy is one strategy to improve treatment of sexual partners. It involves treating the sex partners of patients diagnosed with chlamydia or gonorrhea by providing prescriptions or medications to the patient to take to their partner without the health care provider first examining the partner.
- D. Gonococcal Infection
 1. Penile discharge and dysuria are common in men, but women are often asymptomatic (which can lead to PID); symptoms in women include vaginal discharge and dysuria.
 2. Diagnosis
 - a. Nucleic acid amplification testing (NAAT)
 - i. Preferred method
 - ii. Allows for a wide variety of FDA-cleared specimen types such as vaginal swabs, urethral swabs, endocervical, and urine
 - b. Culture
 - i. Requires endocervical swab (women)
 - ii. Requires urethral swab (men)
 3. Treatment
 - a. Uncomplicated gonococcal infections of cervix, urethra, and rectum: Ceftriaxone 500 mg intramuscularly for persons weighing less than 150 kg (for persons >150 kg, ceftriaxone 1 gram). If chlamydial infection has not been excluded, also treat with doxycycline 100 mg orally 2 times/day for 7 days.
 - b. Gonococcal infection of the pharynx: Ceftriaxone 500 mg intramuscularly for persons weighing less than 150 kg (for persons > 150 kg, ceftriaxone 1 gram)
 - c. Allergy to cephalosporins, may consider dual treatment with single dose of intramuscular gentamicin 240 mg plus azithromycin 2 g orally. Should consult an infectious disease specialist if patient has a cephalosporin allergy or immunoglobulin E-mediated penicillin allergy

- d. Abstain from sexual intercourse for at least 7 days and until sexual partners are adequately treated.
 - e. All sexual partners within the past 60 days should be assessed and treated.
- E. Urethritis
- 1. Undiagnosed: Treat for both chlamydia and *Gonococcus*.
 - 2. Nongonococcal
 - a. Treat for chlamydia.
 - b. Also consider *Mycoplasma genitalium*.
 - i. Responsible for 15%–20% of nongonococcal urethritis (NGU), 20%–25% of non-chlamydial NGU, and about 30% of persistent or recurrent urethritis
 - ii. Treatment: Doxycycline 100 mg orally 2 times/day for 7 days
 - iii. Alternate: Azithromycin 1 g orally in a single dose or 500 mg orally for one dose then 250 mg orally for 4 days
 - 3. Recurrent or persistent: Ensure adherence and no reinfection from infected partner; if these are ensured, treat with metronidazole or tinidazole for *Trichomonas vaginalis* and azithromycin.
 - 4. All sexual partners within the past 60 days should be assessed and treated.
- F. Pelvic Inflammatory Disease
- 1. Ascending infection of the female genital tract involving primarily the fallopian tubes
 - 2. Clinical presentation
 - a. Lower abdominal tenderness
 - b. Adnexal tenderness
 - c. Cervical motion tenderness
 - d. Oral temperature greater than 101°F
 - e. Abnormal cervical or vaginal discharge
 - f. Elevated erythrocyte sedimentation rate
 - g. Elevated C-reactive protein
 - h. Menorrhagia
 - i. Dysuria
 - 3. Sequelae: Abscess in pelvic or fallopian tubes, tubal occlusion, fibrosis, infertility; PID leads to infertility and ectopic pregnancies.
 - 4. In general, sexually transmitted and caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, anaerobes, gram-negative facultative bacteria, and streptococci.
 - 5. Treatment
 - a. Parenteral treatment
 - i. Recommended regimens:
 - (a) Ceftriaxone 1 g intravenously every 24 hours plus doxycycline 100 mg orally or intravenously every 12 hours plus metronidazole 500 mg orally or intravenously every 12 hours
 - (b) Cefotetan 2 g intravenously every 12 hours plus doxycycline 100 mg orally or intravenously every 12 hours
 - (c) Cefoxitin 2 g intravenously every 6 hours plus doxycycline 100 mg orally or intravenously every 12 hours.
 - (d) Parenteral therapy can be discontinued 24–48 hours after clinical improvement and changed to oral therapy for 14 days.

- ii. Alternative regimens:
 - (a) Ampicillin/sulbactam 3 g intravenously every 6 hours plus doxycycline 100 mg intravenously or orally every 12 hours
 - (b) Clindamycin 900 mg intravenously every 8 hours plus gentamicin 2 mg/kg body weight intravenously or intramuscularly for a single dose then 1.5 mg/kg body weight every 8 hours
- b. Treatment for *M. genitalium* should be considered if PID treatment for 7–10 days has failed. Recommended to start moxifloxacin 400 mg orally daily for 14 days.
- c. Sexual partners of patients with PID within the past 60 days should be tested and treated.

Patient Case

Questions 11 and 12 pertain to the following case:

M.A. is a 24-year-old woman who presents to the emergency department with severe abdominal pain, fever, dysuria, and a vaginal discharge. She is sexually active. Her medical history is unremarkable except for recurrent genital herpes (one or two episodes a year). Her medications on admission include birth control pills (ethinyl estradiol 30 mcg/desogestrel 0.15 mg) and fluticasone nasal spray as needed. On physical examination, M.A.'s vital signs include temperature 101.2°F (38°C), heart rate 92 beats/minute, respiration rate 15 breaths/minute, and blood pressure 117/75 mm Hg. M.A. has adnexal tenderness, cervical motion tenderness, and a vaginal discharge.

- 11. Which is the best empiric therapy for M.A.?
 - A. Ampicillin/sulbactam intravenously 2 g every 6 hours for 14 days
 - B. Metronidazole 500 mg intravenously three times daily for 7 days
 - C. Cefotetan 2 g intravenously every 12 hours with doxycycline 100 mg orally every 12 hours for 14 days
 - D. Ceftriaxone 125 mg intramuscularly once with doxycycline 100 mg intravenously twice daily for 7 days
- 12. Which statement is best for M.A. to tell her sexual partners?
 - A. There is no need for concern because this condition is not transmittable to or acquired from a sexual partner.
 - B. Her partner can resume having sexual intercourse with M.A. as soon as her symptoms improve.
 - C. If her partner has had sex with M.A. within the past 60 days, he should be assessed for possible treatment.
 - D. Her partner does not need to be tested for human immunodeficiency virus (HIV) because there is no relationship between HIV and this condition.

G. Bacterial Vaginosis

1. Malodorous vaginal discharge caused by an overgrowth of anaerobic bacteria (circumventing the normal flora of *Lactobacillus*); more than 50% with bacterial vaginosis are asymptomatic.
2. Infection risk is increased in relation to sexual activity, but it is unknown whether acquired through sexual partner.
3. Diagnosis is based on a malodorous vaginal discharge that is high in pH, contains clue cells, and is whiff test positive (fishy odor after potassium hydroxide 10% added to sample).
4. Bacterial vaginosis has been implicated in PID and is possibly linked to endometritis.
5. Treatment
 - a. Nonpregnant women: Metronidazole 500 mg orally twice daily for 7 days or clindamycin 2% cream, 1 full applicator intravaginally at bedtime for 7 days, or metronidazole 0.75% gel, 1 full applicator intravaginally once daily for 5 days
 - b. Alternatives: Clindamycin ovules 100 mg intravaginally at bedtime for 3 days, clindamycin 300 mg orally twice daily for 7 days, tinidazole 2 g orally once daily for 2 days, tinidazole 1 g orally once daily for 5 days, secnidazole (Solosec) 2 g packet of granules, sprinkle on pudding, apple-sauce, or yogurt (do not chew or crush granules, do not dissolve in a liquid) and consume within 30 minutes
 - c. Treatment of sexual partners is not necessary.

H. Trichomoniasis

1. Caused by *T. vaginalis*
2. Men often have no symptoms, but women generally have a malodorous, yellow-green vaginal discharge and vaginal irritation.
3. Diagnosis most sensitive with NAAT, many times detecting five times more *T. vaginalis* infections than wet-mount microscopy.
4. Treatment
 - a. Recommended treatment for women: Metronidazole 500 mg orally 2 times/day for 7 days
 - b. Recommended treatment for men: Metronidazole 2 g orally in a single dose
 - c. Alternative: Tinidazole 2 g orally in a single dose
 - d. All sexual partners should be treated.
 - e. Metronidazole-allergic patients should be desensitized.

I. Vulvovaginal Candidiasis

1. Seventy-five percent of women have at least one episode (40%–45% will have many episodes).
2. Symptoms include pruritus and vaginal discharge.
3. Predisposing factors include OCs, pregnancy, obesity, diabetes mellitus, corticosteroid use, chemotherapy, and antibiotics.
4. Diagnosed by symptoms and potassium hydroxide smear

5. Therapeutic regimens: 1- and 3-day regimens may take up to 7 days for full effect (Table 20).

Table 20. Therapeutic Regimens for Treatment of Vulvovaginal Candidiasis

Drug	Dose	Length of Therapy
Butoconazole	2% cream: 5 g intravaginally	1 dose
Clotrimazole	1% cream: 5 g intravaginally at bedtime (OTC)	7–14 days
	2% cream: 5 g intravaginally at bedtime (OTC)	3 days
Miconazole	2% cream: 5 g intravaginally at bedtime (OTC)	7 days
	4% cream: 5 g intravaginally at bedtime (OTC)	3 days
	100-mg vaginal suppository at bedtime (OTC)	7 days
	200-mg vaginal suppository at bedtime (OTC)	3 days
	1200-mg vaginal suppository × 1 (OTC)	1 dose
Terconazole	0.4% cream: 5 g intravaginally at bedtime	7 days
	0.8% cream: 5 g intravaginally at bedtime	3 days
	80-mg vaginal suppository at bedtime	3 days
Tioconazole	6.5% ointment: 5 g intravaginally (OTC)	1 dose
Fluconazole	150-mg oral tablet	1 dose

OTC = over the counter

6. Recurrent vulvovaginal candidiasis (four or more episodes a year): Needs prescription drug treatment, not OTC.
 - a. Initial treatment for 7–14 days or fluconazole 100-, 150-, or 200-mg dose every third day for three doses
 - b. Maintenance: Oral fluconazole 100, 150, or 200 mg/week for 6 months
 - c. Consider conditions precipitating recurrent vulvovaginal candidiasis: HIV, diabetes mellitus.
7. Prophylaxis needed for vulvovaginal candidiasis while taking antibiotics; recommend OTC 7-day treatment and use a full applicator at bedtime while taking antibiotics; oral fluconazole is also sometimes used.
8. Pregnant women: Drugs of choice are topical azoles, 7-day treatment.

XVI. PROSTATIC INFECTIONS

A. Prostatitis

1. Symptoms
 - a. Urethritis
 - b. Asymptomatic
 - c. Primarily gram-negative organisms: *C. trachomatis*, *N. gonorrhoeae*, *Escherichia coli*
2. Acute bacterial prostatitis
 - a. Therapy duration: 14–28 days
 - b. Depends on organism
 - i. Ceftriaxone 500 mg for persons weighing less than 150 kg (for persons > 150 kg, ceftriaxone 1 g) intramuscularly for gonorrhea
 - ii. Fluoroquinolones: Ciprofloxacin 500 mg twice daily, levofloxacin 500–750 mg once daily, ofloxacin 400 mg twice daily
 - iii. Cotrimoxazole (trimethoprim/sulfamethoxazole DS [TMP 160 mg/SMX 800 mg]) twice daily or trimethoprim 200 mg twice daily

3. Chronic bacterial prostatitis (symptoms should have been present for at least 6 months)
 - a. Therapy duration: 28 days, may be longer up to 6 weeks and in some refractory cases 6–12 weeks
 - b. Depends on organism
 - i. Fluoroquinolones: Ciprofloxacin 500 mg twice daily, levofloxacin 500–750 mg daily, ofloxacin 200 mg twice daily, norfloxacin 400 mg twice daily (not for gonorrhea)
 - ii. Minocycline 100 mg twice daily, doxycycline 100 mg twice daily, trimethoprim 200 mg twice daily, cotrimoxazole (TMP/SMX) DS twice daily
- B. Epididymitis
 1. Initial therapy: If caused by gonococcal or chlamydial infection, ceftriaxone 500 mg for persons weighing less than 150 kg (for persons > 150 kg, ceftriaxone 1 g) intramuscularly once plus doxycycline 100 mg twice daily for 10 days
 2. If caused by enteric organisms:
 - a. Levofloxacin 500 mg/day orally for 10 days (not for gonorrhea)
 3. If caused by chlamydia, gonorrhea, or enteric organisms:
 - a. Ceftriaxone 500 mg intramuscularly (for weight < 150 kg) in a single dose + levofloxacin 500 mg orally once daily for 10 days

XVII. MALE SEXUAL DYSFUNCTION

- A. Types
 1. Reduced libido from organic or psychological causes
 - a. Low serum testosterone concentrations
 - b. Elevated concentrations of serum prolactin
 2. Ejaculation
 - a. Premature
 - b. Retarded
 - c. Absent
 - d. Retrograde
 3. Erectile dysfunction
 - a. Persistent (at least 6 months) inability to achieve or maintain an erection of sufficient duration and firmness to complete satisfactory intercourse through vaginal penetration
 - b. Psychological
 - c. Organic
 - d. Mixed
 - e. Causes
 - i. Vasculogenic
 - (a) CVD (hypertension, coronary artery disease)
 - (b) Diabetes mellitus
 - (c) Hyperlipidemia
 - (d) Smoking
 - (e) Major pelvic surgery or radiotherapy
 - ii. Neurogenic
 - (a) Central causes: Degenerative disorders, spinal cord trauma or disorders, stroke, CNS tumors
 - (b) Peripheral causes: Type 1 or 2 diabetes, chronic renal failure, neuropathy, abdominal surgery, or urethral surgery

- iii. Hormonal abnormalities because of excess prolactin (hyperprolactinemia) or decreased testosterone concentrations (hypogonadism), hyperthyroidism or hypothyroidism, hypercortisolism or hypocortisolism
- iv. Medical conditions such as angina, shortness of breath because of asthma or chronic obstructive pulmonary disease
- v. Drugs such as antihypertensives, psychiatric medications (antidepressants and antipsychotics), antiandrogens, recreational drugs
- vi. Anatomical
 - (a) Hypospadias
 - (b) Micropenis
 - (c) Peyronie's disease
- vii. Trauma: Penile fracture, pelvic fracture

B. Treatment of Erectile Dysfunction

1. Control risk factors
 - a. Stop smoking.
 - b. Control chronic conditions (diabetes, hyperlipidemia, hypertension)
 - c. Decrease alcohol intake.
 - d. Discontinue illicit drugs.
 - e. Lose weight and increase physical activity.
 - f. CVD must be stabilized and assessed before treatment; must assess whether sexual activity in stable relationship does not increase risk of cardiovascular events or put undue stress on heart.
2. Nonpharmacologic treatment
 - a. Vacuum pump devices (may cause adverse effects such as pain and bruising)
 - b. Venous constriction rings (may cause adverse effects such as pain and bruising)
 - c. Shockwave therapy
 - d. Penile implant
 - e. Counseling
3. Testosterone replacement if testosterone concentrations are low
 - a. Oral testosterone, Jatenzo oral capsules: Recommended dosage is 237 mg by mouth in the morning and evening with food. May decrease dose to 158 mg twice daily or maximal dose of 396 mg twice daily, depending on testosterone concentration obtained 6 hours after the morning dose after 7 days of administration.
 - b. Depot intramuscular injection of testosterone enanthate 200 mg or cypionate 300 mg every 2–4 weeks, undecanoate initially 4 weeks after first injection; then every 10 weeks
 - c. Transdermal patches placed daily: Androderm 2–6 mg at bedtime on back, abdomen, or arms; rotate sites; available in 2 mg/day and 4 mg/day transdermal systems
 - d. Testosterone gel applied every morning
 - i. Testim 1% has 50 mg of testosterone per tube; apply to shoulders, upper arms only.
 - ii. AndroGel 1.62% packets, 20.25 mg and 40.5 mg of testosterone or in a pump; 2 pumps = 40.5 mg of testosterone and should be applied once daily in the morning.
 - iii. AndroGel 1% packets available in 25 mg and 50 mg of testosterone or in a pump; 4 pumps = 50 mg of testosterone that should be applied once daily in the morning; may be applied to shoulders, upper arms, and abdomen; should not be applied to genitals, chest, or back.
 - iv. Fortesta 2% gel, may apply 10–70 mg; 1 pump = 10 mg; apply to thighs; avoid genitals.
 - v. Vogelxo 1% 50 mg/one tube or packet and Vogelxo 1% Pump (4 actuations, 1 actuation = 12.5 mg); apply to clean, dry, intact skin of shoulders or upper arms; do not apply to genitals or abdomen.

- e. Axiron topical solution, apply 60 mg (1 actuation = 30 mg) to underarms once daily.
 - f. Testopel 75-mg pellet, implanted; provides hormone for 3–4 months.
 - g. Striant 30-mg buccal system; placed on gum tissue above incisors with flat section facing cheek; used twice daily.
 - h. Natesto nasal gel, recommended dosage is 11 mg of testosterone (5.5 mg/actuation, 2 pump actuations, 1 per nostril) applied intranasally three times daily; should not be administered with sympathomimetic decongestants (e.g., oxymetazoline).
 - i. Adverse effects and contraindications
 - i. Contraindicated in patients with prostate cancer
 - ii. Patches may cause redness and irritation at site of application.
 - iii. May cause increase in blood pressure, acne, enlarged prostate, liver toxicity, cholesterol changes, edema, polycythemia.
 - j. Monitor serum testosterone within 1–3 months and at 6- to 12-month intervals.
 - k. If no improvement after 3 months, may discontinue treatment.
 - l. The 2020 ACP guidelines recommend the following:
 - i. Discussions of testosterone treatment in men with age-related low testosterone and sexual dysfunction should include the potential benefits, harms, costs, and patient preferences.
 - ii. Symptoms should be reevaluated within 12 months (and then periodically). Testosterone should be discontinued if sexual function does not improve.
 - iii. Given lower costs, intramuscular testosterone rather than transdermal should be considered. Efficacy and risk profiles are similar between the formulations.
4. Phosphodiesterase (PDE) inhibitors (first-line drug therapy for men without contraindications to use) (Table 21)
- a. Sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra/Staxyn), avanafil (Stendra)
 - b. Inhibits PDE-5 in the penile tissue, preventing the breakdown of cyclic guanosine monophosphate, thus increasing smooth muscle relaxation in the corpora cavernosa and increasing penile rigidity.
 - c. Adverse effects: Headache, hot flashes, heartburn, diarrhea, myalgias, hypotension, dizziness, difficulty discriminating blue from green
 - d. Contraindications, cautions, and drug interactions
 - i. Contraindicated with nitrate use; should not be used together.
 - ii. Use caution with CVD, hypotension, uncontrolled hypertension, MI, or stroke within 6 months, life-threatening arrhythmias, penile deformities, renal or hepatic dysfunction, and degenerative retinal disorders.
 - iii. Drug interactions such as protease inhibitors; decrease PDE inhibitor dosage by half in some cases; precautions with CYP3A4 inhibitors and macrolides because they increase PDE inhibitor levels; may also need to decrease PDE inhibitor doses in these situations or possibly avoid combined use with CYP3A4 inhibitors.

Table 21. Summary of Phosphodiesterase-5 Medications

Name	Dosage	Comments
Sildenafil (Viagra)	50 mg PO 1 hr before intercourse (dose range 25–100 mg)	May require hepatic and renal dosage adjustments Take on empty stomach
Vardenafil (Levitra)	10 mg PO 1 hr before intercourse (dose range 5–20 mg)	May require hepatic dosage adjustment Fatty meal delays onset
Vardenafil oral disintegrating tablet (Staxyn)	10 mg PO 1 hr before intercourse	Not recommended with hepatic conditions Do not use with CYP3A4 inhibitors
Tadalafil (Cialis)	5 mg PO up to 36 hr before intercourse (dose range 5–20 mg) 2.5–5 mg PO daily for daily dosing	May require hepatic or renal dose adjustments Food has no effect on onset
Avanafil (Stendra)	100 mg PO 30 min before intercourse (dose range 50–200)	Fatty food may delay onset

PO = by mouth

5. Alprostadil (second-line therapy if PDE-5 inhibitors fail)
 - a. Caverject intracavernosal injection 2.5–40 mcg
 - b. MUSE urethral pellets 125–1000 mcg
 - c. Effect may last 30–90 minutes.
 - d. Adverse effects: Penile pain, cavernosal scarring, priapism, hypotension
 - e. Drug interactions: Do not use with PDE inhibitors.
6. Yohimbine
 - a. Derivative of African yohimbine tree
 - b. α_2 -Antagonist
 - c. Efficacy controversial; not recommended according to the American Urological Association guidelines.
 - d. Adverse effects: Headaches, dizziness, insomnia, and anxiety
 - e. Dose: 5.4 mg orally three times daily
- C. Treatment of Premature Ejaculation
 1. Antidepressants: Off-label use
 - a. Selective serotonin reuptake inhibitors: Fluoxetine, paroxetine, sertraline
 - b. Tricyclic antidepressant: Clomipramine
 - c. Continuous (daily), or episodic dosing 2–12 hours before intercourse
 2. Topical anesthetics: Lidocaine/prilocaine cream (EMLA [eutectic mixture of local anesthetic]) 2.5 g applied to the glans penis and penile shaft 20–30 minutes before intercourse

Patient Case

13. A 65-year-old man presents to his physician with symptoms that are determined to be erectile dysfunction. He has a history of hyperlipidemia, gastroesophageal reflux disease, and glucose intolerance. His medications include atorvastatin 40 mg orally daily, omeprazole 20 mg orally daily, and aspirin 81 mg orally daily as tolerated. He states that he has heard of medications to help with his symptoms but does not want to have to plan his intimate moments. Which drug would work best for this patient?
- A. Tadalafil
 - B. Avanafil
 - C. Yohimbine
 - D. Bupropion

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

DVT is increased with conjugated estrogens and medroxyprogesterone acetate (Prempro) (Answer A is correct). Myocardial infarction and strokes are also increased (Answers B and C are incorrect). Fractures are decreased (Answer D is incorrect).

2. Answer: C

The patient has an intact uterus; therefore, she needs both an estrogen and a progestogen. Conjugated estrogens and medroxyprogesterone acetate (Prempro) is the only product listed that includes a progestogen (Answer C is correct). The patient has hot flashes in addition to vaginal dryness; therefore, a systemic product is recommended (Answer B is incorrect). A vaginal insert or cream would be appropriate for GSM symptoms but not for hot flashes, and ospemifene is indicated for vaginal atrophy. The patch would be appropriate if a progestogen were added to the regimen (Answers A and D are incorrect).

3. Answer: C

The definitions of bone mineral density and T-scores are as follows:

Normal = BMD within 1 standard deviation (SD) of the young adult mean, Low bone mass (osteopenia) = BMD between -1 SD and -2.5 SD,

Osteoporosis = BMD at least -2.5 SD,

Severe osteoporosis = BMD less than -2.5 and history of a fracture. The patient has a T-score of -2.6 at the hip, which is indicative of osteoporosis (Answer C is correct; Answers A and B are incorrect). The patient does not have severe osteoporosis of the spine because her T-score at the spine is -2.1 and not less than -2.5 (Answer D is incorrect).

4. Answer: D

Drug therapy is indicated for the following: A hip or vertebral fracture; a BMD T-score below -2.5 at the femoral neck or spine, excluding secondary causes; or a BMD T-score between -1.0 and -2.5 at the femoral neck or spine and a 10-year probability of hip fracture 3% or greater or a 10-year probability of major osteoporosis-related fracture of 20% or greater based on the FRAX system. The patient needs therapy because her

T-score is less than -2.5 at the hip, and her 10-year probability of hip fracture is at least 3% or her 10-year probability of major osteoporosis-related fracture at least 20% based on the FRAX system (Answer D is correct; Answer A is incorrect). Bisphosphonates such as alendronate and risendronate are considered first-line drugs because they inhibit normal and abnormal bone resorption and reduce vertebral and non-vertebral fractures by 30%–50%. For risendronate, the treatment dosage is 35 mg orally weekly, further indicating that Answer D is correct. In addition, the patient's CrCl is 60–70 mL/minute, which allows use of a bisphosphonate. Use of a bisphosphonate is contraindicated at a CrCl less than 30–35 mL/minute. Abaloparatide (Tymlos) is reserved for treating women at a high risk of fracture, including those with a very low BMD (T-score less than -3.0) and a previous vertebral fracture (Answer B is incorrect). The patient should receive vitamin D 800 international units daily because she is older than 70 years and takes calcium 1200 mg daily in divided doses (again, Answer D is correct; Answers A and B are incorrect). In addition, the patient is likely not receiving calcium from her diet due to her lactose intolerance and minimal intake of dairy products. Romosozumab is not indicated as first-line treatment and is indicated for those at high risk of fracture, those with a previous fracture, or those for whom other osteoporosis therapies have failed (Answer C is incorrect).

5. Answer: C

Lisinopril is an ACE inhibitor known to have some teratogenicity. It is not recommended for women who are trying to conceive or who are pregnant (Answers A and D are incorrect). This patient needs treatment for hypertension, particularly while pregnant, because hypertension can lead to detrimental effects in the fetus and mother (Answer B is incorrect). Labetalol and nifedipine are the preferred agents for treating hypertension in women who are trying to conceive or pregnant, with labetalol used more often in recent years (Answer C is correct). β -Blockers are not specifically teratogenic but may cause adverse effects in the fetus such as intrauterine growth retardation, particularly with atenolol (Answer D is incorrect). Diuretics such as hydrochlorothiazide are not first line. They can be used as a second- or third-line agent. (again, Answer A is incorrect).

6. Answer: B

Estrogen deficiency causes early or midcycle breakthrough bleeding (days 1–14). There is possible deficiency in estrogen and progestin at mid-cycle. Progestin deficiency results in late breakthrough bleeding (days 14–28). An OC with stronger estrogenic properties is needed because the patient is bleeding through early in the cycle. Ethinyl estradiol 30 mcg/desogestrel 0.3 mg (Reclipsen) has higher estrogenic properties (intermediate) than ethinyl estradiol 20 mg/levogestrel 0.1 mg (Lessina) while the other OC options have low estrogenic properties (Answer B is correct; Answers C and D are incorrect). The patient has been using Lessina for 4 months, which is past the trial period of 3 months, with continued breakthrough bleeding. Therefore, the patient could switch to another product (Answer A is incorrect).

7. Answer: C

Estrogen-containing products (ethinyl estradiol/drospirenone and contraceptive patch) are contraindicated for this patient because she is a smoker older than 35. In addition, the patient cannot use the contraceptive patch (ethinyl estradiol and norelgestromin [Xulane]) because her weight is more than 90 kg. Even though she smokes only ½ pack of cigarettes per day, her other risk factors such as age and hypertension increase the risk of events with tobacco use. In addition, she takes an ACE inhibitor, which would not be the best choice with drospirenone because of the possibility of hyperkalemia (Answer B is incorrect). Depot medroxyprogesterone acetate has a long return to fertility time, and the patient is 37 years old (Answer D is incorrect). Moreover, DMPA may cause weight gain, and the patient already has obesity. Norethindrone has a quick return to fertility and will not affect her hypertension or interact with her ACE inhibitor (Answer C is correct).

8. Answer: A

The patient has obesity, with a BMI of 32 kg/m². To optimize her chances of ovulation, she should try to lose weight and lower her BMI. Her ultrasonography, hirsutism, and acne indicate she has PCOS. Clomiphene citrate would be a first-line agent to help stimulate ovulation (Answer A is correct). She and her husband have been trying to conceive for 13 months, which meets the definition of infertility necessitating intervention (Answer B is incorrect). Human chorionic gonadotropin injections are not appropriate to provide at this time; they are usually used to help the

ovum rupture once the follicle has been stimulated to increase (Answer D is incorrect). Follicle-stimulating hormone would not be recommended at this time as it is not a first-line treatment (Answer C is incorrect). If the patient fails clomiphene or letrozole (another option instead of clomiphene but not an option in the answers) then FSH injections might be appropriate at that time.

9. Answer: B

Treatment of HSV infection substantially decreases the duration of viral shedding, pain, and time to complete healing but does not affect the risk, frequency, latency, or severity of recurrences (Answer B is correct; all others are incorrect).

10. Answer: D

Patient-initiated therapy is important for people with occasional recurrences (fewer than six per year) of HSV infection because recurrent infections resolve more rapidly than the initial infection. Antiviral agents should be initiated as soon as possible. Because the patient is having several recurrences (six or more a year), patient-initiated therapy is insufficient (Answers A and B are incorrect). Suppressive therapy is given twice daily or once daily, not three times daily; therefore, suppressive therapy with famciclovir 250 mg orally three times daily is inappropriate (Answer C is incorrect). Suppressive therapy with valacyclovir 500 mg/day orally should be offered (Answer D is correct).

11. Answer: C

Cefotetan 2 g intravenously every 12 hours with doxycycline 100 mg orally or intravenously every 12 hours is an appropriate empiric antibiotic combination for PID (Answer C is correct). The combination has activity against *N. gonorrhoeae* and *C. trachomatis* and against the gram-negative and anaerobic organisms that are often involved. Metronidazole alone would have activity only against anaerobes and would miss the other organisms often involved in PID (Answer B is incorrect). Ampicillin/sulbactam has good activity against most organisms in PID; however, it has no activity against atypical organisms (e.g., *C. trachomatis*) (Answer A is incorrect). Ceftriaxone and doxycycline are likely not sufficient for empiric coverage of PID as there is not anaerobic coverage. Additionally, the ceftriaxone dosage should be 1 g, the duration of doxycycline should be 14 days, and metronidazole should be a component of the regimen (Answer D is incorrect).

12. Answer: C

Pelvic inflammatory disease is related to sexual activity; therefore, until all partners and the patient have been treated, abstinence from intercourse for at least 7 days is indicated, (Answers A and B are incorrect). Patients should be encouraged to be tested for HIV because of the strong relationship between STDs and the risk of HIV (Answer D is incorrect). The most appropriate recommendation for a sexually active patient with PID is to have all sexual partners within the past 60 days tested and treated (Answer C is correct).

13. Answer: A

Tadalafil may be dosed daily without respect to timing of sexual intercourse (Answer A is correct). Avanafil should be taken 30 minutes before sexual intercourse (Answer B is incorrect). Yohimbine and bupropion are not first line for erectile dysfunction (Answers C and D are incorrect). Bupropion is usually used in women with sexual dysfunction caused by serotonin reuptake inhibitors and not usually used in men for the treatment of sexual dysfunction.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

The patient's T-score at the hip and spine are between -1 and -2.5 SD, which is considered low bone mass (Answer A is correct). Normal BMD is defined as a T-score within 1 SD of the young adult mean, which the patient does not have (Answer D is incorrect). Osteoporosis is defined as having BMD with a T-score of at least -2.5 SD, which the patient does not have in either the hip or the spine (Answers B and C are incorrect).

2. Answer: A

Even though the patient is currently thought to have osteopenia, his 10-year probability of a major osteoporosis-related fracture is 14%, and his 10-year probability of a hip fracture is 6.7% according to the FRAX score, which indicates a need for drug therapy (Answer A is correct). Bisphosphonates such as alendronate and risendronate are considered first-line drugs because they inhibit normal and abnormal bone resorption and reduce vertebral and non-vertebral fractures by 30%–50%. Raloxifene is indicated for preventing osteoporosis in postmenopausal women. It works as a selective estrogen receptor modulator and is best for preventing vertebral fractures, not hip fractures (Answer C is incorrect). Calcium and vitamin D are both recommended for this patient as well. Because of the patient's age and poor diet, the recommended dosage of vitamin D is 800 international units orally per day (Answer A is correct; Answer D is incorrect); 600 international units orally per day is recommended for those younger than 70 years (Answer B is incorrect). Answer B is also incorrect because the patient requires pharmacotherapy and not just calcium and vitamin D. He walks 30 minutes/day, which satisfies the recommendation of weight-bearing activity (Answers B and D are incorrect).

Drug therapy begins with the following:

- (a) A hip or vertebral fracture
- (b) BMD T-score below -2.5 at the femoral neck or spine, excluding secondary causes
- (c) BMD T-score between -1.0 and -2.5 at the femoral neck or spine and a 10-year probability of hip fracture 3% or greater or 10-year probability of major osteoporosis-related fracture 20% or greater according to the FRAX system.

3. Answer: C

Warfarin is contraindicated in pregnancy and a known teratogen (Answers A, B, and D are incorrect). Warfarin should not be used at any time during pregnancy unless the benefit outweighs the risk in very rare and special cases. If a woman needs anticoagulation and is planning to conceive or is pregnant, she should find an alternative anticoagulant such as a low-molecular-weight heparin (e.g., enoxaparin) or heparin (although with heparin, there may be a risk of osteoporosis with extended duration of use (Answer D is incorrect). A low-molecular-weight heparin would be the agent of choice (Answer C is correct).

4. Answer: D

Medroxyprogesterone acetate is added to conjugated estrogens to decrease the risk of endometrial cancer; venlafaxine is not relieving her hot flashes, therefore it should be discontinued (Answer D is correct). The addition of medroxyprogesterone acetate does not decrease the risk of stroke (Answer C is incorrect). Estrogen alone is insufficient because the patient has an intact uterus, as indicated by her medical history (no surgical procedures) (Answer A is incorrect). Venlafaxine is not relieving her hot flashes; therefore, it should be discontinued (Answer B is incorrect).

5. Answer: C

The patient is experiencing systemic symptoms such as hot flashes, and she has localized genitourinary atrophy, which probably results in pain during sexual intercourse. Estradiol vaginal cream and ospemifene are indicated for genitourinary atrophy, not for vasomotor symptoms (Answers A and D are incorrect). The best treatment would be an oral or transdermal systemic agent (Answer C is correct). The patient has had a hysterectomy; therefore, a progestogen in combination with estrogen is unnecessary (Answer B is incorrect).

6. Answer: C

The efficacy of lamotrigine may be decreased (Answer C is correct; Answer B is incorrect). Estrogen and drospirenone are not affected by lamotrigine (Answers A and D are incorrect). (*See Answer 6 table.*)

7. Answer: B

The number of patients needed to treat with valacyclovir over acyclovir to prevent one recurrent HSV genital infection (1 year of follow-up of study participants receiving suppressive therapy [acyclovir or valacyclovir], with 25% and 20%, respectively, experiencing a recurrent infection) is $20 = 1/(0.25-0.20)$ (Answer B is correct; all other answers are incorrect). The only information needed is the absolute risk in both groups (which is provided).

8. Answer: B

The patient has a history of migraine with aura, which precludes any estrogen product (oral ethinyl estradiol/desogestrel oral tablet and transdermal contraceptive patch). Her blood pressure is slightly elevated but not greater than 160/100 mm Hg, which would not be a contraindication for estrogen use; however, her migraine with aura rules out the use of estrogen products (Answers C and D are incorrect). She also has obesity at 215 lb (98 kg) and weighs more than 90 kg, so the patch is not recommended (again, Answer C is incorrect). The levonorgestrel IUS (Mirena, Kyleena, Skyla, Liletta) may be an option, but the patient is interested in conceiving in a year or so, which makes the IUS not cost-effective because they last 3–6 years. (Answer A is incorrect). Norethindrone oral tablet is a progestogen-only pill and the best choice (Answer B is correct).

9. Answer: D

Clomiphene citrate is the first-line choice to stimulate ovulation (Answer D is correct). Another first-line option could be an aromatase inhibitor such as letrozole; however, this was not an answer choice. Menopur (hMG), Synarel (GnRH agonist), and Ovidrel (hCG) are not first-line agents and are usually used after clomiphene citrate or aromatase inhibitors have failed or when the patient is undergoing assisted reproductive therapies (Answers A, B, and C are incorrect).

10. Answer: B

Clinical studies suggest that levonorgestrel emergency contraception is still effective for up to 120 hours after unprotected intercourse though package labeling only states 72 hours, and the patient does not need a prescription (Answer B is correct; Answer A is incorrect). She stated that her vaginal ring slipped out of place. If the vaginal ring had been out of place longer than

3 hours and unprotected intercourse had occurred, EC should have been recommended (Answers C and D are incorrect). When inserting a new vaginal ring, she should also be instructed to use a BUM for at least 7 days (again, Answer D is incorrect).

11. Answer: A

The patient's laboratory values are within normal limits, indicating that his disease states are not necessarily the cause of his erectile dysfunction. A phosphodiesterase inhibitor such as vardenafil may be initiated (Answer A is correct). Testosterone replacement would not be effective because the patient has normal testosterone concentrations (Answer B is incorrect). Yohimbine would not be considered first-line therapy because its efficacy is controversial (Answer C is incorrect). Fluoxetine is inappropriate because the patient does not have premature ejaculation (Answer D is incorrect).

12. Answer: B

Penicillin G 4 million units every 4 hours intravenously for 14 days after penicillin desensitization is the correct therapy for a patient with neurosyphilis who is allergic to penicillin (Answer B is correct). Levofloxacin would not cover syphilis (Answer A is incorrect). Three doses of benzathine penicillin G are indicated for late latent syphilis, not neurosyphilis (Answer C is incorrect). Furthermore, although azithromycin is an alternative for patients who are penicillin allergic in other situations, patients with neurosyphilis should be desensitized and given penicillin (Answer D is incorrect).

13. Answer: A

Data are continuous and probably normally distributed (given the large population of 360 patients in the study); therefore, a parametric test is indicated. Because ANOVA is a parametric test used to compare more than two groups, it would be appropriate (Answer A is correct). The Student t-test is a parametric test for comparing only two groups (Answer D is incorrect). A chi-square test is used to assess nominal data between two groups (Answer B is incorrect). The Mann-Whitney U test is a nonparametric analog to the Student t-test (Answer C is incorrect).

Answer 6 Table.*

Drugs Interfering with Oral Contraceptive Efficacy		Oral Contraceptives Interfering with the Efficacy of Other Drugs	
Increased	Decreased	Increased	Decreased
Ascorbic acid	Anticonvulsants ^a	Benzodiazepines ^b	Benzodiazepines ^c
Acetaminophen-scheduled	Antibiotics	Theophylline and caffeine	Warfarin
Atorvastatin	Rifampin	Cyclosporine	Thyroid agents
Rosuvastatin	Theophylline	Corticosteroids	Hypoglycemics
Ginseng	St. John's wort	Alcohol	Methyldopa
NNRTIs ^d	NNRTI-nevirapine	β-Blockers	Metformin
Protease inhibitors ^e	Protease inhibitors ^f	Tricyclic antidepressants	Amprenavir
Tranexamic acid	Sulfonamides	Ropinirole	Lamotrigine
Voriconazole	Griseofulvin	Zolmitriptan	Fosamprenavir
	Bosentan		
	Tacrolimus		
	Modafinil		

Note. *Table not all-inclusive of all drug interactions; some interactions may exist that are not listed in this table.

^aBarbiturates, phenytoin, primidone, carbamazepine, oxcarbazepine, felbamate, topiramate, vigabatrin

^bAlprazolam, chlordiazepoxide, diazepam

^cTemazepam

^dDelavirdine, efavirenz

^eAtazanavir, indinavir

^fNelfinavir, ritonavir, lopinavir/ritonavir, amprenavir

NNRTI = nonnucleoside reverse transcriptase inhibitor