Men's and Women's Health

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Learning Objectives

1. Recommend appropriate treatment options for patients with menopausal symptoms, osteoporosis, and conditions in pregnancy, infertility, and sexual dysfunction.
2. Identify drugs that are considered safe and unsafe in pregnancy and lactation.
3. Modify contraceptive regimens on the basis of estrogen- and progestin-related adverse effects or drug interactions.
4. Devise a pharmacotherapeutic plan for appropriate contraceptive use, contraceptive method mishaps, and use of emergency contraception.
5. Identify common sexually transmitted diseases and recommend appropriate pharmacotherapy.

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 with a history of hypertension who admits smoking 1 pack of cigarettes per day. He states that he walks on his treadmill 30 minutes a day. He is 69 inches tall and weighs 150 lb (68 kg). His bone mineral density (BMD) T-score is –2.1 at the hip and –2.2 at the spine. His fracture history includes an adult fall at age 68 with an ankle fracture. His Fracture Risk Assessment Tool (FRAX) score (10-year 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 who is 65 inches tall and weighs 140 lb (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?
   A. Continue current warfarin dose to prevent clots during pregnancy.
   B. Continue warfarin therapy but increase the dose to prevent clots during pregnancy.
   C. Discontinue warfarin; start enoxaparin 40 mg subcutaneously daily until pregnant and continue through pregnancy.
   D. Discontinue warfarin; start heparin 5000 units subcutaneously every 8 hours daily until 12 weeks pregnant, and then reinitiate warfarin.

4. J.K. is a 51-year-old postmenopausal woman suffering from 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.?
   A. No other drug is required; estrogen alone is sufficient for hot flashes.
   B. No other drug is required because J.K. is otherwise healthy and should continue on venlafaxine.
   C. Medroxyprogesterone acetate should be added to decrease the risk of stroke.
   D. 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 uterine heavy 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.?
   A. Estradiol vaginal cream 0.1 mg/g.
   B. Conjugated estrogen and medroxyprogesterone acetate (Prempro) 0.625 mg/2.5 mg tablets.
   C. Conjugated estrogen (Premarin) 0.3-mg tablets.
   D. Ospemifene (Osphena) 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?
   A. The effectiveness of ethinyl estradiol and drospirenone may be decreased.
   B. The effectiveness of lamotrigine may be increased.
   C. The effectiveness of lamotrigine may be decreased.
   D. 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 that in patients receiving acyclovir or 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?
   A. 5.
   B. 20.
   C. 25.
   D. Insufficient information to calculate this number.

8. K.M. is a 28-year-old woman with a history of migraine with aura seeking contraception. She is 68 inches tall and weighs 215 lb (98 kg), with blood pressure (BP) today of 135/82 mm Hg; she denies smoking and alcohol use and states she would like to have children in a year or so. Which is the best contraceptive agent for K.M.?
   A. Levonorgestrel intrauterine system (IUS).
   B. Oral tablet norethindrone (Micronor).
   C. Transdermal ethinyl estradiol/etonogestrel patch.
   D. Oral ethinyl estradiol/desogestrel oral tablet (Mircette).

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. Ovidrel (human chorionic gonadotropin [hCG]).
   B. Synarel (nafarelin/gonadotropin-releasing hormone [GnRH] agonist).
   C. Pergonal (human menopausal gonadotropin [hMG]).
   D. Clomid (Clomiphene).

10. T.G. is a 22-year-old woman who comes to a community pharmacy and requests 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-C) 106 mg/dL, high-density lipoprotein cholesterol (HDL-C) 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 dermal 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, a laboratory profile was performed, which was positive for the Venereal Disease Research Laboratory test (syphilis test) with 10 white blood cells per cubic millimeter. 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). Which therapy is best for T.M.?
    A. Levofloxacin 750 mg intravenously × 1.
    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.

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 ranges from age 40 to 58 years.
   3. Common symptoms
      a. Vasomotor symptoms, also known as hot flashes
         i. Most common reason treatment is sought
         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): Recent nomenclature change to encompass both vaginal and urinary symptoms (Portman DJ, Gass MLS. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. Menopause 2014;21(10):1-6)
         i. Decrease in estrogen causes thinning of hair of the mons and shrinkage of the labia minora; atrophy of vulva 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 and urgency with dysuria.

B. Treatments
   1. Individualization of therapy is essential. Need to consider the woman's medical history
      a. History of cancer, specifically breast cancer
      b. History of cardiovascular disease, stroke, hypertension
      c. Quality of life with menopausal symptoms
   2. Hormone therapy (HT): Estrogen and progestogen therapy (also known as EPT)
      a. Primary indication: Treatment of moderate to severe menopause symptoms and osteoporosis when other treatments have failed
      b. 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-C and increase HDL-C; however, it was not shown to lower coronary heart disease (CHD) according to the Heart and Estrogen/Progestin Replacement Study (HERS; Hulley S, Grady D, Bush T et. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-13) or the Women's Health Initiative (WHI; Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33) trials.
(e) Insomnia and fatigue: May help improve sleep by decreasing hot flashes
(f) Mood changes: May help stabilize mood swings but not indicated for mood disorders
(g) Sexual function: May help with vaginal atrophy, thus decreasing pain with sexual intercourse

ii. Risks of estrogen
(a) Endometrial cancer: Risk increases with unopposed estrogen use in women with an intact uterus.
(1) Cancer risk depends on duration of estrogen use.
(2) Cancer risk increases 8-fold for 10–20 years of estrogen use.
(3) Not recommended for use in women with a history of endometrial cancer.
(4) A progestogen is recommended in all women with an intact uterus using estrogen (PEPI trial; Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA 1996;275:370-5).
(b) Breast cancer with unopposed estrogen: Uncertain
(1) WHI showed no increased risk in women who use estrogen for an average of 7.1 years. May increase relative risk among women who take estrogen for 10–20 years
(2) Not recommended for use in women with a history of breast cancer (Stefanick ML, Anderson GL, Margolis KL et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA 2006;295:1647-57)
(3) Risk seems to increase with the addition of the progestogen and related to the length of use. The risk is small and decreases after discontinuation of use.
(c) CHD: Possible increased risk of cardiovascular outcomes; not recommended for coronary protection at any age (see below for further information)
(d) Other adverse effects: Bloating, headache, breast tenderness (5%–10%)

iii. Benefits of progestogen (progestogen umbrella term for progesterone [natural] and progestins [synthetic])
(a) Decreased risk of estrogen-induced irregular bleeding, endometrial hyperplasia, and carcinoma
(b) Protection against breast carcinoma
(c) Enhancement of estrogen prophylaxis of osteoporosis

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%)

c. Selected trials related to HT
   i. Cardiovascular outcomes with conjugated estrogens and medroxyprogesterone acetate (HERS trial; Hulley S, Grady D, Bush T et. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-13)
      (a) A longer duration of use leads to a greater decrease in relative hazards in nonfatal myocardial infarction (MI) and CHD death; however, there was an increased risk of venous thromboembolism (VTE) and gallbladder disease.
      (b) 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.
      (c) 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 (HERS II trial; Hulley S, Furberg C, Barrett-Connor E et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002;288:58-66).
   ii. Other findings related to cardiovascular outcomes from various trials
      (a) Venous thromboembolism
         (1) Observational studies indicated increased risk.
         (2) A randomized controlled trial, the WHI, (Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. 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 (seven additional VTEs per 10,000 women per year of ET).
         (3) In WHI, when EPT and ET were initiated in women 50–59 years of age, they had a lower risk of VTE (11 additional VTEs per 10,000 women per year of EPT and 4 additional VTEs per 10,000 women per year of ET).
      (b) Stroke
         (1) 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).
         (2) Younger women 50–59 years of age showed no significant increase in stroke with EPT in the WHI, but in the ET group alone, risk doubled. Nurses' Health Study showed similar results.
      (c) Coronary heart disease
         (1) 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.
         (2) 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.
         (3) 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 levels of coronary artery calcium after 7 years of treatment.

iii. WHI (Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. 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 cardiovascular disease could be caused by age.

Table 1. Summary of WHI Outcomes for EPT Use

Risk or Benefit	Relative Risk	Absolute Risk Each Year
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
Strokes	1.41, or 41% ↑	8 more cases in 10,000 women
Blood clots	2.11, or 111% ↑	18 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
Dementia[a]	2.05, or 105% ↑	23 more cases in 10,000 women older than 65

[a]Women's Health Initiative Memory Study.

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

iv. Further information suggests increased risk of ovarian cancer (considered rare, data conflicting); long-term use greater than 5 years may increase risk, particularly in estrogen-only therapy; overall risk of occurrence considered rare.

v. Lung cancer may be increased in older women with a history of smoking (Mørch LS, Løkkegaard E, Andreasen AH et al. Hormone therapy and ovarian cancer. JAMA 2009;302:298-305; Chlebowski RT, Schwartz AG, Wakelee H et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. Lancet 2009;374:1243-51); some data are conflicting. Seems to be more associated with EPT use than with ET use

vi. Helpful references for further information

(a) Updated position statement by North American Menopause Society (North American Menopause Society. The 2012 hormone therapy position statement of the North American Menopause Society. Menopause 2012;19:257-71)

(b) Updated guidelines by the Endocrine Society (Santen RJ, Allred DC, Ardoin SP, Postmenopausal hormone therapy: An Endocrine Society Scientific Statement. J Clin Endocrinol Metab 2010;95(suppl 1):S1-66)

d. Formulations

i. Oral: Used for systemic symptoms, also covers GSM if concomitant

ii. Transdermal: For women who are intolerant of oral preparations, used for systemic symptoms, also covers GSM if concomitant

iii. 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.

e. Hormone regimens (Guidelines for counseling postmenopausal women about preventive hormone therapy. American College of Physicians. Ann Intern Med 1992;117:1038-41)

i. Therapy duration: Lowest dose for least amount of time. Check after 3 months to 1 year, and attempt to discontinue if asymptomatic; if symptoms recur, treat for an additional 3 months; best to limit treatment to less than 5 years

ii. Unopposed estrogen
   (a) Women with a uterus must have a progestogen and cannot use estrogen alone (use of estrogen alone in women with a uterus increases the risk of endometrial cancer, PEPI trial; Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA 1996;275:370-5).
   (b) Estrogen taken daily without interruption is suggested for women with a hysterectomy.
   (c) Transdermal estradiol patches in women who are intolerant of oral preparations
   (d) Vaginal preparations for women with GSM. In general, topical treatment is sufficient and should be tried before oral preparations for patients experiencing no other symptoms.

iii. Estrogen plus cyclic progestogen
   (a) Continuous estrogen daily
   (b) Cyclic progestogen such as medroxyprogesterone acetate 5−10 mg/day or the equivalent for 10–14 days/month
   (c) Similar to female cycle, with a withdrawal bleed each cycle

iv. Estrogen plus continuous progestogen
   (a) Continuous estrogen daily
   (b) Continuous progestogen 1.5–2.5 mg/day or the equivalent without interruption
   (c) Irregular menstrual cycle for the first 8–12 months of therapy

v. Intermittent
   (a) Continuous estrogen daily
   (b) Three days on progestogen, 3 days off
   (c) Seldom used

f. Monitoring criteria
   i. Monthly: Breast self-examination
   ii. Annually: Breast examination by provider, mammography (or biannually per U.S. Preventive Services Task Force), pelvic examination
   iii. Evaluation of vaginal bleeding
      (a) Unopposed estrogen: Any episode of vaginal bleeding unless the woman has had a health assessment deemed normal in the past 6 months
      (b) Estrogen plus cyclic progestogen: If bleeding occurs other than at the time of expected withdrawal bleeding
      (c) 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

g. Products and dosing

Table 2. Oral Estrogen Products

Brand Name	Generic Name	Strengths (mg)
Cenestin	Synthetic conjugated estrogens, A	0.3, 0.45, 0.625, 0.9, 1.25
Enjuvia	Synthetic conjugated estrogens, B	0.3, 0.45, 0.625, 0.9, 1.25
Estrace	17β-Estradiol	0.5, 1.0, 2.0
Menest	Esterified estrogens	0.3, 0.625, 1.25, 2.5
Ortho-Est	Estropipate	0.625 (0.75 mg), 1.25 (1.5 mg), 2.5 (3 mg, generic only)
Premarin	Conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25, 2.5

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 weeks; then gradually reduced to half the initial dose for 1-2 weeks, followed by maintenance of 1 g/day applied vaginally 1-3 ×/week
	Premarin	Conjugated estrogens (0.625 mg/g)	0.5–2 g/day applied vaginally
Vaginal rings	Estring	17β-Estradiol (2-mg ring that delivers 7.5 mcg/day)	One ring every 3 months inserted vaginally
	Femring	Estradiol acetate (0.05 mg/day or 0.10 mg/day)	
Vaginal tablet	Vagifem	Estradiol hemihydrate (10 mcg/day)	One vaginal tablet once daily for 2 weeks; then 1 tablet twice weekly

Table 4. Transdermal Estrogen Products

Brand Name	Formulation	Estrogen Provided (mg/day)	Dose	Unique Traits and Counseling Points
Alora	17β-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		0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	Minivelle should be placed on dry skin below umbilicus on abdomen or buttocks
Vivelle		0.0375,0.05, 0.075, 0.1	1 patch twice weekly	
Vivelle Dot		0.025, 0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	
Menostar		0.014	1 patch weekly	Menostar is lowest-dose transdermal patch available
Divigel 0.1%	17β-Estradiol transdermal gel	Unknown	0.25, 0.5, 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)	Apply 0.87 g/day or 1.7 g/day (1 pump, 2 pumps)	Must prime pumps before using Apply Elestrin on upper arm
EstroGel 0.06%		0.75 (0.035 absorbed)	Apply 1.25 g/day (1 pump)	Apply EstroGel from wrist to shoulder
Evamist	17β-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, Mimvey	17β-Estradiol/ norethindrone acetate	0.5 mg of estrogen, 0.1 mg of progestogen 1 mg of estrogen, 0.5 mg of progestogen (Mimvey)	1 tablet daily
Angeliq	17β-Estradiol/ drospirenone	1 mg of estrogen, 0.5 mg of progestogen 1 mg of estrogen, 0.25 mg of progestogen	1 tablet daily
Climara Pro	17β-Estradiol/ levonorgestrel	0.045 mg of estrogen, 0.015 mg of progestogen	1 patch weekly
CombiPatch	17β-Estradiol/ norethindrone acetate	0.05 mg of estrogen, 0.14 mg of progestogen 0.05 mg of estrogen, 0.25 mg of progestogen	1 patch twice weekly
Femhrt, Jinteli	Ethinyl estradiol/ norethindrone acetate	2.5 mcg of estrogen, 0.5 mg of progestogen 5 mcg of estrogen, 1 mg of progestogen (Jinteli)	1 tablet daily
Prefest	17β-Estradiol/ norgestimate	1 mg of estrogen, 0.09 mg of progestogen	3 days of estrogen tablets only, 3 days of estrogen and progestogen
Premphase	Conjugated estrogens/ medroxyprogesterone acetate	0.625 mg of estrogen with 5 mg of 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 of estrogen with 2.5 or 5 mg of progestogen 0.3 or 0.45 mg of estrogen with 1.5 mg of progestogen	1 tablet daily

Table 6. Progestogen Products[a]

Brand Name	Generic Name	Dosage Strengths and Formulation
Aygestin	Norethindrone acetate	5-mg oral tablets
Megace	Megestrol acetate	20-, 40-mg oral tablets
Micronor, Nor-QD	Norethindrone	0.35-mg oral tablets
Mirena	Levonorgestrel	20 mcg/day released from intrauterine system
Skyla	Levonorgestrel	14 mcg/day released from intrauterine system
Crinone 4%, 8%	Progesterone gel	45 mg/applicator vaginally, 90 mg/applicator vaginally
Prometrium	Micronized progesterone in peanut oil	100- and 200-mg oral capsules
Provera	Medroxyprogesterone acetate	2.5-, 5-, and 10-mg oral tablets

[a]Not all products approved for menopause therapy.

3. Selective estrogen receptor modulators (SERMs) indicated for use in menopause symptoms
   a. Ospemifene 60 mg oral tablets (Osphena): 1 tablet orally daily
      i. Indicated for the treatment of moderate to severe dyspareunia caused by vulvar and vaginal atrophy due to menopause
      ii. 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. There are no studies available evaluating the use of ospemifene with a progestin.

iii. Adverse reactions (greater than 1%)
(a) Hot flashes
(b) Muscle cramps
(c) Vaginal discharge
(d) Hyperhidrosis
iv. Dose: 60 mg/day orally
v. Contraindications similar to those of estrogen (e.g., history of estrogen-dependent cancer, undiagnosed vaginal bleeding)
(a) Pregnancy, nursing, pediatrics
(b) History of VTE
(c) Hepatic impairment
vi. Drug interactions
(a) Rifampin decreases ospemifene exposure by 59%, and they should not be used together.
(b) Fluconazole increased ospemifene levels 2.7-fold and should not be used concomitantly; ketoconazole increases ospemifene 1.4-fold.
(c) Highly protein bound about 99%; may affect other medications that are protein bound
(d) Should not be given with estrogen products, including other SERMs

b. Conjugated estrogens 0.45 mg plus bazedoxifene 20 mg oral tablets (Duavee); 1 tablet orally daily (see "Osteoporosis" section for more information)
i. Indicated for treatment of moderate to severe vasomotor symptoms, prevention of osteoporosis
ii. SERM used instead of a progestin (estrogen + SERM is called "tissue selective estrogen complex"– TSEC)
iii. May be used in women with intact uteruses
iv. May increase risk of DVT; should not be used in women with a history of blood clots; has contraindications similar to those of estrogen
v. Common adverse effects: Muscle spasms; nausea and vomiting; throat, neck, or upper abdominal pain; and indigestion

4. Other hormone products
a. Bioidentical hormones: May still have adverse effects similar to those of conjugated estrogens
b. DHEA: Mixed data, may help lower vaginal pH and improve vaginal atrophy but not approved for use
c. Androgens: Testosterone may help with sexual dysfunction but not vasomotor symptoms; not approved for use
d. Phytoestrogens (see below for soy isoflavones): Act similarly to estrogen and carry similar contraindications
e. Megestrol (progestogen, see above section on progestogens)

5. 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 [SSRI] with indication for hot flashes)
b. Venlafaxine 75 mg orally once daily (Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059-63)
c. Fluoxetine 20 mg orally once daily
d. Paroxetine 20 mg orally once daily
e. Sertraline 100 mg orally once daily
f. Others that have shown efficacy: escitalopram, desvenlafaxine

6. 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
7. Others: Used for vasomotor symptoms (no FDA indication)
   a. Clonidine
   b. Gabapentin

Patient Cases

1. 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 her hot flashes are interfering with her daily activities and wants to try HT. When counseling E.L. on the use of HT and explaining the WHI trial, which is best to mention and has been proved statistically significant with conjugated estrogen and medroxyprogesterone acetate?
   A. Increased risk of DVT.
   B. Decreased risk of stroke.
   C. Decreased risk of MI.
   D. Increased risk of fractures.

2. Which HT treatment is best to recommend to E.L.?
   A. Estrogen patch 0.025 mg (17β-estradiol); change patch twice weekly.
   B. Estradiol vaginal cream 0.1 mg/g; apply vaginally once daily.
   C. Conjugated estrogen 0.3 mg/medroxyprogesterone acetate 1.5 mg; take 1 tablet daily.
   D. Ospemifene 20 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 BMD, fracture risk increases 2-fold)
   1. Normal = BMD within 1 SD of the young adult mean
   2. Low bone mass (osteopenia) = BMD between 1 SD and 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)

B. Guidelines are based on the 2010 American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for the Prevention and Treatment of Postmenopausal Osteoporosis, the 2012 American College of Obstetricians and Gynecologists (ACOG) Clinical Management of Osteoporosis, the 2010 North American Menopause Society (NAMS) Position Statement on the Management of Osteoporosis in Postmenopausal Women, and the 2014 Clinician's Guide to Prevention and Treatment of Osteoporosis by the National Osteoporosis Foundation (NOF) and 2012 Endocrine Society's (ES) Clinical Guidelines, Osteoporosis in Men.

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) or prolonged premenopausal amenorrhea
    e. Estrogen deficiency
    f. Drugs: glucocorticoids, heparin, anticonvulsants, excessive levothyroxine, gonadotropin-releasing hormone (GnRH) agonists, lithium, cancer drugs
    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. Alcoholism
    m. Dementia
    n. Impaired eyesight despite adequate correction
    o. Previous fractures
    p. History of falls
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 age 70 years or older and men age 80 years or older with BMD T-score of –1.0 or less at spine, total hip, or femoral neck
            (b) Women age 65–69 years and men age 70–79 years if BMD T-score is –1.5 or less at spine, total hip, or femoral neck
            (c) Postmenopausal women or men age 50 and older with 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. FRAX score (www.sheffield.ac.uk/FRAX/tool.jsp)
            (a) Used to estimate fracture risk
            (b) Most useful to estimate for patients with low BMD of hip
            (c) Recommended for postmenopausal women and men 50 years or older but validated in women 40–90 years of age
            (d) Useful to determine whether patients with low bone mass (osteopenia) need pharmacologic treatment
            (e) Not validated for patients on drug therapy for osteoporosis

e. Recommended BMD testing
   i. All women 65 years and older (NAMS, ACOG, AACE, NOF), men older than 70 (NOF, ES)
   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)
      (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)
      (f) Starting or taking long-term systemic glucocorticoids for 3 months or longer (AACE, NOF)

f. Initiation of drug therapy (AACE, 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 greater than or equal to 3% or the 10-year probability of major osteoporosis-related fracture is greater than or equal to 20% based on the FRAX system

g. Follow up on BMD-DXA every 2 years. Some situations may require a follow-up BMD sooner than 2 years.

C. Osteoporosis Treatments
   1. Bisphosphonates
      a. Alendronate (Fosamax, Binosto, Fosamax Plus D), risedronate (Actonel, Atelvia), ibandronate (Boniva), zoledronic acid (Reclast)
      b. Inhibits normal and abnormal bone resorption
      c. First-line therapy; exception: ibandronate second-line therapy
      d. Efficacy: Reduces vertebral and nonvertebral fractures by 30%–50% (see individual agents; exception: ibandronate reduces only vertebral fractures)
      e. 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. 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.

vi. Atrial fibrillation: Possible increased risk of atrial fibrillation but not of stroke or cardiovascular mortality (Sharma A, Chatterjee S, Arbab-Zadeh A et al. Risk of serious atrial fibrillation and stroke with use of bisphosphonates: evidence from a meta-analysis. Chest 2013;144:1311-22)

f. Drug-food interactions: Wait at least 30 minutes after taking bisphosphonate before taking any medications, food, or drinks except for water. Exception: With ibandronate, must wait 60 minutes. Atelvia (risedronate sodium, delayed release) must be taken with food.

g. Dosage for osteoporosis

i. Alendronate: 10 mg/day or 70 mg/week; taken for 3 years. 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 D_3 or 70 mg/week with 5600 international units of vitamin D_3

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 at 30 minutes after administration

iv. Risedronate: 5 mg/day or 35 mg/week or 150 mg once monthly; decreases nonvertebral fracture risk by 33%–39% and vertebral fracture by 41%–49%

v. Ibandronate: 2.5 mg/day or 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; intravenous administration is also available.

vi. Zoledronic acid: 5 mg intravenously annually for treatment and every 2 years for prevention (infuse over a minimum of 15 minutes); reduces nonvertebral 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. FDA warning in 2011 regarding contraindication in patients with acute renal impairment or with CrCl less than 35 mL/minute; shown to decrease mortality in high-risk patients who have suffered a hip fracture (only bisphosphonate shown to decrease mortality)

h. Renal impairment: See Table 7.

Table 7. Bisphosphonates

Drug	Indications	Osteoporosis Dosing and Routes
Alendronate (Fosamax, Binosto) Alendronate + vitamin D_3 (Fosamax D)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget's 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/week or 5600 international units/week 5 mg PO daily for prevention 35 mg PO weekly for prevention Not recommended for CrCl <35 mL/minute
Risedronate (Actonel) Risedronate delayed release (Atelvia) Risedronate + calcium carbonate (Actonel with calcium)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget's disease	5 mg PO daily 35 mg PO weekly (delayed release available also) 35 mg PO weekly on day 1 and days 2–7, 1250 mg PO calcium carbonate 150 mg PO monthly Not recommended for CrCl <30 mL/minute
Ibandronate (Boniva)	Prevention and treatment of osteoporosis in women	2.5 mg PO daily 150 mg PO monthly 3 mg IV every 3 months Not recommended for CrCl <30 mL/minute
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 years (prevention in women) Not recommended for CrCl <35 mL/minute
Etidronate	Approved for use in Canada	

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

2. 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.
    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)

Table 8. Recommended Daily Calcium Intake

Age Group	Recommended Daily Calcium Intake (mg)
19–50 years 51–70 years: men	1000
Older than 50 years: women 70 years and older: men	1200

3. Vitamin D
    a. Recommended for all patients with osteoporosis; promotes calcium reabsorption
    b. Minimal dose is 800 international units/day for those older than 70 years, 600 international units/day 70 years of age and younger (IOM recommendations November 30, 2010); NOF 2014 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 levels less than 30 ng/mL.
    d. Goal: 30 ng/mL in adults (NOF), although the IOM states that levels of 20 ng/mL may be adequate for most of the population
4. 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.
        iii. Efficacy
            (a) Reduces the risk of vertebral fractures; reduces vertebral fractures by 30%–50%; **has not been shown to decrease hip fractures**
            (b) Lowers total cholesterol by 7% and LDL-C 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 over 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

v. Drug interactions
(a) Bile acid resins decreased 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
iii. Efficacy
(a) Significantly increased total hip BMD at 24 months by 1.96% compared with placebo in women who had been postmenopausal between 1 and 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 between 1 and 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 levels.

5. Calcitonin-salmon (Miacalcin)
a. Inhibition of bone resorption
b. Indicated for treatment of osteoporosis in postmenopausal women for at least 5 years
c. Not a first-line drug; useful for bone pain caused by vertebral compression fractures
d. Efficacy: Nasal calcitonin reduces the incidence of new vertebral fractures by 36%.
e. Adverse effects
i. Nasal (10%–12%): Rhinitis, epistaxis, irritation, nasal sores, dryness, tenderness
ii. Other (3%–5%): Backache, arthralgia, headache
f. Drug interactions: None
g. Dosage: 200 international units/day in one nostril, alternating nostrils daily
i. 200 international units nasally = 50–100 international units by injection
ii. 200 international units per actuation, so one bottle will last about 2–3 weeks

6. Teriparatide (Forteo)
a. Recombinant human parathyroid hormone regulates bone metabolism, intestinal calcium absorption, and renal tubular calcium and phosphate reabsorption.
b. Efficacy
i. 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
ii. Decreases vertebral fractures by 65% and nonvertebral fractures by 53%; not shown to decrease hip fractures

   c. Contraindications: Hypercalcemia, bone metastases, disorders that predispose women to bone tumors such as Paget's disease
   d. Adverse effects: Nausea, orthostatic hypotension
   e. Carcinogenicity: Osteosarcoma in rats
   f. Drug interactions: Increases calcium concentrations and may increase risk of digoxin toxicity
   g. Dosage: 20 mcg/day subcutaneously
7. Denosumab (Prolia): Approved in 2010 for postmenopausal women with 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 AACE guidelines
   c. Administered subcutaneously every 6 months
   d. Not contraindicated in patients with renal dysfunction
   e. Efficacy
      i. Increased BMD hip (6%) and spine (9%)
      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).
8. HT (estrogen and progestogens; see "Hormone Therapy" section above)
9. Lifestyle modifications
   a. Weight-bearing exercise that includes walking, tai chi, dancing, and tennis; recommend 30–40 minutes per session most days of the week, if possible; helps maintain bone strength
   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

Patient Cases

3. R.K. is a 71-year-old white woman with a history of rheumatoid arthritis who smokes ½ pack/day. She takes calcium 1200 mg orally per day in divided doses and vitamin D 600 international units/day orally. She is 63 inches (160 cm) tall and weighs 140 lb (64 kg). Her calculated creatnine clearance is 60-70mls/min. 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%. 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 required; continue calcium 1200 mg/vitamin D 600 international units/day orally.
   B. Teriparatide 20 mcg subcutaneously daily and continue calcium 1200 mg/vitamin D 600 international units/day orally.
   C. Miacalcin nasal spray 1 spray (200 international units) in one nostril daily; continue calcium 1200 mg/day orally, and increase vitamin D to 800 international units/day orally.
   D. 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
   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
   5. Timing of exposure
      a. One 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 FDA pregnancy risk categories appear in Table 9.

Table 9. 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 that a new labeling system be adapted that would include the following:
    a. Fetal risk summary
    b. Clinical considerations
    c. Data section
    d. Information for exposure registries

E. Factors to Consider When Initiating Medications in Pregnant Women
    1. Risk-benefit ratio
    2. Is drug necessary?
    3. Most effective agent with least risk
    4. Lowest effective dose for shortest possible duration
    5. Health of mother without drug

Table 10. Some Category X Drugs Known to Be Teratogens

Alcohol
Androgens
Anticonvulsants
Antineoplastics
Cocaine
Diethylstilbestrol
Isotretinoin
Lead
Mercury
Methotrexate
Thalidomide
Vitamin A (higher than recommended daily doses)
Warfarin

Table 11. Some Category D Drugs Known to Be Teratogens

Angiotensin-converting enzyme inhibitors
Angiotensin II receptor blockers (second and third trimesters)
Fluconazole (high doses)
Iodides
Methimazole
Lithium
Paroxetine
Penicillamine
Statins
Tetracyclines

Table 12. Common Category C Drugs

Corticosteroids
Docusate sodium
Hydrocodone
Tricyclic antidepressants

Table 13. Common Category B Drugs

Acetaminophen
Cetirizine
Erythromycin
Phenothiazines
Cephalosporins
Penicillins

Table 14. Drugs with Nonteratogenic Adverse Effects, Should Be Used with Caution

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

NSAID = nonsteroidal anti-inflammatory drug.

Table 15. 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	

IV. DRUGS IN LACTATION

A. Drugs That Decrease Milk Supply

Table 16. 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)

Table 17. 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. Short-term drug: Mother can pump and discard milk.
2. Choose drugs with short half-lives.
3. Administer drug immediately after a feeding or before a long sleep period.
4. Consider whether the drug is given to neonates.

D. Drugs Contraindicated in Breastfeeding According to the American Academy of Pediatrics

Table 18. Some Drugs Contraindicated in Breastfeeding According to the American Academy of Pediatrics

Amphetamines	Drugs of abuse
Antineoplastics	Ergotamine
Benzodiazepines	Lithium
Bromocriptine	Nicotine
Cocaine	

Table 19. Relatively Safe Agents During Lactation

Analgesics (ibuprofen, acetaminophen)	Caffeine (in moderation [1 or 2 cups/day])
Antibiotics (penicillins, cephalosporins, erythromycins)	Insulin
Anticonvulsants	Laxatives

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
   3. Usually occurs on rising and diminishes as day progresses
   4. Cause: Unknown
   5. Hyperemesis gravidarum: Severe nausea and vomiting leads to dehydration and malnutrition.
   6. Nonmedical treatment: First line
      a. Eat salt crackers.
      b. Keep stomach from becoming completely empty.
      c. Eat small, dry meals.
      d. Avoid spicy and odorous foods.
   7. Symptomatic treatment (Niebyl JR.Clinical practice. Nausea and vomiting in pregnancy. N Engl J Med 2010;363:1544-50)
      a. Doxylamine and pyridoxine (category A)
      b. Pyridoxine (category A)
      c. Meclizine (category B)
      d. Dimenhydrinate (category B)
      e. Diphenhydramine (category B)
      f. Ondansetron (category B)
      g. Metoclopramide (category B)
      h. Phenothiazines (category C)

C. Heartburn
   1. Occurs during 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
        iii. Calcium carbonate
    b. Sucralfate: Not absorbed in GI tract
    c. Second line: Histamine-2 receptor antagonists, 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. Bulk laxatives: Not absorbed
    b. Surfactants
    c. Stimulants: Not recommended as first-line therapy, bisacodyl category B, senna category C
    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.
3. Sitz baths
4. External medications preferred
5. Avoid topical anesthetics and steroids.

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 DVT
    b. Prosthetic heart valve
    c. Deficiencies of clotting factors
    d. Antiphospholipid antibodies
2. Therapy
    a. Avoid warfarin.
    b. Heparin or low-molecular-weight heparin recommended (monitor for osteoporosis if heparin is used long term); should be discontinued 24 hours before C-section or vaginal delivery

H. Gestational Diabetes Mellitus (GDM)
   1. Diagnostic approaches

Table 20. GDM Diagnostic Approaches

Approach	Criteria	Organizations	Comments
Two-step approach	50 g oral glucose test Plasma measured 1 hour after If ≥130 mg/dL or 140 mg/dL, then give 100-g, 3-hour 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 1 and 2 hours	IADPSG, ADA	Given at 24–28 weeks' gestation

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-hr oral glucose test (OGTT) used after initial screening, if greater than or equal to values at 2 or more points, considered GDM

Table 21. Three-hour Oral Glucose Test Reference Range

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

      b. One-step approach: Based on 75-g 2-hr oral glucose test

Table 22. Glucose Reference Range for Two-hour Oral Glucose Test

Time	Plasma Glucose
1 hour	≥180 mg/dL
2 hours	≥153 mg/dL

   3. Insulin (first line)
      a. Regular (most studied, drug of choice in combination with neutral protamine Hagedorn)
      b. Neutral protamine Hagedorn insulin (in combination with regular insulin, drugs of choice)
      c. Lispro and aspart (category B drugs), starting to be used
   4. Sulfonylureas (glyburide) in patients unable to use insulin injections, starting to become more first line (Langer O, Conway DL, Berkus MD et al. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 2000;343:1134-8)
   5. Metformin, ongoing studies (not first line) (Rowan JA, Hague WM, Gao W et al. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med 2008;358:2003-15)

I. Pregnancy-Induced Hypertension: Hypertension occurring after 20 weeks' gestation
   1. Gestational hypertension: More than 140/90 mm Hg without proteinuria or pathologic edema
   2. Preeclampsia: Hypertension plus proteinuria (300 mg or more every 24 hours)
   3. Eclampsia: 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 two- to threefold increase in proteinuria, sudden increase in BP, increased aspartate transaminase–alanine transaminase, thrombocytopenia
   6. Prevention: Women at high risk of development, aspirin 60 mg beginning in weeks 24–28 until labor
   7. Treatment
      a. Delivery if at term
      b. If not at term, get bedrest and monitor BP.
      c. Severe preeclamptic, parenteral magnesium sulfate to prevent seizures
      d. Methyldopa is first-line therapy, although more practices using labetalol as well.
      e. Alternatives: Certain β-blockers, labetalol, calcium channel blockers
      f. Parenteral antihypertensives: Hydralazine, labetalol
      g. Medications to avoid: Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers

J. Preterm Labor
   1. Definitions
      a. Term labor: Between weeks 37 and 40
      b. Preterm labor: Uterine contractions with cervical changes before week 37
   2. Nonpharmacologic treatment
      a. Inhibition of labor not usually attempted before week 20
      b. Bedrest, hydration, and sedation
   3. Prophylaxis for patients with a history of preterm labor between 16 and 36 weeks: 17-hydroxyprogesterone acetate 250 mcg intramuscularly every week from 16 to 36 weeks' gestation
   4. Tocolytic drugs (inhibit uterine contractions), especially if cervix dilated less than 4 cm and membranes intact
      a. β-Agonists
         i. Terbutaline: Often used, unlabeled use, intravenously, subcutaneously, orally
         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
    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
    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. Used to terminate early pregnancy
        iv. Decrease postpartum or postabortion bleeding
        v. Oral and parenteral
    c. Prostaglandins: Used primarily for cervical ripening
        i. Dinoprostone also known as PGE2 (prostaglandin E_2)
            (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 also known as PGE1 (prostaglandin E_1)
            (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.
   B. Discontinue lisinopril and all other medications.
   C. Discontinue lisinopril and start methyldopa.
   D. Continue lisinopril and add atenolol.

VI. OVERVIEW OF CONTRACEPTION

A. Epidemiology
   1. About 48% of pregnancies are unintended in the United States, with about 21% of those resulting in abortions.
   2. According to the Guttmacher Institute, about 10.4 million women in 2006–2008 were using an oral contraceptive (OC) pill in the United States, 1.2 million were using injections, and 2.1 million were using intrauterine devices (IUDs).

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: 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. Properties Desired in Contraceptives
   1. Highly effective
   2. Prolonged duration of action
   3. Rapidly reversible
   4. Privacy of use
   5. Protection against STDs
   6. Easily accessible

D. 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)
   2. Importance of not being pregnant
   3. Likelihood and ability to adhere
   4. Frequency of intercourse: Frequent versus infrequent

5. Age: 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

E. Methods of Birth Control
   1. Abstinence
   2. Male/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. 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

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

A. Indications
   1. FDA label approved
      a. Prevent pregnancy
      b. Acne (Estrostep, Ortho Tri-Cyclen, YAZ, Beyaz)
      c. Premenstrual dysphoric disorder (YAZ, Beyaz)
   2. Off-label use
      a. Acne
      b. Hirsutism
      c. Cycle control
      d. Headaches
      e. Premenstrual syndrome
      f. Iron-deficiency anemia
      g. 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)
         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 values, 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
      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. A condition for which there is no restriction on the use of contraceptive method (category 1)
      b. A condition in which the advantages of using the method generally outweigh the theoretical or proven risks (category 2)
      c. A condition in which the theoretical or proven risks usually outweigh the advantages of using the method (category 3)
      d. A condition that represents an unacceptable health risk if the contraceptive method is used (category 4)
   2. 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), 42 days for women with risk factors for DVT (according to CDC recommendations)
      b. Smoker 35 years and older
      c. Several risk factors for cardiovascular disease
      d. BP greater than 160/100 mm Hg
      e. Vascular disease
      f. Current DVT or pulmonary embolism or history of DVT or pulmonary embolism
      g. Complicated diabetes showing nephropathy, neuropathy, or retinopathy
      h. Presence of liver tumors, severe cirrhosis, or active viral hepatitis
      i. Major surgery with prolonged mobilization
      j. Known thrombogenic mutations
      k. Current or history of ischemic heart disease
      l. Stroke (history of cerebrovascular accident)
      m. Complicated valvular heart disease
      n. Migraine headache with aura or migraine without aura in women 35 years or older
      o. Current breast cancer

D. Adverse Effects (see "Estrogen" and "Progestin" sections above for specific hormone-causing adverse effects)
   1. The main reason for discontinuation of contraceptives. On the basis of a 1998 study, discontinuation was attributable to the following.
      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. Nausea is 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. Acne is 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) (Hatcher RA, Trussell J, Nelson AL, et al. Contraceptive Technology, 20th ed. New York: Ardent Media, 2011.)
   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. K.R. is a 22-year-old woman initiated on Mircette 4 months ago for contraception. She has breakthrough bleeding at the start of her active pills that lasts a few days before resolving. The physician wants to change the OC. Which OC on her formulary is best for the physician to prescribe?

Name of OC	**Estrogen Property**	**Progestin Property**	**Androgen Property**
Mircette (desogestrel 0.15 mg/ethinyl estradiol 20 mcg)	Low	High	Low
Ortho-Cept (desogestrel 0.15 mg/ethinyl estradiol 30 mcg)	Intermediate	High	Low
Lessina (levonorgestrel 0.1 mg/ethinyl estradiol 20 mcg)	Low	Low	Low
Loestrin 21 (norethindrone acetate 1.5 mg/ethinyl estradiol 30 mcg)	Low	High	High

A. Continue taking Mircette (desogestrel 0.15 mg/ethinyl estradiol 20 mcg) for another 3 months.
B. Change to Ortho-Cept (desogestrel 0.15 mg/ethinyl estradiol 30 mcg).
C. Change to Loestrin 21 (norethindrone acetate 1.5 mg/ethinyl estradiol 30 mcg).
D. Change to Lessina (levonorgestrel 0.1 mg/ethinyl estradiol 20 mcg).

E. Common Drug Interactions (list not all-inclusive)
   1. Increase effect of hormonal contraceptives
      a. Acetaminophen
      b. Ascorbic acid
      c. Atazanavir
      d. Atorvastatin

e. Ginseng
f. Indinavir
g. Red clover (may increase or decrease effect of combined hormonal contraceptives)
h. Rosuvastatin
i. Tranexamic acid
j. Voriconazole

2. Decrease effect of hormonal contraceptives
   a. Amprenavir
   b. Aprepitant
   c. Barbiturates
   d. Bexarotene
   e. Bosentan
   f. Carbamazepine
   g. Darunavir
   h. Felbamate
   i. Griseofulvin
   j. Lopinavir
   k. Modafinil
   l. Mycophenolate mofetil
   m. Nelfinavir
   n. Nevirapine
   o. Oxcarbazepine
   p. Phenobarbital
   q. Phenytoin/fosphenytoin
   r. Pioglitazone
   s. Primidone
   t. Red clover (may increase or decrease effect of combined hormonal contraceptives)
   u. Rifamycins
   v. Ritonavir
   w. Rufinamide
   x. Saquinavir
   y. St. John's wort
   z. Tipranavir

3. Drugs that are increased or decreased by hormonal contraceptives
   a. Acetaminophen
   b. Antidepressants, tricyclic
   c. Aspirin
   d. Benzodiazepines
   e. β-Blockers
   f. Caffeine
   g. Clofibric acid
   h. Corticosteroids
   i. Cyclosporine
   j. Lamotrigine
   k. Levothyroxine
   l. Morphine
   m. Paclitaxel

n. Salicylic acid
o. Selegiline
p. Tacrine
q. Tacrolimus
r. Theophyllines
s. Tizanidine
t. Valproic acid

4. Questionable effects that hormonal contraceptives may have on other drugs
   a. Anticoagulants: Hormonal contraceptives may increase certain clotting factors and reduce antithrombin III, so it is questionable whether hormonal contraceptives interfere with anticoagulants.
   b. Lamotrigine levels may be decreased by hormonal contraceptives.
   c. 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 alternative contraception for the length of antibiotic therapy plus 7 days after discontinuing antibiotic.
      iii. U.S. Medical Eligibility Criteria for Contraceptive Use 2010 suggest that no alternative form of contraception is necessary with broad-spectrum antibiotics.
5. Simplified list of drug-drug interactions according to the U.S. Medical Eligibility Criteria for Contraceptive Use 2010 (www.cdc.gov/reproductivehealth/unintendedpregnancy/usmec.htm)
   a. Nucleoside reverse transcriptase inhibitors (NRTIs) (category 1: before treating any patients, recommend to check specific product information)
   b. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) (category 2: before treating any patients, recommend to check specific product information)
   c. Ritonavir-boosted protease inhibitors (category 3)
   d. Antiepileptics (see above) (category 3)
   e. Broad-spectrum antibiotics, antifungals, antiparasitics (category 1)
   f. Rifampin or rifabutin (category 3)

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: 50 mcg or higher (higher than 50 mcg not often used anymore)
   ii. Low-dose estrogen: Less than 50 mcg (generally 30–35 mcg)
   iii. Very low-dose estrogen: Less than 30 mcg (10–25 mcg)
c. Effectiveness: When taken every day at the same time, 99.7% (perfect use), typical use (about 93%) (Hatcher RA, Trussell J, Nelson AL, et al. Contraceptive Technology, 20th ed. New York: Ardent Media, 2011)
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 backup method [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 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 above.
      (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) One method:
         (1) Missed 1 pill: Take as soon as remembered, no BUM.
         (2) Missed 2 pills if in week 1 or 2 of cycle: Take 2 pills for 2 days plus BUM for 7 days (BUM = condoms, condoms plus spermicide, diaphragm, or no intercourse).
         (3) Missed 2 pills in week 3 of cycle
            (A) If day 1 starter, begin new pack that day plus a BUM for 7 days.
            (B) If Sunday starter, take 1 pill daily until Sunday (no placebos); start new pack on Sunday plus a BUM for 7 days.
         (4) Missed 3 pills in first 3 weeks
            (A) If day 1 starter, begin new pack plus a BUM for 7 days.
            (B) If Sunday starter, take 1 pill daily until Sunday (no placebos); start new pack on Sunday plus a BUM for 7 days.
         (5) Missed placebos: Just continue taking pills, no BUM
      (b) Alternative method: If patient has had intercourse in the past 5 days, consider emergency contraception (EC) and then instruct the patient to continue using her birth control until the end of the pack, plus 7 days of a BUM.
      (c) Alternative missed dose recommendations according to Canadian guidelines (Guilbert E, Black A, Dunn S et al. Missed hormonal contraceptives: new recommendations. JOGC 2008; 30 (11):1050-62)
         (1) Missed 1 pill: Take as soon as remembered, no BUM.
         (2) Missed 2 or more pills in week 1 cycle: Take 1 pill as soon as possible plus BUM for 7 days (BUM = condoms, condoms plus spermicide, diaphragm, or no intercourse).

(3) Missed less than 3 pills in week 2 or 3 of cycle: Take active tablet as soon as possible, continue on regular pill schedule, skip hormone-free week (placebos), and start a new pack of active tablets.
(4) Missed 3 or more pills in week 2 or 3 of cycle: Take active tablet as soon as possible, continue on regular pill schedule, skip hormone-free week (placebos), and start a new pack of active tablets plus a BUM for 7 days.

(d) Other recommendations for missed combined oral contraceptives (from Selected Practice Recommendations for Contraceptive Use, 2013: Adapted from the World Health Organization Selected Practice Recommendations for Contraceptive Use, 2nd ed. *MMWR* 2013;62(RR05):1-46)
(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 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) If doses missed were during days 15–21 of a 28-day cycle (e.g., 3 weeks active hormone, 1 week placebo), then continue taking any active hormone tablets in the pack, skip the hormone-free week, and start a new pack of tablets.
(E) If unable to start a new pack immediately, use a BUM or avoid intercourse until 7 consecutive days of active hormone tablet have been taken.
(F) Use EC if active hormonal tablets were missed in the first week of the cycle or unprotected intercourse occurred in the previous 5 days.

(e) Other methods: For a dose of ethinyl estradiol, if taking less than 30 mcg and missed 2 pills, treat as if she missed 3 pills. For quadriphasic product (Natazia), must look at package insert; depends on specific day missed within the pill pack

g. Unique formulations
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, Kariva (ethinyl estradiol/desogestrel)—2 days of placebo and 5 days of estrogen only (10 mcg), instead of 7 days of placebo
iii. Femcon 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 (ethinyl estradiol 25 mcg/norethindrone 0.8 mg): 24 chewable active tablets and 4 tablets of ferrous fumarate 75 mg
vi. Lo Minastrin Fe (ethinyl estradiol 10 mcg/norethindrone acetate 1 mg): Lowest oral estrogen COC chewable tablet, contains 24 active tablets, 2 tablets of ethinyl estradiol 10 mcg, and 2 tablets of ferrous fumarate 75 mg

vii. Drospirenone progestin-containing contraceptives
  (a) Drospirenone: Analog of spironolactone, similar to spironolactone 25 mg
  (b) 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
    (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

h. Advantages and disadvantages

Table 23. Advantages and Disadvantages of COCs

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

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

2. Transdermal patch (Ortho-Evra)
  a. Patch placed on skin; delivers 150 mcg of norelgestromin and provides 60% more estrogen exposure than 35-mcg oral tablet of ethinyl estradiol
  b. Effectiveness
    i. Similar to pills (8% 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
  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 above.
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 (from Selected Practice Recommendations for Contraceptive Use, 2013: Adapted from the World Health Organization Selected Practice Recommendations for Contraceptive Use, 2nd ed. *MMWR* 2013;62(RR05):1-46)
    (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) Generally, EC is not necessary but may be considered 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 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 24. Advantages and Disadvantages of Transdermal Contraception Patch

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

3. Vaginal ring (NuvaRing)
    a. Product inserted vaginally, delivers 15 mcg ethinyl estradiol and 120 mcg etonogestrel (active form of desogestrel) daily
    b. Effectiveness: Similar to pills (8% failure rate for typical use, 0.3% for perfect use) (Hatcher RA, Trussell J, Nelson AL, et al. Contraceptive Technology, 20th ed. New York: Ardent Media, 2011.)
    c. Adherence
        i. One study found that 92.4% of women using a vaginal ring were adherent versus 75.4% using the COC pill (Novák A, de la Loge C, Abetz L, van der Meulen EA.The combined contraceptive vaginal ring, NuvaRing: an international study of user acceptability. Contraception 2003;67:187-94).
        ii. 1950 women aged 18–41 years, 13 cycles of use, 96% satisfied, 97% would recommend the ring (Novák A, de la Loge C, Abetz L, van der Meulen EA.The combined contraceptive vaginal ring, NuvaRing: an international study of user acceptability. Contraception 2003;67:187-94).
        iii. Reasons for liking the ring
            (a) "Not having to remember anything" (45%)
            (b) "Ease of use" (27%)
    d. Counseling
        i. Proper use
            (a) Insert vaginal ring into vagina and leave for 3 weeks. Week 4, remove ring and menses will occur.
            (b) Should not be removed during intercourse
            (c) May be worn with tampon if there is breakthrough bleeding
        ii. Missed doses: Inadvertent removal, expulsion, or prolonged ring-free interval
            (a) If 3 hours or less, rinse with cool to lukewarm water and reinsert as soon as possible.
            (b) If more than 3 hours, reinsert and use a BUM until ring has been used continuously for 7 days.
        iii. Alternative recommendations for missed vaginal ring insertion (from Selected Practice Recommendations for Contraceptive Use, 2013: Adapted from the World Health Organization Selected Practice Recommendations for Contraceptive Use, 2nd ed. *MMWR* 2013;62(RR05):1-46)
            (a) Missed dose = delayed insertion of less than 48 hours or recommended time for insertion
                (1) Insert new vaginal ring as soon as possible (if less than 24 hours, may insert same ring).
                (2) Keep ring in until scheduled ring removal day.
                (3) No BUM needed
                (4) Generally, EC is not necessary but may be considered if the patient missed doses earlier in the cycle or in the last week of the cycle.
            (b) If delayed insertion is more than 48 hours from scheduled administration time may recommend the following:
                (1) Insert ring as soon as possible.
                (2) Keep ring in until scheduled ring removal day.
                (3) Use a BUM or avoid intercourse until vaginal ring has been in place for 7 consecutive days.
                    (A) 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.
                    (B) If unable to insert a new ring immediately, use a BUM or avoid intercourse until new ring has been inserted for 7 consecutive days.
                (4) Use EC if active hormone was missed in the first week of the cycle or unprotected intercourse occurred in the previous 5 days.

iv. Adverse effects
(a) Decreased libido (8%)
(b) Breast tenderness (4%)
(c) Device-related events (2.5%–5%)
(d) Vaginal discomfort and secretions (2.5%)
(e) Irregular bleeding (1.5%–5%)

Table 25. 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
a. Three months: Using active form of combined hormonal contraception for 3 months (results in menses every 3 months instead of once a month)
i. Seasonique, Amethia, Daysee, Camrese (ethinyl estradiol 30 mcg/levonorgestrel 150 mcg, ethinyl estradiol 10-mcg tablets instead of placebo pills)
ii. LoSeasonique, Amethia Lo, Camrese Lo (ethinyl estradiol 20 mcg/levonorgestrel 100 mcg, ethinyl estradiol 10-mcg tablets instead of placebo pills)
iii. Quartette (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)
b. One year: Using active form of combined hormonal contraception for 1 year, product: Lybrel or Amethyst (ethinyl estradiol 20 mcg/levonorgestrel 90 mcg)
c. One year: Vaginal ring, clinical trials

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 below) or those seeking long-term contraception
1. History of or current MI, stroke, DVT, cardiovascular disease
2. Atrial fibrillation
3. BP 160/100 mm Hg
4. Smoker age 35 or older
5. Breast cancer within 5 years
6. Active, symptomatic liver disease
7. Benign or malignant liver tumors
8. History of cholestasis because of OCs
9. Migraine headache with neurologic impairment or aura or migraine without aura in women 35 years or older
10. Retinopathy or neuropathy because of diabetes
11. Surgery within the past 4 weeks
12. Breastfeeding

B. Components: One of the following progestins
   1. Depot medroxyprogesterone acetate (DMPA [Depo-Provera injectable/Depo-Provera subcutaneously])
   2. Norethindrone 0.35 mg (Micronor, Nor-QD)
   3. Norgestrel 0.075 mg (Ovrette)

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: Medroxyprogesterone acetate okay to use with CYP inducers
   5. If taking antibiotic, considered WHO category 1

E. Adverse Effects: See progestin adverse effects in "Combined Hormonal Contraceptives" section above

F. Types
   1. Oral
      a. Effectiveness: 8% failure rate (typical), 0.3% failure (perfect use) (Hatcher RA, Trussell J, Nelson AL, et al. Contraceptive Technology, 20th ed. New York: Ardent Media, 2011)
      b. Start methods: May start on any day or on first day of period. There are no hormone-free days with the POPs.
      c. Adverse effects: Progestin related, see above
      d. Missed doses: Doses of POPs must be at the SAME time every day; a missed dose of POPs means more than 3 hours. If a missed dose occurs, must use a BUM for 48 hours.
      e. Advantages
         i. Efficacy
         ii. Decreased menstrual blood loss, cramps, pain
         iii. Readily reversible
         iv. Preferable in lactating women
      f. Disadvantages
         i. Progestin-related adverse effects (e.g., weight gain, acne)
         ii. Irregular menses
         iii. Adherence: Short time window for a missed pill
         iv. Low-dose progestin, patient may ovulate
         v. Fewer noncontraceptive benefits
   2. Depo-Provera 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: 3%. (Hatcher RA, Trussell J, Nelson AL, et al. Contraceptive Technology, 20th ed. New York: Ardent Media, 2011)
      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 above)
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. Do not massage area for a few hours where shot was given.
ii. Expect irregular bleeding or spotting in beginning, but it decreases over time.
iii. Take calcium if not achieving 1000–1200 mg/day through diet.
iv. Return in 11–13 weeks for next injection. Use backup 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. Depot subcutaneously: Subcutaneous injection of 104 mg of DMPA, information similar to above but, in addition, has FDA indication for endometriosis

IX. INTRAUTERINE DEVICES (IUD) AND SYSTEMS (IUS)

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 Use: 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 (Mirena only)
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: Spermicide
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%. (Hatcher RA, Trussell J, Nelson AL, et al. Contraceptive Technology, 20th ed. New York: Ardent Media, 2011)

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 actinomycosis
   vii. Recent endometritis (past 3 months)
   viii. Allergy to copper; Wilson disease
   ix. Uterine distortion or pathology affecting placement
   x. Known or suspected uterine or cervical cancer
   xi. Unresolved abnormal Papanicolaou test
   xii. Severe anemia (relative contraindication)
e. Advantages and disadvantages

Table 26. Advantages and Disadvantages of Copper IUD

Advantages	Disadvantages
Efficacy (long term, 10 years)	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, Mirena and Skyla)
   a. Mirena: Inserted into uterus by health care professional, stays in for up to 5 years, releases 20 mcg levonorgestrel per day, indicated for contraception and menorrhagia
   b. 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
   c. 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
   d. 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 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

e. Advantages and disadvantages

Table 27. Advantages and Disadvantages of Progestin IUS

Advantages	Disadvantages
Efficacy (long term, 3–5 years)	Progestin-related adverse effects
Adherence	Irregular menses (generally for the first 6 months; 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. Patient Counseling
1. Strings of IUD will be outside the vaginal canal. 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, states that she is getting married soon and that she wants to begin taking birth control pills 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/day. Her medications include hydrochlorothiazide 25 mg orally daily, Lotrel 5/20 (amlodipine/benazepril) orally daily, Prilosec (omeprazole) 20 mg orally daily, and occasional ibuprofen. She is 67 inches tall and weighs 210 lb (95 kg). 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 injection.

X. IMPLANTS (NEXPLANON)

A. Indications: 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: Implanon (etonogestrel) has been discontinued; only Nexplanon (etonogestrel) 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%)

XI. EMERGENCY CONTRACEPTION

A. Definition: "A therapy for women who have had unprotected sexual intercourse, including sexual assault." ACOG definition (ACOG Practice Bulletin. Int J Gynecol Obstet 2002;78:191-8)

B. Mechanism of Hormonal Methods (Yuzpe and progestin-only)
   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 intercourse within 120 hours

D. Timing: Within 120 hours after unprotected intercourse; package insert for marketed products states 72 hours, but studies show up to 120 hours may still prevent pregnancy

E. Effectiveness: 57%–85%

F. Methods
   1. Yuzpe method
      a. High-dose estrogen plus progestin
      b. FDA labeling-approved doses (based on norgestrel or l-norgestrel)
         i. Ogestrel 0.5/50 (ethinyl estradiol 50 mcg/norgestrel 0.5 mg) 2 tablets immediately, then 2 tablets 12 hours later
         ii. Low-Ogestrel, Cryselle, Elinest (ethinyl estradiol 30 mcg/norgestrel 0.3 mg): 4 tablets immediately; then 4 tablets 12 hours later
         iii. Altavera, Chateal, Kurvelo, Levora, Marlissa, Portia, Jolessa, Introvale (ethinyl estradiol 30 mcg/levonorgestrel 0.15 mg): 4 tablets immediately; then 4 tablets 12 hours later
         iv. Trivora, Tri-Levlen, Triphasil (yellow tablets only, ethinyl estradiol 30 mcg/levonorgestrel 0.125 mg): 4 tablets immediately; then 4 tablets 12 hours later
         v. Falmina, Orsythia, Sronyx, Lessina, Lutera, Aviane (ethinyl estradiol 20 mcg/levonorgestrel 0.1 mg): 5 tablets immediately; then 5 tablets 12 hours later
      c. 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 (preferred method)
      a. Products
         i. Plan B One-Step, Next Choice One Dose, My Way, Take Action (1 tablet of levonorgestrel 1.5 mg)
            (a) Available over the counter (OTC) for use by women; men or women may purchase
            (b) Available OTC for all ages
         ii. Generic levonorgestrel (2 tablets of levonorgestrel 0.75 mg)
            (a) May take the 2 tablets at the same time or separated by 12 hours
            (b) Prescription for women younger than 17 years unless state allows pharmacist initiation
            (c) Men and women older than 17 years may purchase.
      b. Adverse effects
         i. Nausea: 18%; vomiting: 4%
         ii. May notice changes in menstrual cycle
         iii. The WHO recommends using levonorgestrel only. A double-blind, randomized study of 2000 women showed that levonorgestrel 750 mcg repeated 12 hours later prevented 85% of pregnancies versus the Yuzpe regimen (ethinyl estradiol 100 mcg/levonorgestrel 0.5 mg repeated 12 hours later), which prevented 57%. Less nausea and vomiting with levonorgestrel 750 mcg (Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Task Force on Postovulatory Methods of Fertility Regulation. Lancet 1998;352:428-33)
      c. Special populations
         i. BMI greater than 26 kg/m^2
            (a) Progestin-only emergency contraceptive pills are not as effective for those with a BMI of 26 kg/m^2 or greater. Either ella (ulipristal acetate) or the copper IUD is recommended for those patients.
            (b) The copper IUD is recommended for those with BMI greater than 35 kg/m^2.

ii. Weight
(a) Some studies state levonorgestrel is less effective in women who weigh more than 75 kg and not effective in women who weigh more than 80 kg.
(b) Controversial: European Medicines Association disagrees and states data are lacking and weight does not determine effectiveness of levonorgestrel.
iii. Breastfeeding women
(a) Progestin-only methods are category 1 for use based on CDC Medical Eligibility Criteria
(b) Progestin-only method preferred

3. ella (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 BMI greater than 35 kg/m^2, copper IUD is recommended instead
h. Use BUM for 7 days after taking ulipristal if using hormonal contraception because ulipristal blocks progesterone receptors.
4. Copper IUD: May be used within 5 days of unprotected intercourse; requires in-office visit
5. RU-486: May be used within 5 days of unprotected intercourse but will disrupt an established pregnancy; requires in-office visit

XII. 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 require zinc.
2. Exercise, although too much may stop ovulation
3. Weight best with BMI of 24–30 kg/m^2 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/m^2 or more than 25 kg/m^2 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
   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 levels
            (c) Women with polycystic ovary syndrome generally fall into this classification.
         iii. WHO group III: Hypergonadotropic anovulation
            (a) About 10%–20% of anovulatory women
            (b) Elevated FSH levels
            (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) Labs may appear similar to WHO group I.
      b. Cervical
         i. Abnormality
         ii. Blockage
         iii. Issues with 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. Polycystic ovary syndrome
   2. Endometriosis
   3. Pelvic inflammatory disease
   4. Uterine fibroids
   5. Idiopathic

G. Fertility Agents
   1. Clomiphene citrate
      a. Brand names: Clomid, Serophene
      b. Used to stimulate or induce ovulation, sperm production in men
      c. Administered on days 2–5 of cycle
      d. Taken by mouth usually 50–150 mg/day
      e. First-line agent
      f. Selective estrogen receptor modulator that works by blocking estrogen receptors; body perceives hypoestrogenic state and increases the release of gonadotropin-releasing hormone (GnRH), which increases levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
      g. Adverse effects: hot flashes, abdominal, breast tenderness, mood swings, visual alterations
   2. Aromatase inhibitors (off-label use)
      a. Brand names: Femara (letrozole), Arimidex (anastrozole)
      b. Increase GnRH and gonadotropins
      c. Help induce ovulation with less risk of multiple follicles stimulated (less risk of multiple births)
      d. Adverse effects: headache, GI complaints, joint pain, bone pain, edema, sweating, and flushing
   3. Human menopausal gonadotropin (hMG)
      a. Brand names: Pergonal, Repronex, Humegon, Menopur
      b. Class known as menotropins, both FSH and LH
      c. Derived from the urine of postmenopausal women
      d. Pergoveris (recombinant FSH and recombinant LH): Not yet available in the United States
      e. Given on day 2 or 3 of cycle and continued for 7–10 days
      f. Adverse effects: flulike symptoms, muscle aches, malaise, headaches, dizziness, pain at site
   4. Follicle-stimulating hormone
      a. Naturally occurring: Fertinex, Bravelle (known as urofollitropin)
      b. Recombinant: Gonal-f (follitropin alpha), Follistim (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. Luteinizing hormone
      a. Recombinant: Luveris (lutropin alfa)
      b. Helps stimulate release of egg
      c. Adverse effects: headache, GI complaints, fatigue, VTE (rare)
   6. 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
   7. 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. May help induce or stimulate ovulation
      d. Administered by nasal spray, injection, or capsule
      e. Also used to treat endometriosis

f. 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
g. Agonists versus antagonists
    i. GnRH agonists
        (a) Leuprolide (Lupron), nafarelin (Synarel), goserelin (Zoladex), and buserelin
        (b) Adverse effects: hot flashes, headache, mood swings, insomnia, vaginal dryness, decreased breast size, bone loss
    ii. GnRH antagonists
        (a) Ganirelix (Antagon) and cetrorelix (Cetrotide)
        (b) Newer agents
        (c) Said to have fewer complications
        (d) Faster onset and action than agonists

8. Metformin
    a. Sometimes used to help ovulation in women with polycystic ovary syndrome
    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: Maintain support, used for luteal phase support, or for patient with frequent miscarriages
    a. Capsules (micronized): orally, vaginally
    b. Injectables
    c. Vaginal suppositories
2. Bromocriptine: Decreases prolactin levels; prolactin lowers progesterone levels, 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: Used before fertility procedures for uterine blood flow and decreased risk of ovarian hyperstimulation syndrome

Patient Case

8. L.L. is a 26-year-old woman who has been trying to conceive for 13 months without success. She and her husband would like to conceive in the next year or so. She is 61 inches tall and weighs 172 lb (78 kg); her BMI is 32 kg/m^2, and she has moderate acne and hirsutism. Her menstrual cycle is fairly regular at 26–27 days. Her husband's physical examination and semen analysis are normal. Her ultrasonography shows polycystic ovaries. Her insulin/glucose ratio is high. Which is the best first-line agent to recommend to L.L. that might help her ovulate?

    A. Lose weight and start metformin.

    B. Continue trying to conceive; make no recommendations at this time.

    C. Start FSH injections.

    D. Start hCG injections.

I. Complications: Ovarian Hyperstimulation Syndrome
1. What is it?
    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. What happens?
    a. Ovary enlargement
    b. Capillary permeability increase
    c. Protein-rich fluid escaping to intravascular 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. Who is at risk?
    a. Young age
    b. Low body weight
    c. High estradiol levels or rapidly increasing
    d. Size and number of follicles stimulated
    e. Number of eggs retrieved
    f. History of polycystic ovary syndrome
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

J. Emotional Reactions to Infertility
1. Feelings of loss
2. Anger
3. Guilt
4. Shock
5. Lower self-esteem
6. Sexual dysfunction
7. Marital distress
8. Social isolation

K. Psychiatric Disorders
1. A reported 69% of women and 21% of men at a fertility clinic had a psychiatric disorder, possibly because of fertility issues but unknown exact reason
2. Depression
    a. Women with history of depression are twice as likely to suffer recurrence.
    b. Survey: 17% of women using assisted reproductive technique had depression.

3. Anxiety
4. Medication contribution: Fertility drugs affect mood.
    a. GnRH analogs; clomiphene can cause mood changes.
    b. Progesterone may induce depressive symptoms.
    c. Drugs may affect libido.

XIII. SEXUALLY TRANSMITTED INFECTIONS INCLUDING PELVIC INFLAMMATORY DISEASE, GYNECOLOGIC INFECTIONS

(NOTE: AWAITING UPDATED GUIDELINES FROM THE CDC)

A. Herpes Simplex Virus (HSV) Infection
    1. Characteristics
        a. Types: HSV-1 and HSV-2 can cause genital herpes.
        b. Diagnosed in at least 50 million people in the United States
        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.
        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. Acyclovir 200 mg orally five times daily for 7–10 days
            iii. Famciclovir 250 mg orally three times daily for 7–10 days
            iv. Valacyclovir 1 g orally twice daily for 7–10 days
        b. Recurrent HSV infection
            i. If treatment is initiated within 1 day of lesion onset, patients with recurrent infections may benefit.
                (a) Acyclovir 400 mg orally three times daily for 5 days
                (b) Acyclovir 800 mg orally three times daily for 2 days
                (c) Acyclovir 800 mg orally twice daily for 5 days
                (d) Famciclovir 125 mg orally twice daily for 5 days
                (e) Famciclovir 500 mg orally × 1; then 250 mg orally twice daily for 2 days (new regimen according to 2010 guidelines)
                (f) Famciclovir 1000 mg orally twice daily for 1 day
                (g) Valacyclovir 500 mg orally twice daily for 3 days
                (h) Valacyclovir 1000 mg orally once daily for 5 days
            ii. 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
                (d) Valacyclovir 1000 mg/day orally

4. Herpes encephalitis
    a. Characteristics
        i. Primarily caused by HSV-1
        ii. Spreads through neural routes during primary or recurrent infection
        iii. Primarily temporal lobe involvement with eventual hemorrhagic encephalitis
        iv. High mortality if untreated and frequent neurologic sequelae
    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: 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

Patient Cases

9. 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. Which statement is best to mention to D.H. regarding the treatment of her herpes infection?

    A. Treatment of the initial infection will decrease the risk of 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 (*Treponema 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. In general, perform a nontreponemal test for screening purposes and confirm with a treponemal test.
   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
      a. From 4 to 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 2 weeks
   4. Late latent syphilis (more than 1 year in duration) or unknown duration. Recommended treatment
      a. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks
      b. 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 (total dose 7.2 million units)
         ii. If penicillin allergy: Doxycycline 100 mg twice daily or tetracycline 500 mg four times daily for 4 weeks
   6. Neurosyphilis
      a. Recommended treatment: Aqueous crystalline penicillin G 3–4 million units intravenously every 4 hours or continuous infusion 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. Treatment
    a. Azithromycin 1 g in a single dose or doxycycline 100 mg twice daily for 7 days
    b. Alternatives: Erythromycin base 500 mg orally four times daily for 7 days, ofloxacin 300 mg orally twice daily for 7 days, levofloxacin 500 mg/day orally for 7 days, or erythromycin ethylsuccinate 800 mg orally four times daily 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.

D. Gonococcal Infection
1. Penile discharge and dysuria common in men, but women are often asymptomatic (which can lead to PID); symptoms in women include vaginal discharge and dysuria.
2. Treatment
    a. Uncomplicated gonococcal infections of cervix, urethra, and rectum: Ceftriaxone 250 mg intramuscularly (increased from 125 mg intramuscularly according to 2010 CDC recommendations) *plus* treatment of chlamydia if not ruled out (azithromycin 1 g in a single dose or doxycycline 100 mg twice daily for 7 days). New in 2012: Alternative if ceftriaxone not an option, cefixime 400 mg orally as single-dose *plus* azithromycin 1 g in a single dose or doxycycline 100 mg twice daily for 7 days and test for cure in 1 week
    b. Gonococcal infection of the pharynx: Ceftriaxone *plus* treatment of chlamydia (azithromycin 1 g in a single dose or doxycycline 100 mg twice daily for 7 days)
    c. Allergy to cephalosporins, may consider azithromycin 2 g orally × 1 and test for cure in 1 week, has significant GI issues, resistance increasing
    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: Treat for chlamydia.
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. Regimen A: Cefotetan 2 g intravenously every 12 hours *or* cefoxitin 2 g intravenously every 6 hours plus doxycycline 100 mg intravenously or orally every 12 hours. Parenteral therapy can be discontinued 24 hours after clinical improvement and changed to oral therapy for 14 days.
      ii. Regimen B: Clindamycin 900 mg intravenously every 8 hours plus gentamicin intravenously or intramuscularly 2-mg/kg loading dose, then 1.5 mg/kg every 8 hours (or once-daily therapy with 3- to 5-mg/kg dosing). Parenteral therapy can be discontinued 24 hours after clinical improvement and changed to oral therapy for 14 days.
      iii. Alternative regimens: Ampicillin/sulbactam 3 g intravenously every 6 hours plus doxycycline 100 mg intravenously or orally every 12 hours
   b. Oral treatment: Ceftriaxone 250 mg intramuscularly once or cefoxitin 2 g intramuscularly plus probenecid 1 g orally once plus doxycycline 100 mg twice daily for 14 days with or without metronidazole 500 mg orally twice daily for 14 days
   c. Sexual partners of patients with PID within the past 60 days should be tested and treated.

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 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 can lead to PID and endometriosis.
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 one 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, or tinidazole 1 g orally once daily for 5 days
   c. Pregnant women: Metronidazole 500 mg orally twice daily for 7 days, metronidazole 250 mg orally three times daily for 7 days, or clindamycin 300 mg orally twice daily for 7 days
   d. Do not use clindamycin cream during pregnancy because of the increased risk of preterm deliveries.
   e. Treatment of sexual partners is not necessary.

Patient Cases

11. 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 with many male partners. 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 BP 117/75 mm Hg. M.A. has adnexal tenderness, cervical motion tenderness, and a vaginal discharge. Which is the best empiric therapy?
    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 × 1 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.

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. Treatment
        a. Metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose
        b. Alternative: Metronidazole 500 mg orally twice daily for 7 days
        c. All sexual partners should be treated.
        d. 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 28. 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
Nystatin	100,000-unit vaginal tablet at bedtime	14 days
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 for vulvovaginal candidiasis while taking antibiotics; recommend OTC 7-day treatment and use a full applicator at bedtime while taking antibiotics
8. Pregnant women: Drugs of choice are OTC azoles 7-day treatment

XIV. 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 250 mg 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
    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; probably gonococcal or chlamydial infection. Ceftriaxone 250 mg intramuscularly once plus doxycycline 100 mg twice daily for 10 days
    2. If probably caused by enteric organisms
        a. Ofloxacin 300 mg twice daily orally for 10 days (not for gonorrhea)
        b. Levofloxacin 500 mg/day orally for 10 days (not for gonorrhea)

XV. 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. Vascular because of atherosclerotic plaques, trauma, or irradiation
            ii. Neurologic because of stroke, seizures, or diabetes mellitus
            iii. Hormonal abnormalities because of excess prolactin (hyperprolactinemia) or decreased testosterone concentrations (hypogonadism)
            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)

B. Treatment of Erectile Dysfunction
    1. Control risk factors.
        a. Stop smoking.
        b. Control diabetes mellitus.
        c. Control hyperlipidemia.
        d. Control hypertension.

e. Decrease alcohol intake.
f. Discontinue illicit drugs.
g. Lose weight.
h. Exercise.
i. Review current medications.
j. Cardiovascular disease 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
3. Testosterone replacement if testosterone levels are found to be low
   a. Oral testosterone should not be used because of potential liver toxicity.
   b. Depot intramuscular injection of testosterone enanthate 200 mg or cypionate 300 mg every 2–3 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 1% gel applied every morning
      i. Testim has 50 mg of testosterone per tube, apply to shoulders, upper arms only
      ii. AndroGel 1.62% and 1% and Androgel Pump; 1 pump = 12.5 mg of testosterone; should not be applied to genitals, chest, or back.
      iii. Fortesta gel may have between 10 and 70 mg applied; 1 pump = 10 mg; apply to thighs; avoid genitals.
      iv. Vogelxo 50 mg/one tube or packet and Vogelxo 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. 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 BP, acne, enlarged prostate, liver toxicity, cholesterol changes, edema, polycythemia
   i. Monitor serum testosterone within 1–3 months and at 6- to 12-month intervals.
   j. If no improvement after 3 months, may discontinue treatment
4. Phosphodiesterase (PDE) inhibitors (first-line drug therapy for men without contraindications to use)
   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. Caution with cardiovascular disease, 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 dose by half in some cases; precautions with CYP3A4 inhibitors and macrolides because they increase PDE inhibitor levels
e. Doses
   i. Sildenafil 50 mg orally × 1; maximal dose 100 mg/day, usually take tablet 1 hour before intercourse
   ii. Tadalafil 10 mg orally × 1; maximal dose 20 mg/day; effects may last up to 36 hours; may also use as daily dose without respect to timing of intercourse, tadalafil 2.5–5 mg orally daily
   iii. Vardenafil 10 mg orally × 1; maximal dose 20 mg/day, usually take tablet 30 minutes to 1 hour before intercourse
   iv. Avanafil 100 mg orally × 1; maximal dose 200 mg/day; also may lower dose to 50 mg/day if needed, but initial recommendation is to start with 100 mg orally per day; usually take tablet 30 minutes before intercourse

Table 29. Summary of Phosphodiesterase-5 Medications

Name	Dose	Comments
Sildenafil (Viagra)	50 mg PO 1 hour before intercourse (dose range 25–100 mg)	May require hepatic and renal dose adjustments Take on empty stomach
Vardenafil (Levitra)	10 mg PO 1 hour before intercourse (dose range 5–20 mg)	May require hepatic dose adjustment Fatty meal delays onset
Vardenafil oral disintegrating tablet (Staxyn)	10 mg PO 1 hour before intercourse	Not recommended with hepatic conditions Do not use with CYP3A4 inhibitors
Tadalafil (Cialis)	5 mg PO up to 36 hours 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 minutes 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. SSRIs: 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
Deep venous thrombosis is increased with Prempro (conjugated estrogens and medroxyprogesterone acetate). Myocardial infarction and strokes are also increased. Fractures are decreased.

2. Answer: C
The patient has an intact uterus; therefore, she needs both an estrogen and a progestogen. Prempro is the only product listed in the choices that includes a progestogen. The patient is suffering from hot flashes in addition to vaginal dryness; therefore, a systemic product is recommended. A vaginal 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.

3. Answer: C
Definitions:
Normal = BMD within 1 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

4. Answer: D
Drug therapy begins with 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 requires 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. Bisphosphonates such as alendronate and risedronate are considered first-line drugs because they inhibit normal and abnormal bone resorption and reduce vertebral and nonvertebral fractures by 30%–50%. For risedronate, the treatment dose is 35 mg orally weekly. Teriparatide (Forteo) is reserved for treating women at high risk of fracture, including those with a very low BMD (T-score worse than –3.0) and a previous vertebral fracture. In addition, the patient's creatinine clearance is between 60 and 70 mL/minute, which allows use of a bisphosphonate. Use of a bisphosphonate is contraindicated at a creatinine clearance of less than 30–35 mL/minute. Teriparatide decreases vertebral fractures by 65% and nonvertebral fractures by 53%. 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.

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. This patient requires treatment for hypertension, particularly while pregnant, because it can lead to detrimental effects in the fetus and mother. Methyldopa, labetalol, and nifedipine are the preferred agents for treating hypertension in women who are trying to conceive or pregnant, with labetalol being used more often in recent years. β-Blockers are not specifically teratogenic but may cause adverse effects in the fetus such as intrauterine growth retardation, particularly atenolol.

6. Answer: B
An OC with stronger estrogenic properties is required because the patient is bleeding through early in the cycle. Ortho-Cept (ethinyl estradiol 30 mcg/desogestrel 0.15 mg) has higher estrogenic properties (intermediate) than Mircette (ethinyl estradiol 20 mg/desogestrel 0.15 mg) and other options (low). Estrogen deficiency is early or midcycle breakthrough bleeding (days 1–10). Progestin deficiency is late breakthrough bleeding (days 10–28).

7. Answer: C
The patient cannot use the contraceptive patch (Ortho-Evra) because her weight is more than 90 kg, and she cannot use estrogen products (ethinyl estradiol/drospirenone and contraceptive patch) because she has hypertension. In addition, she takes an ACE inhibitor, which would not be the best choice with drospirenone because of the possibility of hyperkalemia. Depot medroxyprogesterone acetate has a long return to

fertility time, and the patient is 37 years old. Moreover, DMPA may cause weight gain, and the patient is already obese. Norethindrone has a quick return to fertility and will not affect her hypertension or interact with her ACE inhibitor.

8. Answer: A

The patient is obese, with a BMI of 32 kg/m^2. To optimize her chances of ovulation, she should try to lose weight and lower her BMI. Her ultrasonography, hirsutism, acne, and elevated insulin levels indicate she has polycystic ovary syndrome. Metformin may help her ovulate, and it should be initiated before FSH injections. She and her husband have been trying to conceive for 13 months, which meets the definition of infertility necessitating intervention. Human chorionic gonadotropin injections are not appropriate to provide at this time; usually, they are used to help the ovum rupture once the follicle has been stimulated to increase. Clomiphene citrate would probably be a first-line agent, but this was not an option for this question.

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.

10. Answer: D

Patient-initiated therapy is important for people with occasional recurrences 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 experiencing several recurrences (six or more a year), treatment beyond the patient-initiated therapy (valacyclovir 500 mg orally twice daily for 5 days when a recurrence is noticed) is insufficient. Therapy beyond 5 days is unnecessary because untreated recurrent infections resolve in 7 days; the choice of acyclovir 500 mg orally three times daily for 10 days when a recurrence is noted is therefore incorrect. In addition, suppressive therapy is given twice daily or once daily, not three times a day; therefore, suppressive therapy with famciclovir 250 mg orally three times daily is inappropriate. Suppressive therapy with valacyclovir 500 mg/day orally should be offered.

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. 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. Ampicillin/sulbactam has good activity against most organisms in PID; however, it has no activity against atypical organisms (e.g., *C. trachomatis*). Although ceftriaxone and doxycycline are appropriate, the ceftriaxone dose should be 250 mg, and the duration of doxycycline should be 14 days.

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. In addition, although patients should be encouraged to be tested for HIV because of the strong relationship between STDs and the risk of HIV, 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.

13. Answer: A

Tadalafil may be dosed daily without respect to timing of sexual intercourse. Avanafil should be taken 30 minutes before sexual intercourse. Yohimbine and bupropion are not first line for erectile dysfunction.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

Definitions

Normal = BMD within 1 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

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. Bisphosphonates such as alendronate are considered first-line drugs because they inhibit normal and abnormal bone resorption and reduce vertebral and nonvertebral 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. Calcium and vitamin D are both recommended for this patient as well. Because of the patient's age, the recommended dose of vitamin D is 800 international units orally per day; 600 international units orally per day is recommended for those younger than 70 years. He walks 30 minutes/day, which satisfies the recommendation of weight-bearing activity.

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 a category X drug in pregnancy and a known teratogen. If a woman requires 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). A low-molecular-weight heparin would be the agent of choice. Warfarin should not be used at any time during pregnancy unless the benefit outweighs the risk in very rare and special cases.

4. Answer: D

Medroxyprogesterone acetate is added to conjugated estrogens to decrease the risk of endometrial cancer. Estrogen alone is not sufficient because the patient has an intact uterus, as indicated by her medical history (no surgical procedures). Venlafaxine is not relieving her hot flashes; therefore, it should be discontinued.

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. The best treatment would be an oral or transdermal systemic agent. The patient has had a hysterectomy; therefore, a progestogen in combination with estrogen is not necessary.

6. Answer: C

The efficacy of lamotrigine may be decreased. *(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 on suppressive therapy [acyclovir or valacyclovir], with 25% and 20%, respectively, experiencing a recurrent infection) is $20 = 1/(0.25 - 0.20)$. 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 BP 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. She also is obese at 215 lb (98 kg) and weighs more than 90 kg, so the patch

is not recommended. The levonorgestrel IUS (Mirena, Skyla) may be an option, but the patient is interested in conceiving in a year or so. Mirena works for up to 5 years and Skyla works for up to 3 years, making neither cost-effective for the patient. Norethindrone oral tablet is a POP and the best choice.

9. Answer: D
Clomid (clomiphene citrate) is the first-line choice to stimulate ovulation. Pergonal (hMG), Synarel (GnRH agonist), and Ovidrel (hCG) are not first-line agents and are usually used after clomiphene citrate has failed or when the patient is undergoing assisted reproductive therapies.

10. Answer: B
Emergency contraception is still effective for up to 120 hours after unprotected intercourse. The patient is 22 years old and qualifies for OTC EC from the pharmacist. She does not require a prescription. She stated 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. When inserting a new vaginal ring, she should also be instructed to use a BUM for at least 7 days.

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

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. Levofloxacin would not cover syphilis. Three doses of benzathine penicillin G is indicated for late latent syphilis, not neurosyphilis. Furthermore, although azithromycin is an alternative for patients who are penicillin allergic in other situations, patients with neurosyphilis should be desensitized and given penicillin.

13. Answer: A
Data are continuous and probably normally distributed (given the large population of 350 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. The Student t-test is a parametric test for comparing only two groups. A chi-square test is used to assess nominal data between two groups. The Mann-Whitney U test is a nonparametric analog to the Student t-test.

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	
	Bosentan		
	Tacrolimus		
	Modafinil		

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

[a]Barbiturates, phenytoin, primidone, carbamazepine, oxcarbazepine, felbamate, topiramate, vigabatrin.

[b]Alprazolam, chlordiazepoxide, diazepam.

[c]Temazepam.

[d]Delavirdine, efavirenz.

[e]Atazanavir, indinavir.

[f]Nelfinavir, ritonavir, lopinavir/ritonavir, amprenavir.

NNRTIs = nonnucleoside reverse transcriptase inhibitors.

Questionable effects that hormonal contraceptives may have on other drugs:

a. Anticoagulants: Hormonal contraceptives may increase certain clotting factors and reduce antithrombin III, so it is questionable whether hormonal contraceptives interfere with anticoagulants.
b. Lamotrigine levels may be decreased by hormonal contraceptives.
c. 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 alternative contraception for the length of antibiotic therapy and for 7 days after discontinuing antibiotic.
    iii. U.S. Medical Eligibility Criteria for Contraceptive Use 2010 suggest that no alternative form of contraception is necessary with broad-spectrum antibiotics (although conservative practice is not discouraged); however, rifampin and griseofulvin require an alternative form of contraception.