Chapter 30: Contraception

INTRODUCTION

- *Contraception* is the prevention of pregnancy by inhibiting sperm from reaching a mature ovum or by preventing a fertilized ovum from implanting in the endometrium.

MENSTRUAL CYCLE PATHOPHYSIOLOGY

- The median menstrual cycle length is 28 days (range 21–40 days). Day 1 is the first day of menses and marks the beginning of the follicular phase. Ovulation usually occurs on day 14, followed by the luteal phase that lasts until the beginning of the next cycle.
- The hypothalamus secretes gonadotropin-releasing hormone, which stimulates the anterior pituitary to secrete the gonadotropins follicle-stimulating hormone (FSH) and luteinizinig hormone (LH).
- In the follicular phase, FSH levels increase and cause recruitment of a small group of follicles for continued growth. Between days 5 and 7, one of these becomes the dominant follicle, which later ruptures to release the oocyte. The dominant follicle develops increasing amounts of estradiol and inhibin, providing a negative feedback on the secretion of gonadotropin-releasing hormone and FSH.
- The dominant follicle continues to grow and synthesizes estradiol, progesterone, and androgen. Estradiol stops the menstrual flow from the previous cycle, thickens the endometrial lining, and produces thin, watery cervical mucus. FSH regulates aromatase enzymes that induce conversion of androgens to estrogens in the follicle.
- The pituitary releases a midcycle LH surge that stimulates the final stages of follicular maturation and ovulation. Ovulation occurs 24–36 hours after the estradiol peak and 10–16 hours after the LH peak.
- The LH surge is the most clinically useful predictor of approaching ovulation. Conception is most successful when intercourse takes place from 2 days before ovulation to the day of ovulation.
- After ovulation, the remaining luteinized follicles become the corpus luteum, which synthesizes androgen, estrogen, and progesterone (**Fig. 30-1**).
- If pregnancy occurs, human chorionic gonadotropin prevents regression of the corpus luteum and stimulates continued production of estrogen and progesterone. If pregnancy does not occur, the corpus luteum degenerates, progesterone declines, and menstruation occurs.

FIGURE 30-1

Menstrual cycle events, idealized 28-day cycle. (Hatcher RA, Trussell J, Nelson AL, et al. *Contraceptive Technology*. 21st ed. Ardent, NY: Median, Inc.; 2015.)

(FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone.)

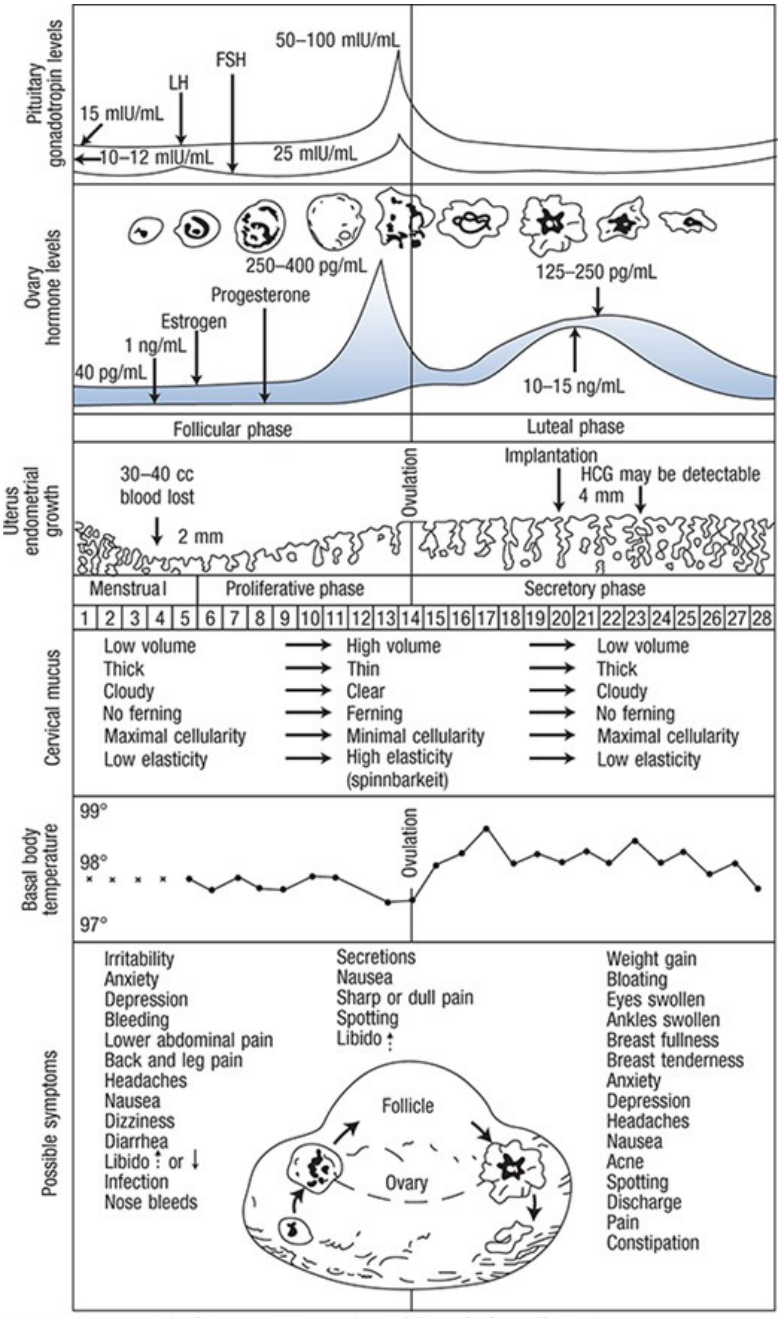
LH: 15 mIU/mL = 15 IU/L; 50–100 mIU/mL = 50–100 IU/L.

FSH: 10–12 mIU/mL = 10–12 IU/L; 25 mIU/mL = 25 IU/L. Estrogen: 40 pg/mL = ~150 pmol/L; 250–400

pg/mL = ~920–1470 pmol/L; 125–250 pg/mL = ~460–920 pmol/L.

Progesterone: 1 ng/mL = 3 nmol/L; 10–15 ng/mL = ~30–50 nmol/L.

Temperatures: 99°F = 37.2°C; 98°F = 36.7°C; 97°F = 36.1°C.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TREATMENT

- Goal of Treatment: The prevention of pregnancy following sexual intercourse. Additional benefits from contraceptive use can also be realized (ie, sexually transmitted infections [STIs] prevention and menstrual cycle regulation).

Nonpharmacologic Therapy

- A comparison of methods of nonhormonal contraception is shown in **Table 30-1**.
- The fertility awareness-based method includes avoiding intercourse on the days when contraception is likely to occur and is associated with relatively high pregnancy rates.
- **Diaphragms** and the **cervical cap** are effective barriers that should be used with spermicide before insertion. They should be inserted up to 6 hours before intercourse and must be left in place for at least 6 hours after. A diaphragm should not be left in place for more than 24 hours because of the risk of toxic shock syndrome (TSS), while the cervical cap should not remain in place for longer than 48 hours to reduce the risk of TSS. Condom use with diaphragms and cervical caps is necessary to protect against STIs including human immunodeficiency virus (HIV).
- Most **condoms** made in the United States are latex, which is impermeable to viruses, but ~5% are made from lamb intestine, which is not. Water-soluble lubricants (ie, Astroglide and K-Y Jelly) are preferred to prevent condom breakdown. Condoms with spermicides are not recommended, as they provide no additional protection against pregnancy or STIs and may increase vulnerability to HIV.
- The **female condom (Reality)** covers the labia as well as the cervix. While the pregnancy rate is higher than with male condoms, it will protect against many viruses, including HIV.

TABLE 30-1

Comparison of Methods of Nonhormonal Contraception

				Percent of Women with Pregnancy[a]	
Method	**Absolute Contraindications**	**Advantages**	**Disadvantages**	**Perfect Use**	**Typical Use**
Condoms, male	Allergy to latex or rubber	Inexpensive STI/STD protection, including HIV (latex only)	High user failure rate Poor acceptance Possibility of breakage Efficacy decreased by oil-based lubricants Possible allergic reactions to latex in either partner	2	13
Condoms, female	Allergy to polyurethane History of TSS	Can be inserted just before intercourse or ahead of time STI/STD protection, including HIV	High user failure rate Dislike ring hanging outside vagina Cumbersome	5	21
Diaphragm with spermicide	Allergy to latex, rubber, or spermicide Recurrent UTIs History of TSS Abnormal gynecologic anatomy	Low cost Decreased incidence of cervical neoplasia Some protection against STIs/STDs	High user failure rate Decreased efficacy with increased frequency of intercourse Increased incidence of vaginal yeast UTIs, TSS Efficacy decreased by oil-based lubricants Cervical irritation	16	17

Cervical cap (FemCap)	Allergy to spermicide History of TSS Abnormal gynecologic anatomy Abnormal papanicolaou smear	Low cost Latex-free Some protection against STIs/STDs FemCap reusable for up to 2 years	High user failure rate Decreased efficacy with parity Cannot be used during menses	9	16[b]
Spermicides alone	Allergy to spermicide	Inexpensive	High user failure rate Must be reapplied before each act of intercourse May enhance HIV transmission No protection against STI/STDs	16	21
Sponge (Today)	Allergy to spermicide Recurrent UTIs History of TSS Abnormal gynecologic anatomy	Inexpensive	High user failure rate Decreased efficacy with parity Cannot be used during menses No protection against STIs/STDs	9[c]	14[d]

[a]Failure rate in the United States during first year of use.

[b]Failure rate with FemCap reported to be 24% per package insert.

[c]Failure rate with Today sponge reported to be 20% in parous women.

[d]Failure rate with Today sponge reported to be 27% in parous women.

HIV, human immunodeficiency virus; STI/STD, sexually transmitted infection/disease; TSS, toxic shock syndrome; UTI, urinary tract infection.

Pharmacologic Therapy

- **Table 30-2** compares unintended pregnancy rates and continuation rates for pharmacologic contraceptive methods.

TABLE 30-2

Pregnancy and Continuation Rates for Various Pharmacologic Contraceptive Methods

Method	Pregnancy Typical Use	Pregnancy Ideal Use	Continuation After 1 Year
Combined oral contraceptive	7%	<1%	67%
Combined hormonal transdermal contraceptive patch	7%	<1%	—
Combined hormonal vaginal contraceptive ring	7%	<1%	—
Depot medroxyprogesterone acetate	4%	<1%	56%
Copper IUD	<1%	<1%	78%
Levonorgestrel IUD	<1%	<1%	80%
Progestin-only implant	<1%	<1%	89%

Spermicides and Spermicide Implanted Barrier Techniques

- Most spermicides contain **nonoxynol-9**, a surfactant that destroys sperm cell walls and blocks entry into the cervical os. They offer no protection against STIs, and when used more than twice daily, nonoxynol-9 may increase the transmission of HIV.
- The **vaginal contraceptive sponge (Today)** is available over the counter and contains nonoxynol-9 and provides protection for 24 hours. After intercourse, the sponge must be left in place for at least 6 hours before removal. It should not be left in place for more than 24–30 hours to reduce the risk of TSS. It should not be reused after removal.

Hormonal Oral Contraceptives

- **Combined Hormonal Contraceptive** (CHC) is the most commonly used form of oral contraception (OC) and contains a combination of synthetic estrogen and synthetic progestin. Some OCs contain progestin alone.
- Estrogens suppress FSH release (which may contribute to blocking the LH surge) and also stabilize the endometrial lining and provide cycle control. **Ethinyl estradiol** (EE) is the most common used synthetic estrogen.
- **Progestins** thicken cervical mucus, delay sperm transport, and induce endometrial atrophy. They also block the LH surge and thus inhibit ovulation. Progestins vary in their progestational activity and are metabolized to substances that differ in their inherent estrogenic, antiestrogenic, and androgenic effects. Androgenic activity depends on the presence of sex hormone (testosterone) binding globulin and the androgen-to-progesterone activity ratio. If sex hormone binding globulin decreases, free testosterone levels increase, and androgenic side effects are more prominent.
- **Table 30-3** lists available oral contraceptives by brand name and hormonal composition.
- With perfect use, OC efficacy is more than 99%, but with typical use, up to 7% of women experience unintended pregnancy.
- Monophasic CHCs contain a constant amount of estrogen and progestin for 21 days, followed by 7 days of placebo. Biphasic and triphasic pills contain variable amounts of estrogen and progestin for 21 days and are followed by a 7-day placebo phase.
- Extended-cycle pills and continuous combination regimens may offer some side effect and convenience benefits. With extended-cycle CHC the number of hormone-containing pills increases from 21 to 84 days, followed by a 7-day placebo phase, resulting in four menstrual cycles per year.

- The progestin-only “minipills” tend to be less effective than combination CHCs and are associated with irregular and unpredictable menstrual bleeding. They must be taken every day of the menstrual cycle at approximately the same time of day to maintain contraceptive efficacy. They are associated with more ectopic pregnancies than other hormonal contraceptives.
- In the first-day start method, women take the first pill on the first day of their menstrual cycle. In the Sunday start method, the first pill is taken on the first Sunday after starting the menstrual cycle. In the quick start method the first pill is taken the day of the office visit. Women should use a second contraceptive method for 7–30 days after OC initiation and resume hormonal contraception no sooner than 5 days after the use of emergency contraception (ie, ulipristal acetate).
- Women should be provided with guidance about what to do if a pill is missed or if vomiting and diarrhea occur.
- An important concern about OCs is their lack of protection against STIs, and condoms should be used to prevent STIs.
- The choice of an initial OC is based on hormonal content and dose, preferred formulation, and coexisting medical conditions.
- A complete medical examination and papanicolaou (Pap) smear are not necessary before a CHC is prescribed. Obtain a medical history and blood pressure measurement, and discuss the risks, benefits, and adverse effects with the patient before prescribing a CHC.
- **Table 30-4** shows graded eligibility criteria for contraceptive use.
- Noncontraceptive benefits of OCs include decreased menstrual cramps and ovulatory pain; decreased menstrual blood loss; improved menstrual regularity; decreased iron deficiency anemia; reduced risk of ovarian and endometrial cancer; and reduced risk of ovarian cysts, ectopic pregnancy, pelvic inflammatory disease, endometriosis, uterine fibroids, and benign breast disease.

  ✔ Serious symptoms that may be associated with CHCs are given in **Table 30-5**.

  ✔ Side effects occurring in the first cycle of OC use (eg, breakthrough bleeding, nausea, and bloating) improve by the third cycle of use. **Table 30-6** shows side effect monitoring of women taking CHCs.

  ✔ Instruct women to immediately discontinue CHCs if they experience warning signs referred to by the mnemonic ACHES (Abdominal pain, Chest pain, Headaches, Eye problems, and Severe leg pain).

TABLE 30-3

Composition of Commonly Prescribed Oral Contraceptives[a]

Product	Estrogen	Micrograms[b]	Progestin	Milligrams[b]	Spotting and Breakthrough Bleeding (%)
50 mcg Estrogen					
Ogestrel 0.5/50	Ethinyl estradiol	50	Norgestrel	0.5	4.5
Zovia 1/50	Ethinyl estradiol	50	Ethynodiol diacetate	1	13.9
Sub-50 mcg Estrogen Monophasic					
Afirmelle, Aubra, Aubra EQ, Aviane, Balcoltra, Delyla, Falmina, Larissia, Lessina, Lutera, Orsythia, Sronyx, Vienva, levonorgestrel/EE	Ethinyl estradiol	20	Levonorgestrel	0.1	26.5

Brevicon, Necon 0.5/35, Nortrel 0.5/35, Norminest Fe, Wera	Ethinyl estradiol	35	Norethindrone	0.5	24.6
Zovia 1/35, Kelnor 1/35	Ethinyl estradiol	35	Ethynodiol diacetate	1	37.4
Apri, Cyred, Desogen, desogestrel/EE, Emoquette, Enskyce, Isibloom, Juleber, Reclipsen	Ethinyl estradiol	30	Desogestrel	0.15	13.1
Altavera, Chateal, Kurvelo, Levora, Lillow, Marlissa, Portia	Ethinyl estradiol	30	Levonorgestrel	0.15	14
Aurovela 1/20, Aurovela Fe 1/20, Hailey Fe 1/20, Junel 1/20, Junel Fe 1/20, Loestrin 1/20; Fe 1/20, Melodetta 24 Fe (chewable), Microgestin 1/20, Microgestin Fe 1/20, norethindrone/EE, norethindrone/EE Fe, Tarina Fe 1/20	Ethinyl estradiol	20	Norethindrone	1	26.5
Aurovela 1.5/30-21, Aurovela 1.5/30-28, Aurovela Fe 1.5/30, Hailey Fe 1/20, Gildess Fe 1.5/30, Junel 1.5/30, Junel Fe 1.5/30, Larin (Fe) 1.5/30, Loestrin Fe 1.5/30, Microgestin 1.5/30, Microgestin Fe 1.5/30	Ethinyl estradiol	30	Norethindrone acetate	1.5	25.2
Cryselle, Elinest, Low-Ogestrel	Ethinyl estradiol	30	Norgestrel	0.3	9.6
Alyacen 1/35, Cyclafem 1/35, Dasetta 1/35, Necon 1/35, Norinyl 1+35, Nortrel 1/35, Ortho-Novum 1/35, Pirmella 1/35	Ethinyl estradiol	35	Norethindrone	1	14.7
Estarylla, Femynor, Norgestimate/ethinyl estradiol, Ortho-Cyclen, Mono-Linyah, Mononessa, Previfem, Sprintec	Ethinyl estradiol	35	Norgestimate	0.25	14.3
Balziva, Briellyn, Femcon Fe chewable, Zenchent, Gildagia, Nexesta Fe, Philith, Vyfemla, Wymzya Fe chewable, Zenchant, Zenchant Fe chewable	Ethinyl estradiol	35	Norethindrone	0.4	11
Drosperinone/EE, Ocella, Safyral[c], Syeda, Tydemy[c], Yasmin, Zarah	Ethinyl estradiol	30	Drospirenone	3	14.5
Generess Fe chewable, Layolis Fe, Kaitlib Fe, norethindrone/EE	Ethinyl estradiol	25	Norethindrone	0.8	14.5
Sub-50 mcg Estrogen Monophasic Extended Cycle (longer than 21 days of active tablets)					
Lo Loestrin-24 FE[d]	Ethinyl estradiol	10	Norethindrone	1	50[e]
Aurovela 24 Fe, Junel Fe 24, Larin (Fe) 1/20, Larin 24 Fe, Minastrin 24 Fe chewable, norethindrone/EE/Fe, Taytulla	Ethinyl estradiol	20	Norethindrone	1	50[e]

(capsules)					
Amethia Lo, Camrese Lo, levonorgestrel/EE, LoSeasonique	Ethinyl estradiol	20/10	Levonorgestrel	0.1	50[e]
Amethyst	Ethinyl estradiol	20	Levonorgestrel	0.09	52[e]
Introvale, levonorgestrel/EE, Jolessa, Quasense Setlakin[f]	Ethinyl estradiol	30	Levonorgestrel	0.15	58.5[e]
Amethia, Ashlyna, Camrese, Daysee, levonorgesterel/EE Seasonique	Ethinyl estradiol	30/10	Levonorgestrel	0.15	50[e]
Quartette, Rivelsa	Ethinyl estradiol	20/25/30/10	Levonorgestrel	0.15	50[e]
Beyaz[c], drospirenone/EE, Gianvi, Loryna, Nikki, Rajani[c], Vestura, Yaz[d]	Ethinyl estradiol	20	Drospirenone	3	52.5[e]
Sub-50 mcg Estrogen Multiphasic					
Caziant, Cyclessa, Velivet	Ethinyl estradiol	25 (7)	Desogestrel	0.1 (7)	11.1
		25 (7)		0.125 (7)	
		25 (7)		0.15 (7)	
Tilia Fe, Tri-Legest Fe	Ethinyl estradiol	20 (5)	Norethindrone acetate	1 (5)	21.7
	Ethinyl estradiol	30 (7)	Norethindrone acetate	1 (7)	
	Ethinyl estradiol	35 (9)	Norethindrone acetate	1 (9)	
Azurette, Bekyree, desogestrel/EE, Kariva, Kimidess, Mircette, Pimtrea, Viorele	Ethinyl estradiol	20 (21)	Desogestrel	0.15 (21)	19.7
	Ethinyl estradiol	10 (5)	Desogestrel		
Necon 10/11	Ethinyl estradiol	35 (10)	Norethindrone	0.5 (10)	17.6
	Ethinyl estradiol	35 (11)	Norethindrone	1 (11)	
Alyacen 7/7/7, Cyclafem 7/7/7, Dasetta 7/7/7, Necon 7/7/7,	Ethinyl	35 (7)	Norethindrone	0.5 (7)	14.5

Nortrel 7/7/7, Ortho-Novum 7/7/7, Pirmella 7/7/7	estradiol					
	Ethinyl estradiol	35 (7)	Norethindrone	0.75 (7)		
	Ethinyl estradiol	35 (7)	Norethindrone	1 (7)		
Ortho Tri-Cyclen, Tri-Estarylla, Tri-Femynor, Tri-Linyah, TriNessa, Tri-Previfem, Tri-Sprintec, Norgestimate/EE	Ethinyl estradiol	35 (7)	Norgestimate	0.18 (7)	17.7	
	Ethinyl estradiol	35 (7)	Norgestimate	0.215 (7)		
	Ethinyl estradiol	35 (7)	Norgestimate	0.25 (7)		
Ortho Tri-Cyclen Lo, Norgestimate/EE Tri-Lo Estarylla, Tri-Lo-Marzia, Tri-Lo-Sprintec, TriNessa Lo	Ethinyl estradiol	25 (7)	Norgestimate	0.18 (7)	11.5	
	Ethinyl estradiol	25 (7)	Norgestimate	0.215 (7)		
	Ethinyl estradiol	25 (7)	Norgestimate	0.25 (7)		
Aranelle, Leena, Tri-Norinyl	Ethinyl estradiol	35 (7)	Norethindrone	0.5 (7)	25.5	
	Ethinyl estradiol	35 (9)	Norethindrone	1 (9)		
	Ethinyl estradiol	35 (5)	Norethindrone	0.5 (5)		
Enpresse, Trivora, levonorgestrel/EE, Levonest, Myzilra	Ethinyl estradiol	30 (6)	Levonorgestrel	0.05 (6)		
	Ethinyl estradiol	40 (5)	Levonorgestrel	0.075 (5)		
	Ethinyl estradiol	30 (10)		0.125 (10)		
Natazia	Estradiol valerate	3 (2)	Dienogest	0 (2)		
		2 (22)		2 (5)		
		1 (2)		3 (17)		
				0 (4)		

Progestin Only					
Camila, Deblitane, Errin, Heather, Incassia, Jencycla Jolivette, Lyza, Ortho Micronor, Nora-BE, Norlyda, Norlyroc, Orthor Micronor, Sharobel,Tulana, norethindrone	Ethinyl estradiol	–	Norethindrone	0.35	42.3

[a]28-day regimens (21-day active pills, then 7-day pill-free interval) unless otherwise noted.

[b]Number in parentheses refers to the number of days the dose is received in multiphasic oral contraceptives.

[c]Also contains levomefolate calcium 0.451 mg in all 28 tablets.

[d]28-day regimen (24-day active pills, then 4-day pill-free interval).

[e]Percent reporting after 6–12 months of use.

[f]91-day regimen (84-day active pills, then 7-day pill-free interval).

TABLE 30-4

U.S. Medical Eligibility Criteria for Contraceptive Use: Classifications for Combined Hormonal Contraceptives

Category 4: Unacceptable health risk (method not to be used)
Breastfeeding or non-breastfeeding <21 days postpartum
Current breast cancer
Severe (decompensated) cirrhosis
Current deep venous thrombosis/pulmonary embolism
History/higher risk of deep venous thrombosis/pulmonary embolism (not on anticoagulant therapy)
History/higher risk of deep venous thrombosis/pulmonary embolism (established on anticoagulant therapy for 3 months or greater)
Thrombogenic mutations
Major surgery with prolonged immobilization
Migraines with aura, any age
Systolic blood pressure ≥160 mm Hg or diastolic ≥100 mm Hg
Hypertension with vascular disease
Current and history of ischemic heart disease
Benign hepatocellular adenoma or malignant liver tumor
Peripartum cardiomyopathy, moderately or severely impaired cardiac function; normal or mildly impaired cardiac function <6 months
Smoking ≥15 cigarettes per day and age ≥35
Complicated solid organ transplantation
History of cerebrovascular accident
SLE; positive or unknown antiphospholipid antibodies
Complicated valvular heart disease
Category 3: Theoretical or proven risks usually outweigh the advantages
Breastfeeding 21–30 days postpartum with or without risk factors for VTE
Breastfeeding 30–42 days postpartum with risk factors for VTE
Diabetes mellitus (type 1 or type 2), nonvascular disease
Gallbladder disease; symptomatic and treated by cholecystectomy or asymptomatic
Migraines without aura

History of pregnancy-related cholestasis
History of high blood pressure during pregnancy
Benign liver tumors; focal nodular hyperplasia
Obesity
Breastfeeding 30–42 days without other VTE risk factors
Breastfeeding 42 days or more postpartum
Non-breastfeeding 21–42 days postpartum without risk factors for VTE
Rheumatoid arthritis on or off immunosuppressive therapy
Smoking and <35 years old
Uncomplicated sold organtransplantation
Stable SLE without antiphospholipid antibodies
Unexplained vaginal bleeding before evaluation
Uncomplicated valvular heart disease
Use of antiretrovirals other than fosamprenavir (*category 1 or 2 depending on agent*)
Use of St. John's wort
Inflammatory bowel disease (*possibly category 3 for those with increased risk of VTE*)
Non-breastfeeding 21–42 days postpartum with other risk factors for VTE
Past breast cancer and no evidence of disease for 5 years
History of DVT/PE (not on anticoagulant therapy or established on anticoagulant therapy for at least 3 months), but lower risk for recurrent DVT/PE
Current gallbladder disease, symptomatic, and medically treated
History of bariatric surgery; malabsorptive procedures (*COCs only, vaginal ring/transdermal patch category 1*)
History of cholestasis, past COC-related
Hypertension; systolic blood pressure 140–159 mm Hg or diastolic 90–99 mm Hg
Adequately controlled hypertension
Peripartum cardiomyopathy, normal or mildly impaired cardiac function ≥6 months
Smoking <15 cigarettes per day and age ≥35
Use of fosamprenavir
Use of certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, and lamotrigine)
Use of rifampicin or rifabutin therapy
Diabetes with vascular disease or >20 years duration (*possibly category 4 depending upon severity*)
Multiple risk factors for arterial cardiovascular disease (older age, smoking, diabetes, low HDL, high LDL, or high triglycerides and hypertension) (*possibly category 4 depending on category and severity*)
Acute flare of viral hepatitis (*possibly category 4 depending on severity[initiation]*)
Multiple sclerosis with prolonged immobility
Current or history of superficial venous thrombosis
Acute flare of viral hepatitis occurring during use of product (*continuation, category 3 or 4 for initiation of product*)

Category 1: No restriction (method can be used)

Thalassemia, iron deficiency anemia
Mild compensated cirrhosis
Benign ovarian tumors
Benign breast disease or family history of cancer
Family history of cancer
Schistosomiasis
Cystic fibrosis
Cervical ectropion
Viral hepatitis (carrier/chronic)
Minor surgery without immobilization
DepressionEndometrial cancer/hyperplasia, endometriosisEpilepsyGestational trophoblastic diseaseNonmigrainous headachesHistory of bariatric

surgery; restrictive proceduresHistory of pelvic surgeryHIV infected or high riskMalariaMultiple sclerosis without prolonged immobility
Ovarian cancer
Past ectopic pregnancy
Parity, parous, or nulliparous
PID
Postabortion
Non-breastfeeding >42 days postpartum
Severe dysmenorrhea
Sexually transmitted infections

Category 2: Advantages generally outweigh theoretical or proven risks

Age ≥40 (in the absence of other comorbid conditions that increase CVD risk)
Sickle cell disease
Undiagnosed breast mass
Cervical cancer and awaiting treatment; cervical intraepithelial neoplasia
Family history (first-degree relatives) of DVT/PE
Major surgery without prolonged immobilization
Varicose veins
Vaginal bleeding—irregular pattern without heavy bleeding or heavy, prolonged bleeding
Thyroid disorders
Tuberculosis
Uterine fibroids
Use of SSRIs
Use of broad-spectrum antibiotics, antifungals, and antiparasitics

CHC, combined hormonal contraception; CVD, cardiovascular disease; HIV, human immunodeficiency virus; PE, pulmonary embolism; PID, pelvic inflammatory disease; VTE, venous thromboembolism.

TABLE 30-5

Symptoms of a Serious or Potentially Serious Nature Associated with Combined Hormonal Contraception

Symptom	Possible Cause
SERIOUS: Stop immediately	
Loss of vision, proptosis, diplopia, papilledema	Retinal artery thrombosis
Unilateral numbness, weakness, or tingling	Hemorrhagic or thrombotic stroke
Severe pains in chest, left arm, or neck	Myocardial infarction
Hemoptysis	Pulmonary embolism
Severe pains, tenderness or swelling, warmth or palpable cord in legs	Thrombophlebitis or thrombosis
Hepatic mass or tenderness	Liver neoplasm
POTENTIALLY SERIOUS: May continue with caution while being evaluated	
Absence of menses Spotting or breakthrough bleeding Breast mass, pain, or swelling Right upper-quadrant pain Mid-epigastric pain Mid-epigastric pain Severe nonvascular headache Galactorrhea Jaundice, pruritus Depression, sleepiness Uterine size increase	Cervical endometrial or vaginal cancer Cholecystitis, cholelithiasis, or liver neoplasm Pituitary adenoma Cholestatic jaundice B_6 deficiency Leiomyomata, adenomyosis

TABLE 30-6

Drug Monitoring Table for Hormonal Contraception

Drug (or Drug Class)	Adverse Drug Reactions	Monitoring Parameter	Comments
Combined hormonal contraception	Nausea/vomiting Breast tenderness Weight gain Acne, oily skin Depression, fatigue Breakthrough bleeding/spotting Application site reaction (transdermal) Vaginal irritation (vaginal ring)	Patient symptoms Patient symptoms Weight Visual inspection Depression screening Menstrual symptoms Visual inspection Patient symptoms	Typically improves after two to three cycles; consider changing to lower estrogenic Consider changing to lower androgenic Data are limited and conflicting Consider changing to higher estrogenic
Depo-medroxyprogesterone acetate	Menstrual irregularities[a] Weight gain Acne Hirsutism Depression Decreased bone density	Menstrual symptoms Weight Visual inspection Visual inspection Depression screening BMD	Typically improves after 6 months Data are limited and conflicting Do not routinely screen with DXA
Levonorgestrel IUD	Menstrual irregularities[a] Insertion-related complications Expulsion Pelvic inflammatory disease	Menstrual symptoms Cramping, pain Cramping, pain, spotting, dyspareunia, missing strings Lower abdominal pain, unusual vaginal discharge, fever	Typically spotting, amenorrhea Prophylactic nonsteroidal anti-inflammatory drugs (NSAIDs) or local anesthetic may reduce occurrence IUD strings should be checked regularly by women to ensure IUD properly placed Overall risk of developing is rare, but counseling on STI/STD prevention is important
Copper IUD	See levonorgestrel IUD above	See levonorgestrel IUD above	Menstrual irregularities are typically heavier menses with copper IUD
Progestin-only implant	Menstrual irregularities[a] Insertion-site reactions	Menstrual symptoms Pain, bruising, skin irritation, erythema, pus, fever	Typically well-tolerated and resolve without treatment; infection is rare

[a]Suggested management of irregular bleeding may include use of NSAIDs for 5–7 days; hormonal treatment (if medically eligible) with COC or estrogen therapy for

10–20 days of treatment.

Transdermal Contraceptives

- A combination contraceptive is available as a **transdermal patch** (Xulane) that includes 0.75 mg of EE and 6 mg of norelgestromin. It is as effective as CHCs in women weighing less than 90 kg (198 lb) but is not first line in women weighing more than 90 kg.

  ✔ The patch should be applied to the abdomen, buttocks, upper torso, or upper arm at the beginning of the menstrual cycle and replaced every week for 3 weeks. The fourth week is patch-free. Women should be counseled on the steps to follow should the patch detach or is forgotten.

  ✔ Approved labeling includes a warning regarding VTE risk.

Vaginal Rings

- **NuvaRing** releases ~15 mcg/day of EE and 120 mcg/day of etonogestrel over a 3-week period. On first use, the ring should be inserted on or prior to the fifth day of the cycle, remain in place for 3 weeks, and then be removed. One week should lapse before the new ring is inserted on the same day of the week as it was for the last cycle. A second form of contraception should be used for the first 7 days of ring use or if the ring has been expelled for more than 3 hours.

Long-Acting Injectable and Implantable Contraceptives

- Women who particularly benefit from progestin-only methods, including minipills, are those who are breastfeeding, intolerant of estrogens, and those with concomitant medical conditions in which estrogen is not recommended (**Table 30-4**).

- Injectable and implantable contraceptives are also beneficial for women with adherence issues as failure rates are lower than with CHC.

Injectable Progestins

- **Depot medroxyprogesterone acetate (DMPA)** 150 mg is administered by deep intramuscular injection in the gluteal or deltoid muscle within 5 days of onset of menstrual bleeding, and the dose should be repeated every 12 weeks. Another formulation contains 104 mg of DMPA (Depo-SubQ Provera 104), which is injected subcutaneously into the thigh or abdomen. Exclude pregnancy in women more than 1 week late for repeat injection of the intramuscular formulation or 2 weeks late for repeat injection of the subcutaneous formulation. Return of fertility may be delayed after discontinuation.

- DMPA can be given immediately postpartum in women who are not breastfeeding, and at 6 weeks postpartum in women breastfeeding. The median time to conception from the first omitted dose is 10 months.

  ✔ DMPA is contraindicated in women with a current diagnosis of breast cancer and should be used cautiously in those with a history of breast cancer, cardiovascular disease, or lupus.

  ✔ The most frequent adverse effect of DMPA is menstrual irregularity, which decreases after the first year. Breast tenderness, weight gain, and depression occur less frequently.

  ✔ DMPA is associated with reduced bone mineral density (BMD), and has a black box warning, but this is controversial as data do not demonstrate increased fracture risk. Loss of BMD seems to be greater with increasing duration of use, and effects on BMD may not be completely reversible upon discontinuation. DMPA should not be continued beyond 2 years unless other contraceptive methods are inadequate.

Subdermal Progestin Implants

- **Etonogestrel implant** (Nexplanon) is a radiopaque, 4-cm implant containing 68 mg of etonogestrel that is placed under the skin of the upper arm. It releases 60 mcg daily for the first month, decreasing gradually to 30 mcg/day at the end of the 3 years of recommended use. Efficacy

exceeds 99%, but it may be less in women who weigh more than 130% of their ideal body weight.

- Need for backup contraception varies based on prior contraceptive use and where in the menstrual cycle the implant is inserted. Fertility returns 30 days after removal.

  ✔ The major adverse effect is irregular menstrual bleeding. Other side effects are headache, vaginitis, weight gain, acne, and breast and abdominal pain. It does not appear to decrease BMD. Fertility returns within 30 days of removal.

Intrauterine Devices (IUDs)

- The contraceptive activity occurs before implantation. Endometrial suppression is caused by progestin-releasing IUDs. Efficacy rates are greater than 99%.
- Strong consideration of an IUD is appropriate in nulliparous and adolescent women due to high efficacy rates and low complication rates. Need for backup contraception varies based on prior contraceptive use and where in the menstrual cycle the implant is inserted.
- The risk of pelvic inflammatory disease among users is low with no long-term effects on fertility.
- ParaGard (copper) can be left in place for 10 years. Mirena, Liletta, Skyla, and Kyleena release levonorgestrel and must be replaced after 5 years (Mirena, Liletta, and Kyleena) and 3 years (Skyla).

  ✔ Major adverse effects include increased menstrual blood flow and dysmenorrhea with ParaGard, while levonorgestrel IUDs are associated with reduced menstrual blood loss and possible amenorrhea.

Special Consideration for Contraceptive Use

Women Over 35 Years of Age

- Use of CHCs containing less than 50 mcg estrogen may be considered in healthy nonsmoking women older than 35 years.
- CHCs are not recommended for women older than 35 years with migraine, uncontrolled hypertension, smoking, or diabetes with vascular disease.
- Studies have not demonstrated an increased risk of cardiovascular disease with low-dose CHCs in healthy, nonobese women.
- Smoking 15 or more cigarettes per day by women over 35 years is a contraindication to the use of CHCs. Progestin-only methods should be considered in this group.

Smoking

- Use of a CHC with less than 50 mcg EE should be used in women under the age of 35 who smoke to reduce the risk of myocardial infarction (MI).

Hypertension

- CHCs, regardless of estrogen dose, can cause small increases in blood pressure (6–8 mm Hg). Use of low-dose CHCs is acceptable in women younger than 35 years with well-controlled and monitored hypertension to reduce the risk of MI and stroke.
- Women with a systolic blood pressure of 140–159 or a diastolic blood pressure of 90–99 mm Hg should avoid CHCs. Their use is contraindicated for women with blood pressure ≥160/100 mm Hg.
- Monitor potassium in women taking potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or aldosterone antagonists if they are also using an OC-containing drospirenone.

Diabetes

- Women younger than 35 years with diabetes but no vascular disease who do not smoke can safely use CHCs. Women who have had diabetes for

more than 20 years or have vascular disease should not use CHCs.

Dyslipidemia

- Generally, synthetic progestins decrease high-density lipoprotein (HDL) and increase low-density lipoprotein (LDL). Estrogens decrease LDL but increase HDL and may moderately increase triglycerides. Most low-dose CHCs have no significant impact on HDL, LDL, triglycerides, or total cholesterol.
- The mechanism for the increased cardiovascular disease in CHC users is believed to be thromboembolic and thrombotic changes, not atherosclerosis.
- CHCs use in women with dyslipidemia as the single cardiovascular risk factor is generally acceptable; however, care should be taken in women with dyslipidemia and other cardiovascular risk factors. An alternative method of contraception may be recommended.

Thromboembolism

- The risk of venous thromboembolism (VTE) in women using OCs is three times the risk in nonusers. However, this risk is less than the risk of thromboembolic events during pregnancy.
- Estrogens increase hepatic production of factors involved in the coagulation cascade. Risk for thromboembolic events is increased in women with underlying hypercoagulable states or those with acquired conditions (eg, obesity, pregnancy, immobility, trauma, surgery, and certain malignancies) that predispose them to coagulation abnormalities.
- OCs containing the newer progestins (eg, drospirenone, desogestrel, norgestimate) carry a slightly increased risk of thrombosis compared to other progestins due to unknown mechanisms.
- The transdermal patch and vaginal ring provide continuous higher exposure to estrogen and have an increased thromboembolic risk.
- For women at increased risk of thromboembolism (older than 35 years, obesity, smoking, personal or family history of venous thrombosis, prolonged immobilization), consider low-dose oral estrogen contraceptives containing older progestins or progestin-only methods.

Obesity

- OCs have lower efficacy in obese women, and low-dose OCs may be especially problematic. IUDs, implants, and DMPA have very low failure rates, and progestin-only contraceptives are considered safe in obese women.
- Obese women are at increased risk for VTE, and progestin-only contraception may be better for obese women over 35 years.

Migraine Headache

- CHCs may decrease or increase migraine frequency.
- CHCs may be considered for healthy, nonsmoking women (less than 35 years old) with migraines without aura. Discuss continued use of CHC risks and benefits with women developing migraines without aura.
- Women of any age who have migraine with aura should not use CHCs due to the risk of stroke. Women who develop migraines with aura while receiving CHCs should discontinue their use and consider a progestin-only option.

Breast Cancer

- There is a small increase in the relative risk of having breast cancer while CHCs are taken and for up to 10 years following discontinuation.
- For women over the age of 40 or those who have an elevated risk of breast cancer because of family history or other factors, alternatives may be considered.

- The choice to use CHCs should not be influenced by the presence of benign breast disease or a family history of breast cancer. For women with either BRCA1 or BRCA2 mutation, CHC use is controversial, and women with a current or past history of breast cancer should not use CHCs.

Systemic Lupus Erythematosus (SLE)

- OCs with less than 50 mcg EE do not increase the risk of flare among women with stable SLE and without antiphospholipid/anticardiolipin antibodies. CHCs should be avoided in women with SLE and antiphospholipid antibodies or vascular complications. The copper IUD may be the best option in this situation.
- For women with SLE without antiphospholipid antibodies or vascular complications, progestin-only contraceptives or the copper IUD may be an alternative. Copper IUD and DMPA injection should be avoided in those with SLE and severe thrombocytopenia.

Postpartum

- In the first 21 days postpartum (when the risk of thrombosis is higher), estrogen-containing hormonal contraceptives should be avoided due to increased VTE risk. Progestin-only methods should be used if contraception is necessary.
- CHC should be avoided in the first 42 days postpartum in women with VTE risk factors and for 30 days for those without VTE risk factors who are breastfeeding.

Drug Interactions

- Tell women to use an alternative method of contraception if there is a possibility of a drug interaction compromising OC efficacy.
- Rifampin reduces the efficacy of OCs. Additional nonhormonal contraception should be used for at least 7–28 days after rifampin therapy.
- There is a small risk of interaction with other antimicrobials, and additional nonhormonal contraceptives can be considered if desired. An alternate method of contraception should be used when receiving an antimicrobial for more than 2 months.
- Phenobarbital, carbamazepine, and phenytoin potentially reduce the efficacy of OCs, and many anticonvulsants are known teratogens. IUDs, injectable medroxyprogesterone, or nonhormonal options may be considered for women taking these drugs.
- Combined OCs may decrease the efficacy of lamotrigine and increase the risk of seizures.
- Certain antiretroviral therapies and St. John's Wort may decrease the efficacy of OCs.
- Monitor potassium in patients taking drospireneone and concomitant medications that increase potassium levels or those taking strong CYP3A4 inhibitors.

Return of Fertility After Discontinuation

- There is no evidence that OCs, patches, or vaginal rings use decreases subsequent fertility.
- There is no greater chance of miscarriage or a birth defect in the first month after an OC discontinuation compared to the general population.

Emergency Contraception (EC)

- EC is used to prevent unintended pregnancy after unprotected or inadequately protected sexual intercourse.
- FDA-approved progestin-only and progesterone receptor modulator products are recommended as first-line EC options. They will not disrupt the fertilized egg if implantation has already occurred.
- Progestin-only EC formulations containing one 1.5 mg tablet of levonorgestrel are a regimen of choice and are available without a prescription in the United States. They may be less effective in women weighing greater than 75 kg.

- **Ulipristal** (Ella) is a prescription selective progesterone receptor modulator. It is taken as a single dose of 30 mg within 120 hours (5 days) of unprotected intercourse. It is considered noninferior to levonorgestrel-containing ECs and is not recommended in breastfeeding women.
- Common adverse effects of EC include nausea, vomiting, and irregular bleeding.
- Insertion of a copper IUD or prescribing higher doses of combined OCs (Yuzpe method) are other EC options.
- EC should be given within 72 hours (3 days) of unprotected intercourse, but the sooner it is taken, the greater the efficacy. There is some evidence that it may be effective for up to 5 days after unprotected intercourse, but in this situation ulipristal or a copper IUD may be a better option.
- Backup non-hormonal contraceptive methods should be used after EC for at least 7 days.

Pregnancy Termination

- Medications used in early pregnancy (≤70 days) termination include **mifepristone, misoprostol**, and **methotrexate**. Misoprostol can be used alone or more effectively in combination with mifepristone and methotrexate. The FDA has approved mifepristone 600 mg on day 1 and then misoprostol 400 mcg administered orally 48 hours after the mifepristone dose as a pregnancy termination regimen.
- Mifepristone binds progesterone receptors to block progesterone, resulting in cervical softening and increasing prostaglandin synthesis, leading to contraction stimulation. Mifepristone is usually administered orally, and prescribing is limited to trained prescribers who also dispense the medication. It is contraindicated in patients with bleeding disorders or those on anticoagulants.
- Misoprostol is a prostaglandin 1 analog that may be given orally, vaginally, bucally, or sublingual resulting in cervical ripening and contractions.
- Methotrexate is an immunomodulator that inhibits cell replication. It is effective in the first 7 weeks of pregnancy.

  ✔ Side effects of misoprostol and methotrexate may include stomach upset, diarrhea, headache, dizziness, and fever. Mifepristone has a boxed warning regarding infection and bleeding and women experiencing bleeding that soaks two maxi pads per hour for 2 consecutive hours should contact their healthcare provider.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor blood pressure annually in all CHC users.
- Monitor glucose levels closely when CHCs are started or stopped in women with a history of glucose intolerance or diabetes mellitus.
- For all contraceptive users do annual cytologic screening (more often if they are at risk for STIs), pelvic and breast examination, and well woman consultation. Also, regularly evaluate for problems that may relate to the CHCs (eg, breakthrough bleeding, amenorrhea, weight gain, and acne). These screenings do not have to occur before prescribing hormonal contraceptives.
- Annually monitor women using Nexplanon for menstrual cycle disturbances, weight gain, local inflammation or infection at the implant site, acne, breast tenderness, headaches, and hair loss.
- Evaluate women using DMPA every 3 months for weight gain, menstrual cycle disturbances, and fractures.
- Monitor women with IUDs at 1- to 3-month intervals for proper positioning of the IUD, changes in menstrual bleeding patterns, upper genital tract infection, and protection against STIs.
- Clinicians should monitor and when indicated screen for HIV and STIs. Counsel all women about healthy sexual practices, including the use of condoms to prevent transmission of STIs when necessary.

See Chapter 18, Contraception, authored by Shareen Y. El-Ibiary, Sarah P. Shrader, and Kelly R. Ragucci, for a more detailed discussion of this topic.