

WOMEN'S HEALTH

CHAPTER 45

Contraception

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The world population is about 6.3 billion. At the predicted rate of growth, the population is projected to reach 7.5 billion by 2020 and >9 billion by 2050.¹ In the United States, there are approximately 290 million people, and there is one birth every 8 seconds and 1 death every 13 seconds. This results in an increase in one person every 11 seconds.²

Preventing unwanted pregnancy is an important goal of contraceptive use. Is it estimated that nearly 20% of adolescents have had sex before the age of 15. About 15% of 14-year-old girls who have had sex report having been pregnant.³

Contraceptive policies established and implemented in this decade will help determine how quickly the population will grow in the United States and worldwide and can help reduce the number of unwanted pregnancies.

MENSTRUAL CYCLE PHYSIOLOGY

Feedback biologic mechanisms involving the hypothalamus, anterior pituitary gland, ovaries, and endometrial lining of the uterus control the average 28-day menstrual cycle.^{4,5} The hy-

pothalamus synthesizes gonadotropin-releasing hormone (GnRH) and secretes the hormone in a pulse-like manner with varying frequencies throughout the menstrual cycle. GnRH stimulates the anterior pituitary to produce and release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH act on the ovaries to produce estrogen and progesterone. Estrogen in turn acts on the hypothalamus and anterior pituitary, in a negative feedback manner, to stop FSH and LH secretion (Fig. 45-1).

The menstrual cycle can be divided into three phases: the follicular phase, ovulation, and the luteal phase (Fig. 45-2).⁴⁻⁶ The day bleeding begins is referred to as the first day (or day 1) of the menstrual cycle. Bleeding usually occurs from days 1 to 5 of the cycle. The follicular phase begins at the onset of menstruation (menstrual phase) and lasts approximately 10 to 14 days (see Fig. 45-2). At the beginning of this phase, several follicles begin to develop within the ovary. In the second half of the follicular phase, most of the developing follicles atrophy, while the dominant follicle develops further and produces estrogen in increasing amounts. Elevated estradiol levels results in a surge in LH and FSH. This LH surge is responsible for final-stage growth and maturation of the follicle, ovulation, and the formation of the corpus luteum. Ovulation usually occurs 14 days before the last day of the cycle, and is followed by the luteal phase. In 90% of women, the luteal phase is 13 to 15 days in duration and is the least variable part of the human reproductive cycle. During this progesterone-dominant phase, the corpus luteum produces progesterone and estrogen. Progesterone prepares the endometrium for implantation of a fertilized ovum. If implantation does not occur, corpus luteum regression causes a decrease in the levels of estrogen and progesterone. When these hormone levels decrease, the endometrium cannot be maintained and is sloughed off (menstrual phase). Using the average 28-day cycle as an example, day 28 is the last day of the cycle and is the day before bleeding begins again for the next menstrual cycle.

COMPARISON OF CONTRACEPTIVE METHOD EFFECTIVENESS

The effectiveness of any contraceptive method depends on its mechanism of action, availability (e.g., if a prescription is required, cost), and acceptability (e.g., side effects, ease of use, religious and social beliefs). Any or all of these reasons can account for the discrepancy between the lowest observed fail-

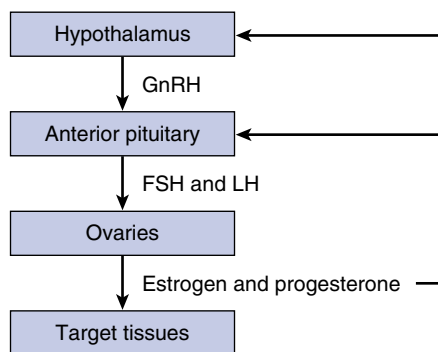


FIGURE 45-1 Menstrual cycle physiology. GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

ure rate and the actual failure rate in typical users. Table 45-1 compares the first-year failure rates of various contraceptive methods.⁵

HORMONAL CONTRACEPTION PHARMACOLOGY

Estrogens prevent the development of the dominant follicle by suppressing FSH secretion. Estrogens also stabilize the endometrial lining to minimize breakthrough bleeding with oral contraceptives (OCs).^{4,5} Progestins prevent ovulation by suppressing LH secretion. They also hamper the transport of sperm through the cervical canal by thickening cervical mucus and causing alterations in the endometrial lining (so that it is not favorable for implantation) and in the fallopian tubes (affecting ovum transport).

COMBINATION ORAL CONTRACEPTIVE PILLS

Manipulating the normal physiologic feedback mechanisms of the menstrual cycle using estrogen and progestin has proven to be an effective method of contraception. In 1960, the U.S. Food and Drug Administration (FDA) released the OC Enovid 10.⁴ Enovid 10 (containing 150 μg mestranol and 9.85 mg norethynodrel) exposed the patient to much higher doses of estrogen and progestin than are in today's OCs. The resulting side effects prompted the search for better OC products. Table 45-2 lists the available brand-name and generic OCs.

The failure rate of OCs ranges from 0.1 to 5 pregnancies per 100 women-years (see Table 45-1).⁵ All low-dose OCs available in the United States contain the synthetic estrogen ethinyl estradiol (EE). Mestranol is another estrogen that has been used in the United States and is used in other countries. Mestranol is inactive and must be converted in the body to EE. Mestranol 50 μg has approximately the same activity as EE 35 μg .⁷ OCs contain one of the following progestins: ethynodiol diacetate, desogestrel, drospironone, levonorgestrel, norethindrone, norethindrone acetate, norgestimate, and norgestrel (a mixture of dextronorgestrel and levonorgestrel; dextronorgestrel appears to be progestationally inert compared with levonorgestrel).⁸ These progestins differ significantly in their progestational potency and also in the extent of their metabolism to estrogenic substances. Progestins have both estrogenic and antiestrogenic effects. Because the progestins have a chemical structure similar to that of testosterone, they also have varying degrees of androgenic activity (Table 45-3).⁹ Minor structural changes in all of the progestins may lead to significant changes in their progestational, estrogenic, antiestrogenic, and androgenic activities, which may vary widely in effect from patient to patient (see Table 45-2).

Different terminology is used to describe the classes of pills that have been approved over the years. The OCs most commonly used today are also called low-dose OCs. They contain <50 μg of EE per day. In the literature, OCs are commonly referred to as first, second, or third generation.⁴ First-generation OCs contain >50 μg EE per day. Second-generation OCs contain the progestins levonorgestrel, norgestimate, norethindrone, norethindrone acetate, or ethynodiol diacetate, along with 30 to 35 μg EE. Third-generation OCs contain desogestrel and 20 to 30 μg EE. There are also generations of progestins; first-generation progestins include norethindrone,

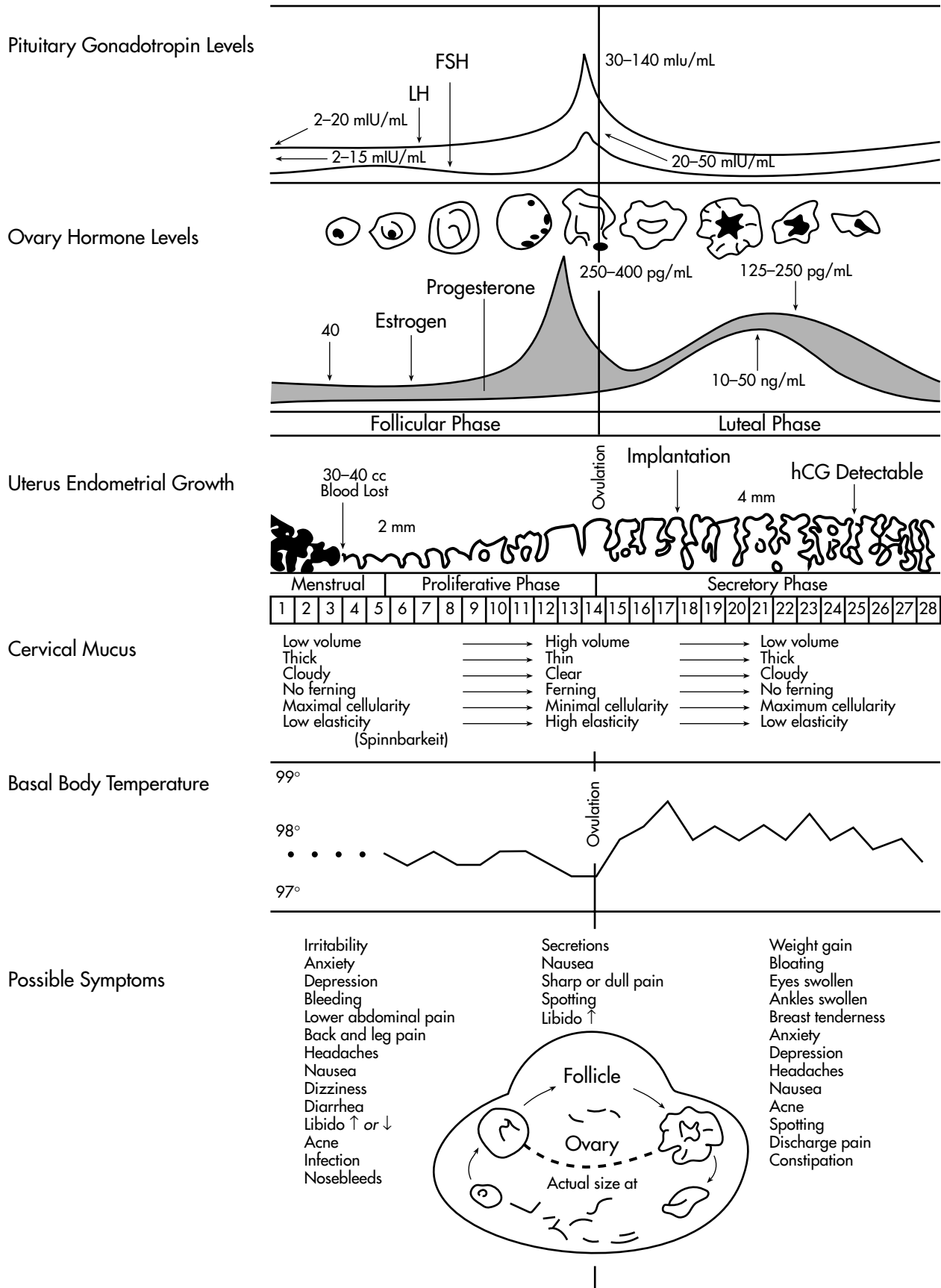


FIGURE 45-2 The menstrual cycle. FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone. (Adapted with permission from Hatcher RA et al. Contraceptive Technology, 16th ed. New York: Irvington Publishers, 1994;41, Figure 2.2)

Table 45-1 Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year: United States

Method (1)	% of Women Experiencing an Unintended Pregnancy Within the First Year of Use		% of Women Continuing Use at One Year (4)
	Typical Use ^a (2)	Perfect Use ^b (3)	
Chance ^d	85	85	
Spermicides ^e	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation method		3	
Symptothermal ^f		2	
Postovulation		1	
Cap ^g			
Parous women	40	26	42
Nulliparous women	20	9	56
Sponge			
Parous women	40	20	42
Nulliparous women	20	9	56
Diaphragm ^g	20	6	56
Withdrawal	19	4	
Condom ^h			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin only		0.5	
Combined		0.1	
IUD			
Copper T 380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Patch		1	
Ring		1–2	
Norplant and Norplant-2	0.05	0.05	88
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100
Emergency Contraceptive Pills			
Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%. ⁱ			
Lactational Amenorrhea Method			
LAM is a highly effective, <i>temporary</i> method of contraception. ^j			

^aAmong *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

^bAmong couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. For patch and ring, the percentage comes from the package insert.

^cAmong couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

^dThe percentages becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentages who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

^eFoams, creams, gels, vaginal suppositories, and vaginal film.

^fCervical mucus (ovulation) method supplemented by calendar in the preovulatory and basal body temperature in the postovulatory phases.

^gWith spermicidal cream or jelly.

^hWithout spermicides.

ⁱThe treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 4 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).

^jHowever, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breast-feeding is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

Adapted with permission from Hatcher RA et al. Contraceptive Technology, 17th ed. New York: Ardent Media, 1998:216, Table 9-2 and references 133 and 134.

Table 45-2 Commercially Available Brand-Name and Generic Oral Contraceptive and Progesterone-Only Pills

Brand Name	Generic Name	Progestin Type and Dose	EE Dose (μg)	Progestin Activity	Estrogen Activity	Androgen Activity
<i>Monophasic OCs</i>						
Alesse	Aviane	Levonorgestrel 0.1 mg	20	L	L	L
Demulen 1/35	Zovia 1/35	Ethinodiol diacetate 1 mg	35	H	L	L
Desogen	Apri	Desogestrel 0.15 mg	30	H	I	L
Levlen	Levora, Portia	Levonorgestrel 0.15 mg	30	I	L	I
LevLite	Lessina	Levonorgestrel 0.1 mg	20	L	L	L
Lo-Ovral	Cryselle, Low-Ogestrel	Norgestrel 0.3 mg	30	I	L	I
Loestrin 1.5/30 ^a	Microgestin Fe 1.5/30	Norethindrone acetate 1.5 mg	30	H	L	H
Loestrin 1/20 ^a	Microgestin Fe 1/20	Norethindrone acetate 1 mg	20	H	L	I
Mircette ^b	Kariva	Desogestrel 0.15	20	H	L	L
Modicon	Brevicon, Nortel 0.5/35 Necon 0.5/35	Norethindrone 0.5 mg	35	L	H	L
Nordette	Levora, Portia	Levonorgestrel 0.15 mg	30	I	L	I
Ortho Cyclen	Sprintec, MonoNessa	Norgestimate 0.25 mg	35	L	I	L
Ortho-Cept	Apri	Desogestrel 0.15 mg	30	H	I	L
Ortho-Novum 1/35	Norinyl 1+35, Nortrel 1/35, Necon 1/35, Genora 1/35	Norethindrone 1 mg	35	I	H	I
Ovcon-35		Norethindrone 0.4 mg	35	L	H	L
Yasmin		Drosperinone 3 mg	30	No data	I	None
<i>Biphasic OCs</i>						
Ortho-Novum 10/11	Necon 10/11, Jenest	Norethindrone 0.5, 1 mg	35	I	H	L
<i>Triphasic OCs</i>						
Cyclessa		Desogestrel 0.1, 0.125, 0.15 mg	25	H	L	L
Estrostep ^a		Norethindrone acetate 1 mg	20, 30, 35	H	L	I
Ortho Tri-Cyclen	Tri-Sprintec	Norgestimate 0.18, 0.215, 0.25 mg	35	L	I	L
Ortho Tri-Cyclen Lo		Norgestimate 0.18, 0.215, 0.25 mg	25	L	L	L
Ortho-Novum 7/7/7	Necon 7/7/7, Nortrel 7/7/7	Norethindrone 0.5, 0.75, 1 mg	35	I	H	L
Tri-Norinyl		Norethindrone 0.5, 1, 0.5 mg	35	L	H	L
Tri-Levlen	Enpresse, Trivora	Levonorgestrel 0.05, 0.075, 0.125 mg	30, 40, 30	L	I	L
Triphasil	Enpresse, Trivora	Levonorgestrel 0.05, 0.075, 0.125 mg	30, 40, 30	L	I	L
<i>Progesterone Only Pills</i>						
Micronor	Errin	Norethindrone 0.35 mg	None			
Nor-QD	Nora-BE, Camila	Norethindrone 0.35 mg	None			
Ovrette		Norgestrel 0.075 mg	None			

^aAlso available with iron tablets instead of placebo tablets during the usual placebo week.

^bHas 2 days of placebo followed by 5 days of EE 10 μg during the usual placebo week.
EE, ethinyl estradiol; H, high; I, intermediate; L, low.

Table 45-3 Estrogenic, Progestogenic, and Androgenic Effects of Oral Contraceptive Pills

<i>Estrogenic Effects</i>	<i>Progestogenic Effects</i>	<i>Androgenic Effects</i>
<ul style="list-style-type: none"> • Nausea • Increased breast size (ductal and fatty tissue) • Cyclic weight gain due to fluid retention • Leukorrhea • Cervical eversion or ectopy • Hypertension • Rise in cholesterol concentration in gallbladder bile • Growth of leiomyomata • Telangiectasia • Hepatocellular adenomas or hepatocellular cancer (rare) • Cerebrovascular accidents (rare) • Thromboembolic complications including pulmonary emboli (rare) • Stimulation of breast neoplasia (exceedingly rare) <p>(Most pills with <50 µg of ethinyl estradiol do not produce troublesome estrogen-mediated side effects or complications.)</p>	<p>Both the estrogenic and the progestational components of oral contraceptives may contribute to the development of the following adverse effects:</p> <ul style="list-style-type: none"> • Breast tenderness • Headaches • Hypertension • Myocardial infarction (rare) 	<p>All low-dose combined pills suppress a woman's production of testosterone, which has a beneficial effect on acne, oily skin, and hirsutism. The progestin component may have androgenic as well as progestational effects:</p> <ul style="list-style-type: none"> • Increased appetite and weight gain • Depression, fatigue, tiredness • Decreased libido and/or enjoyment of intercourse • Acne, oily skin • Increased breast tenderness or breast size • Increased LDL cholesterol levels • Decreased HDL cholesterol levels • Decreased carbohydrate tolerance; increased insulin resistance • Pruritus

Adapted with permission from Hatcher RA et al. *Contraceptive Technology*, 17th ed. NY: Ardent Media, 1998:419, Table 19-4.

second-generation progestins include levonorgestrel and norgestrel, and third-generation progestins include desogestrel and gestodene (not available in the United States).¹⁰

Contraindications to Oral Contraceptive Use

1. M.F., a healthy 32-year-old woman, wants to know if she is a good candidate for OCs. She smokes a pack of cigarettes per day. What contraindications to OC therapy must be considered? Is M.F. a good candidate for OCs?

To determine if any contraindications or precautions exist, the clinician should first obtain baseline health information from M.F.¹¹ (Table 45-4). M.F. should be encouraged to stop smoking. She does not currently have any contraindications to OC use, but she should be informed that OCs will no longer be prescribed for her in a few years if she continues to smoke (see Question 8). Since M.F. does not have any medical problems, she is an acceptable candidate for OCs.

Choice

2. M.F. has decided to start OCs. Which OC should be selected for her?

Confusion abounds in selecting an OC because of the multitude of OCs available, the lack of studies comparing one product with others, and managed care formulary restrictions. The information in Figure 45-3 may be used to select an initial OC for most patients and to change pills when side effects necessitate an alternative choice.¹² Any pill containing <50 µg EE can be used for M.F. because she is a healthy woman without medical complications.

However, since higher body weight (≥ 70.5 kg) has been associated with increased OC failure, a pill with a higher dose of EE (e.g., 35 µg) may be a better choice if M.F. is heavier.¹⁴

21-Day Versus 28-Day Cycle

Most 28-day OC pill packs contain 21 days of active pills (pills that contain estrogen and progestin) followed by 7 days of placebo pills. The 21-day pill packs contain only the active pills. Many clinicians prefer the use of 28-day cycle OCs to minimize confusion; the patient takes one tablet daily regardless of whether it is an active or placebo pill. After taking the last tablet of a 28-day pack of OCs, the patient should begin a new pack the next day. However, when continuous ovarian suppression is indicated to treat estrogen-dependent disorders such as endometriosis, the 21-day cycle OCs are preferred to facilitate taking active tablets continuously. Alternatively, the placebo tablets could be removed from 28-day cycle packs. M.F. will not be taking OCs continuously, so a 28-day pack is recommended.

Multiphasic Oral Contraceptives

3. Should M.F. start a monophasic or triphasic OC? What are the advantages and disadvantages of the triphasic OCs relative to other OCs?

Because of metabolic and physiologic effects related to the progestin component of OCs, the biphasic and triphasic products were formulated to contain less progestin overall (with the exception of Mircette). These products attempt to provide adequate endometrial support while also providing adequate contraception.¹⁴

The multiphasic products contain varying amounts of progestin and/or estrogen during each of the active phases. Currently, Necon 10/11, Ortho-Novum 10/11, and Jenest 28 are the only biphasic OCs marketed in the United States, and they are rarely used. Mircette has been classified as a monophasic or biphasic OC. It provides a novel regimen containing 21 days of 0.15 mg desogestrel plus 20 µg EE, then only 2 days of placebo, and finally 5 days of 10 µg EE alone.

Table 45-4 Medical Eligibility Criteria for Contraceptive Use¹²

Condition	Contraceptive Method						
	OC	CIC	POP	DMPA	Norplant	Cu-IUD	LNG-IUD
I = Initiation, C = Continuation							
<i>Personal Characteristics and Reproductive History</i>							
Smoking							
a) Age <35	2	2	1	1	1	1	1
b) Age >35							
(i) <15 cigarettes/day	3	2	1	1	1	1	1
(ii) >15 cigarettes/day	4	3	1	1	1	1	1
Obesity >30 kg/m ² body mass index (BMI)	2	2	1	2	2	1	2
<i>Cardiovascular Disease</i>							
Multiple Risk Factors for Arterial Cardiovascular Disease (such as older age, smoking, diabetes and hypertension)	3/4	3/4	2	3	2	1	2
Hypertension							
a) History of hypertension where blood pressure <i>cannot</i> be evaluated (including hypertension during pregnancy)	3	3	2	2	2	1	2
b) Adequately controlled hypertension, where blood pressure <i>can</i> be evaluated	3	3	1	2	1	1	1
c) Elevated blood pressure levels (properly taken measurements)							
(i) Systolic 140–159 or diastolic 90–99	3	3	1	2	1	1	1
(ii) Systolic >160 or diastolic >100	4	4	2	3	2	1	2
d) Vascular disease	4	4	2	3	2	1	2
History of High Blood Pressure During Pregnancy (where current blood pressure is measurable and normal)	2	2	1	1	1	1	1
Deep Venous Thrombosis (DVT)/ Pulmonary Embolism (PE)							
a) History of DVT/PE	4	4	2	2	2	1	2
b) Current DVT/PE	4	4	3	3	3	1	3
c) Family history (first-degree relatives)	2	2	1	1	1	1	1
d) Major surgery							
(i) With prolonged immobilization	4	4	2	2	2	1	2
(ii) Without prolonged immobilization	2	2	1	1	1	1	1
e) Minor surgery without immobilization	1	1	1	1	1	1	1
Superficial Venous Thrombosis							
a) Varicose veins	1	1	1	1	1	1	1
b) Superficial thrombophlebitis	2	2	1	1	1	1	1
Stroke (history of cerebrovascular accident)			I C		I C		
	4	4	2 3	3	2 3	1	2
Known Hyperlipidemias (screening is NOT necessary for safe use of contraceptive methods)	2/3	2/3	2	2	2	1	2
<i>Neurologic Conditions</i>							
Headaches	I C	I C	I C	I C	I C		I C
a) Nonmigrainous (mild or severe)	1 2	1 2	1 1	1 1	1 1	1	1 1
b) Migraine							
(i) Without focal neurologic symptoms							
Age <35	2 3	2 3	1 2	2 2	2 2	1	2 2
Age >35	3 4	3 4	1 2	2 2	2 2	1	2 2
(ii) With focal neurologic symptoms (at any age)	4 4	4 4	2 3	2 3	2 3	1	2 3
Epilepsy	1	1	1	1	1	1	1

Continued

Table 45-4 Medical Eligibility Criteria for Contraceptive Use—cont'd

Condition	Contraceptive Method								
	OC	CIC	POP	DMPA	Norplant	Cu-IUD		LNG-IUD	
<i>Reproductive Tract Infections and Disorders</i>									
Unexplained Vaginal Bleeding (suspicious for serious condition)						I	C	I	C
Before evaluation	2	2	2	3	3	4	2	4	2
Endometriosis	1	1	1	1	1	2		1	
Benign Ovarian Tumors (including cysts)	1	1	1	1	1	1		1	
Cervical Intraepithelial Neoplasia (CIN)	2	2	1	2	2	1		2	
Cervical Cancer (awaiting treatment)						I	C	I	C
	2	2	1	2	2	4	2	4	2
<i>Breast Disease</i>									
a) Undiagnosed mass	2	2	2	2	2	1		2	
b) Benign breast disease	1	1	1	1	1	1		1	
c) Family history of cancer	1	1	1	1	1	1		1	
d) Cancer									
(i) Current	4	4	4	4	4	1		4	
(ii) Past and no evidence of current disease for 5 years	3	3	3	3	3	1		3	
<i>Endometrial Cancer</i>									
	1	1	1	1	1	I	C	I	C
						4	2	4	2
<i>Ovarian Cancer</i>									
	1	1	1	1	1	I	C	I	C
						3	2	3	2
<i>Uterine Fibroids</i>									
a) Without distortion of the uterine cavity	1	1	1	1	1	2		2	
b) With distortion of the uterine cavity	1	1	1	1	1	4		4	
<i>Pelvic Inflammatory Disease (PID)</i>									
a) Past PID (assuming no current risk factors of STDs)						I	C	I	C
(i) With subsequent pregnancy	1	1	1	1	1	1	1	1	1
(ii) Without subsequent pregnancy	1	1	1	1	1	2	2	2	2
b) PID-current or within the last 3 months	1	1	1	1	1	4	3	4	3
<i>HIV/AIDS</i>									
High Risk of HIV	1	1	1	1	1	3		3	
HIV-Positive	1	1	1	1	1	3		3	
AIDS	1	1	1	1	1	3		3	
<i>Endocrine Conditions</i>									
<i>Diabetes</i>									
a) History of gestational disease	1	1	1	1	1	1		1	
b) Nonvascular disease									
(i) Non-insulin dependent	2	2	2	2	2	1		2	
(ii) Insulin dependent	2	2	2	2	2	1		2	
c) Nephropathy/retinopathy/neuropathy	3/4	3/4	2	3	2	1		2	
d) Other vascular disease or diabetes of >20 years' duration	3/4	3/4	2	3	2	1		2	
<i>Gastrointestinal Conditions</i>									
<i>Gallbladder Disease</i>									
a) Symptomatic									
(i) Treated by cholecystectomy	2	2	2	2	2	1		2	
(ii) Medically treated	3	2	2	2	2	1		2	
(iii) Current	3	2	2	2	2	1		2	
b) Asymptomatic	2	2	2	2	2	1		2	
<i>Viral Hepatitis</i>									
a) Active	4	3/4	3	3	3	1		3	
b) Carrier	1	1	1	1	1	1		1	

Table 45-4 Medical Eligibility Criteria for Contraceptive Use—cont'd

Condition	Contraceptive Method						
	OC	CIC	POP	DMPA	Norplant	Cu-IUD	LNG-IUD
<i>Gastrointestinal Conditions—cont'd</i>							
Cirrhosis							
a) Mild (compensated)	3	2	2	2	2	1	2
b) Severe (decompensated)	4	3	3	3	3	1	3
Liver Tumors							
a) Benign (adenoma)	4	3	3	3	3	1	3
b) Malignant (hepatoma)	4	3/4	3	3	3	1	3
Anemias							
Sickle Cell Disease	2	2	1	1	1	2	1
Iron Deficiency Anemia	1	1	1	1	1	2	1

1, a condition for which there is no restriction for the use of the contraceptive method;

2, a condition where the advantages of using the method generally outweigh the theoretical or proven risks;

3, a condition where the theoretical or proven risks usually outweigh the advantages of using the method;

4, a condition which represents an unacceptable health risk if the contraceptive method is used.

CIC, combined injectable contraceptive; Cu-IUD, copper intrauterine device; DMPA, depot medroxyprogesterone acetate; LNG-IUD, levonorgestrel intrauterine device; OC, oral contraceptive; POP, progestin-only pills.

Adapted with permission from reference 12.

The patient does not need to take missed 10- μ g EE doses or use a backup method when missed. The 5 days of 10 μ g EE alone help minimize breakthrough bleeding with this product and may be useful for patients who have estrogen deficiency symptoms such as headaches during the hormone-free week.

The triphasic OCs (e.g., Ortho-Novum 7/7/7, Tri-Levlen, Triphasil, Ortho Tri-Cyclen) appear to support the endometrium more consistently than the biphasic OCs.⁹ No studies, however, show a superiority of one triphasic over another or compared to monophasic OCs. The reduced progestin content is desirable for women complaining of side effects caused by too much progestin or women with cardiovascular disease or metabolic abnormalities.^{5,9} Women with side effects related to progestin deficiency (e.g., late-cycle bleeding) or conditions necessitating progestin dominance (e.g., benign breast disease) may do better with monophasic OCs.

One drawback associated with triphasic OC use is the confusion caused by the different-colored tablets in each of the three different phases, making the missed-dose instructions more complicated. Monophasic OCs would be preferred for women who will be taking OCs continuously (i.e., skipping the placebo pills). M.F. may be started on either a monophasic or triphasic OC.

Patient Instructions

4. What instructions should be given to M.F. about her OC?

When to Start Oral Contraceptives

M.F. should start the first cycle of OCs according to the manufacturer's package instructions or according to one of the two following recommendations:⁵

1. Day 1 Start: Take the first tablet in the OC pack on the first day of menses.
2. Sunday Start: Take the first tablet in the OC pack on the first Sunday after the beginning of menstruation. If menses begins on Sunday, start that day.

A newer method for initiating OCs is the quick start method,¹⁵ in which the patient takes her first OC tablet while still in the health care provider's office. This method can minimize the confusion that many patients have about when to start their first pack and can increase rates of method continuation. Also, the quick start method provides contraceptive protection sooner and would, therefore, likely lower the risk of unintended pregnancy. More research on and awareness about this method are needed for it to be used routinely by health care providers.

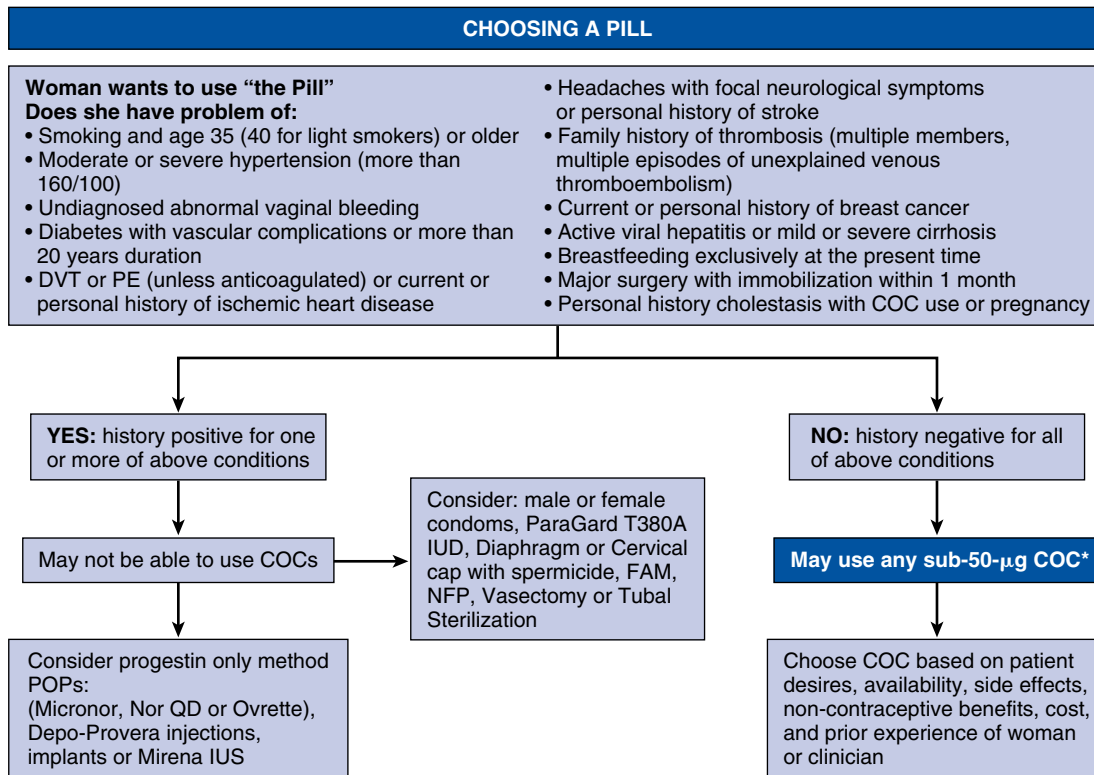
When to Use a Backup Method of Contraception

Some clinicians recommend that the woman use an alternative method of contraception for the entire first cycle. Others believe that alternative methods of contraception are unnecessary if the OC is started on or before the fifth menstrual day. Most OC package inserts state that a backup method of contraception (e.g., condoms) is not necessary if patients use the Day 1 start method.^{5,7} If patients use the Sunday start method, backup contraception should be used for the first week of the OC cycle. A backup method is also recommended when doses are missed, as described in the following section. M.F. has decided to use the Sunday start method, so her partner will need to use condoms for the first week of her first cycle of pills.

Proper Pill Taking

M.F. should take the OC tablets at exactly the same time each day. If she experiences nausea with OCs, she may find that the nausea improves if she takes her pill at bedtime or with food. The best time for OCs to be taken depends on the patient. The optimal time for M.F. is the time when she will have the fewest problems remembering to take her pill each day.

If a woman forgets to take one pill, she must take it as soon as she remembers and refer to the patient instructions in the package insert for further information.⁵ Most manufacturers recommend that if she forgets to take one pill, she should take two pills on the day she remembers (e.g., if she forgets her pill



- The World Health Organization and the Food and Drug Administration both recommend using the **lowest dose pill** that is effective. All combined pills with less than 50 µg of estrogen are effective and safe.
- There are no studies demonstrating a decreased risk for deep vein thrombosis (DVT) in women on 20-µg pills. Data on higher dose pills have demonstrated that the less the estrogen dose, the lower the risk for DVT.
- All OCs lower free testosterone. In the US, only Ortho Tri-Cyclen and Estrostep have FDA labeling indicating it as a treatment of moderate acne vulgaris, based on results of randomized, placebo controlled trials. Other formulations are under study. Class labeling in Canada for all combined pills states that use of pills may improve acne. In Canada only, Tri-Cyclen has "treatment of moderate acne vulgaris" as an indication for use.
- To minimize discontinuation due to spotting and breakthrough bleeding, warn women in advance, reassure that spotting and breakthrough bleeding become better over time.
- To attain the most favorable lipid profile, consider norgestimate, desogestrel pill or low dose norethindrone acetate, or lowest dose norethindrone (Ovcon-35) or ethnodiol diacetate (Demulen 1/35 or Zovia 35). No clinical benefits have been demonstrated to be attributable to difference in lipids caused by these pills. Estrogen has a beneficial effect on the walls of blood vessels. All currently available COCs raise triglycerides.

*The package insert for women on Yasmin states [Berlex-2001]: "Yasmin is different from other birth control pills because it contains the progestin drospirenone. Drospirenone may increase potassium. Therefore, you should not take Yasmin if you have kidney, liver or adrenal disease, because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your health-care provider about whether Yasmin is right for you, and during the first month that you take Yasmin, you should have a blood test to check your potassium level: NSAIDs (ibuprofen [Motrin®, Advil®], naproxen [Naprosyn®, Aleve®, and others] when taken long-term and daily for treatment of arthritis or other problems); potassium-sparing diuretics (spironolactone and others); potassium supplementation; ACE inhibitors (Capoten®, Vasotec®, Zestril® and others); Angiotensin-II receptor antagonists (Cozaar®, Diovan®, Avapro® and others); heparin."

FIGURE 45-3 Choosing a pill. Reprinted with permission from Reference 13.

on Monday, she should take two pills on Tuesday). Then she should take the remaining pills as usual. A backup method of contraception is not necessary. If she misses two tablets in a row in week 1 or 2 of her pack, she must take two pills on the day she remembers and two pills the next day. She should use an alternative method of contraception for 7 days after missing the pills.

If a woman misses two tablets in a row in the third week (for day 1 starters), she must discard the rest of the pack and start a new pack on that same day. For Sunday starters, she should keep taking one pill every day until Sunday, then start a new pack on Sunday. She must use an alternative method of contraception for 7 days after missing the pills. She may not have her menstrual period this month.

If a woman misses three or more pills in a row during the first 3 weeks (for day 1 starters), she must discard the rest of her pack and start a new pack that same day; Sunday starters should keep taking one pill every day until Sunday, start a new pack on Sunday, and use an alternative method of contraception for 7 days after missing the pills. She may not have a menstrual period this month.

Drug Interactions

Antibacterials

5. G.H. is a 26-year-old woman whose last menstrual period (LMP) was 7 weeks ago. She has a history of regular menstrual cycles both before and during the use of OCs. Six weeks ago, she developed an *Escherichia coli* urinary tract infection, which was treated with ampicillin 500 mg po QID for 7 days. This coincided with the first seven tablets of her OC cycle. She has been taking Ortho-Novum 1/35 for 3 years and tetracycline 250 mg po QD for acne. What is the clinical significance of the potential drug interactions in G.H.?

EE is conjugated in the liver, excreted in the bile, hydrolyzed by intestinal bacteria, and reabsorbed as active drug.¹⁶ Antibiotics, by reducing the population of intestinal bacteria, interrupt the enterohepatic circulation of the estrogen, resulting in a decreased concentration of circulating estrogen. The existence of similar antibiotic interactions with contraceptive progestins is unlikely. Although this proposed mechanism for the drug interaction is not firmly established, various antibiotics have been reported to decrease OC efficacy. This interaction may cause unintended pregnancy or abnormal bleeding patterns. The antibiotics rifampin and griseofulvin are known to cause contraceptive failure, as these products also increase the metabolism of estrogen.

Theoretically, any antimicrobial with significant effects on intestinal bacterial flora could affect OC efficacy by interfering with the enterohepatic recycling of exogenous estrogen. Numerous reports of changes in bleeding patterns and contraceptive failure have been documented.¹⁶ About 30 case reports of contraceptive failure with concomitant OC and antibiotic use have been published. The antibiotics in the case reports include rifampin, ampicillin, penicillin G, tetracycline, and minocycline. In addition, surveys conducted on patients in clinics have revealed about 20 other cases of OC failure. A major limitation of survey data is that it relies on patients' memories, which are often unreliable. The Committee on the Safety of Medicines in the United Kingdom received 63 reports of unplanned pregnancies between 1968 and 1984 in women on antibiotics and OCs. Penicillins, tetracyclines, sulfamethoxazole-trimethoprim, metronidazole, cephalosporins, and erythromycin were among the antibiotics used. Finally, >200 reports of OC failure have been documented in women seeking family planning services.

The probability of a clinically significant drug interaction between OCs and antimicrobials depends on numerous factors: the hormonal content of the OC relative to the patient's requirements, the dosage and duration of use of the interacting drug, variation in the patient's response to bacterial flora alteration, and the fertility of the couple.¹⁷ The number and complexity of these variables make prediction of outcome in a specific patient exceedingly difficult. Even if a drug pro-

duces a several-fold increase in unwanted pregnancies in women taking OCs, the likelihood of pregnancy in a given patient still will be low. Long-term, low-dose tetracycline use for G.H.'s acne therapy (tetracycline 250 mg daily) is unlikely to interfere with her OC efficacy, but there are no data to support this supposition. Topical antibiotics often can control acne and are viable alternatives to oral tetracycline.¹⁸

A practical approach to managing patients taking OCs and antibiotics is to educate patients to be conservative by using a backup method of contraception until menses occurs. In addition, the clinician should discuss what little is described in the literature about these interactions (Table 45-5). Whether

Table 45-5 Oral Contraceptive Drug Interactions

Interacting Drug	Net Effect
<i>Drugs that may reduce OC enterohepatic circulation</i>	
Ampicillin ¹⁹⁻²⁶	
Cephalosporins ^{24,27}	
Chloramphenicol ²⁸	
Dapsone ²⁴	
Erythromycin ^{24,29}	Spotting, breakthrough bleeding, or pregnancy
Isoniazid ²⁸⁻³¹	
Penicillins ^{24,29}	
Sulfonamides ²⁴	
Tetracyclines ^{24,27,32}	
TMP-SMX ^{20-22,24,27,29,33}	
<i>Drugs that may induce the metabolism of OCs</i>	
Butabarbital ^{24,34,35}	
Carbamazepine ^{24,34,35}	
Ethosuximide ^{24,35,35}	
Griseofulvin ^{22,36}	
Nelfinavir ³⁷	
Phenobarbital ^{24,34,35}	Spotting, breakthrough bleeding, or pregnancy
Phenytoin ^{24,34,35}	
Primidone ^{24,34,35}	
Rifabutin ³⁸	
Rifampin ^{17,22,28-35,39}	
Secobarbital ⁴⁰	
St. John's wort ^{41,42}	
<i>Miscellaneous drug interactions with OCs</i>	
Amprenavir ⁴³	↓ concentrations of amprenavir; ↑ or ↓ concentrations of EE or progestin
Anticoagulants ^{44,45}	↓ anticoagulation
Atorvastatin ⁴⁶	30% ↑ norethindrone; 20% ↑ EE
Benzodiazepines ^{47,48}	Enhanced benzodiazepine effect
Cyclosporine ⁴⁹	Doubling of cyclosporine level
Insulin ⁵⁰	19% require ↑ insulin dose
Phenytoin ^{34,58}	↑ concentrations of phenytoin
Corticosteroids ⁵¹	↓ metabolism of corticosteroids
Ritonavir ⁵²	40% ↓ in AUC of EE
Tacrolimus ⁵³	↑ tacrolimus level
Theophylline ⁵⁴	33% reduction in theophylline clearance
Tizanidine ⁵⁵	50% reduction in tizanidine clearance
Topiramate ⁵⁶	18-30% ↓ concentrations of EE

AUC, area under the time-concentration curve; EE, ethinyl estradiol; OC, oral contraceptives; TMP-SMX, trimethoprim-sulfamethoxazole.

ampicillin inhibits OC efficacy is not certain; however, all clinical data are consistent with the premise that ampicillin occasionally impairs OC efficacy. In this case, G.H. should take a pregnancy test. If she is pregnant, harm to the fetus from the OC or antibiotics is unlikely (see Question 25).

Liver Enzyme Induction

6. S.R., a 22-year-old woman, is taking phenytoin (Dilantin) 300 mg po QD and phenobarbital 60 mg po BID. Her serum concentrations of these drugs have been consistently in the therapeutic range for at least 2 years, and she has not experienced seizures for 18 months. Is S.R. a good candidate for OCs?

EE is a substrate of cytochrome P450 3A4 (CYP3A4), so drugs that induce CYP3A4 may decrease OC efficacy. In earlier years, OC efficacy was not decreased significantly by other drugs because of their high hormone content. Because the estrogen and progestin concentrations of OCs have gradually been decreasing, reports of menstrual irregularities (e.g., spotting, BTB) and unintended pregnancies attributable to drug interactions have been increasing (see Table 45-5).

Carbamazepine, phenytoin, phenobarbital, and primidone are CYP3A4 inducers and are known to cause increased metabolism of OCs. Another possible inducer of CYP3A4 is St. John's wort.⁴² The newer anticonvulsants topiramate and oxcarbazepine have also been shown to lower serum levels of estrogen. Although drugs can influence the OC efficacy, OCs also can affect the activity of other drugs. OCs have been reported to increase or decrease serum levels of lamotrigine and can affect seizure control (see Table 45-5). Also, one report claims that OCs might increase serum phenytoin concentrations substantially.⁵⁷

Unlike many drug classes that are carefully dosed to maintain a therapeutic range of monitored blood levels, contraceptive estrogen and progestin blood levels are obtained only in clinical drug studies. Therefore, patients are managed by monitoring side effects and by changes in menstrual patterns. It is no wonder, therefore, that the drug interaction literature is less than satisfactory and that patient management may be haphazard. Although some prescribers suggest using a 50- μ g EE OC in patients on interacting drugs, most would recommend that S.R. use a contraceptive method other than OCs.

Oral Contraceptive Risks and Adverse Effects

Some patients may not be candidates for OCs because of the risks and adverse effects associated with their use. Other patients may experience minor side effects with OCs that may be managed by changing to an OC with different types and doses of estrogen or progestin.

Breakthrough Bleeding (BTB), Spotting, and Amenorrhea

7. V.S. comes to the family planning clinic after taking Ovcon-35 for 2 months. She had been started on Ovcon-35 to help with her acne. Her only complaint is spotting at various times during her past two menstrual cycles. What action should be taken to correct V.S.'s bleeding pattern?

Intermenstrual bleeding that requires a pad or tampon is designated BTB, while a lesser amount of intermenstrual bleeding is called spotting. Intermenstrual bleeding is the most frequent explanation for the discontinuation of OCs.⁵⁸

Most clinicians will continue with the same OC for at least 3 months if irregular bleeding is the only complaint, since BTB usually resolves on its own.^{12,59} Early-cycle intermenstrual bleeding, which usually starts before the 14th day of the menstrual cycle (or never ceases completely after menses), usually is due to insufficient estrogen. Late-cycle intermenstrual bleeding, occurring after day 14, is usually due to insufficient progestational support of the endometrium. Another cause of intermenstrual bleeding is drug interactions (see Questions 5 and 6).

The balance between estrogen and progestin components in OCs determines its endometrial activity and, therefore, the likelihood of intermenstrual bleeding problems. It is helpful to envision the estrogen component as the basic building blocks or "bricks" of the endometrium and the progestational component providing the mortar that holds the bricks together. In addition, the estrogenic activity of the progestational component increases the number of bricks, while its antiestrogenic activity decreases their numbers. If there are not enough bricks or mortar or if they are present in the wrong proportions, the wall will crumble and bleeding will ensue (see Table 45-2).

If V.S.'s intermenstrual bleeding irregularities continue late in her cycle after 3 months, another OC with the same estrogen dose and more progestin should be prescribed. Desogen/Ortho-Cept would be a good choice because progestational activity would be increased and estrogenic activity would be maintained with minimal androgenic liability (see Table 45-2). If V.S. develops intermenstrual bleeding early in the cycle after several months of use, she should be changed to a pill with a higher ratio of estrogen to progesterone or should try Mircette, which provides a low dose of estrogen during the usual placebo week.

Some patients experience amenorrhea with OCs. If this occurs, pregnancy should first be ruled out. If the patient is not pregnant and amenorrhea is acceptable to the patient, then the OC need not be changed. If the patient would prefer a monthly menstrual period, then an OC with more estrogen or less progestin or a triphasic pill should be tried.

Cardiovascular Disease

8. M.F. (from Questions 1 to 4) and her fiancé, who is with her in the health care provider's office, have been reading about the cardiovascular risks of estrogen in the lay press. What is the effect of OCs on M.F.'s risk of morbidity and mortality from cardiovascular disease?

In women who do not smoke or use OCs, the risk of death due to cardiovascular disease is 0.59 per 100,000 women <35 years old and 3.18 per 100,000 women \geq 35 years.⁵⁹ This risk is increased by 0.06 and 3.03 for OC users <35 or \geq 35, respectively. For OC users who smoke, the risk is increased by 1.73 and 19.4 for women <35 or \geq 35, respectively.

Both the Royal College of General Practitioners and the Oxford/Family Planning Association OC studies showed that women <35 years, regardless of smoking status, taking the new low-dose OCs did not have a significantly increased mortality risk from cardiovascular disease.⁶⁰⁻⁶² The increase in mortality is concentrated in smokers >35 years of age.

Several studies have focused on the effect of OCs on serum lipoprotein concentrations because of the association between lipoproteins and atherosclerotic cardiovascular disease.⁶³⁻⁶⁵

High levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) cholesterol, and very-low-density lipoprotein (VLDL) cholesterol serum concentrations are associated with the risk of developing atherosclerotic circulatory diseases, whereas high-density lipoprotein (HDL) cholesterol has an inverse relationship. Apolipoprotein levels also affect atherosclerotic risk (e.g., elevations in Lp(a) increase risk).

Estrogen tends to increase serum concentrations of HDL, while decreases in HDL are linked to progestin dose and potency.^{63,64} Progestins can modify the composition of total HDL by changing the relative amounts of HDL₂ and HDL₃.^{66,67} HDL₂ is protective against cardiovascular disease, unlike HDL₃.⁶⁸ Decreases in HDL are associated with increasing age, weight, and cigarette smoking. Increased serum triglyceride concentrations are related to the estrogen content of the OC as well as to the antiestrogenic effect of the progestin component.

Studies evaluating the effect of OCs on lipids have reported similar results.⁶³⁻⁶⁵ One study found an increase in HDL from baseline with a low-androgenic progestin compared to a high-androgenic progestin.⁶⁴ Another study compared OCs with phasic EE and levonorgestrel or desogestrel.⁶³ After six cycles, significant increases in HDL₃ and apolipoproteins (apo A-I, apo A-II, and apo B), were seen in both groups. HDL₂ also increased significantly in the desogestrel group but decreased in the levonorgestrel group. After nine cycles, levels of TG and VLDL in both groups and HDL in the desogestrel group were significantly increased from baseline. HDL did not change significantly in the levonorgestrel group after six cycles. In another study, a reduction in the OC doses of EE and levonorgestrel by one third improved levels of LDL, TG, Lp(a), and HDL.⁶⁵

Lipid serum concentrations also are altered in adolescent (ages 12 to 17) OC users. These adolescents had significantly higher TC levels compared to nonusers, although the type of OC used was not specified.⁶⁹

Patients taking OCs containing levonorgestrel may be more likely to suffer a myocardial infarction (MI) than users of OCs containing desogestrel or gestodene.⁷⁰ When confounding factors for cardiovascular disease were accounted for, women taking levonorgestrel-containing OCs were 2.5 times more likely to have an MI than nonusers. Another study found the opposite effect of the two types of OCs, but the results were not significant.⁷¹ Heavy smoking, especially in women >35 years old, increases the risk of MI.⁵⁹

M.F. and her fiancé should understand that the risk of a cardiovascular adverse effect may be increased with OC use, but the risk is still very low no matter which OC is used. Cigarette smoking is a much more significant risk factor for MI, causing a reported 8- to 13-fold increase in risk.

Cervical Dysplasia and Cervical Cancer

9. J.M. has an older sister who had cervical dysplasia that progressed to carcinoma in situ. Her sister never took OCs. What can you tell J.M. about the risks of cervical dysplasia and cancer associated with OCs?

An estimated 12,200 new cases of cervical cancer and 4,100 deaths from cervical cancer will occur in 2003.⁷² Behavior, not genetics, is the usual cause of cervical cancer. Women at highest risk for cancer are those who are positive

for certain subtypes of human papilloma virus (HPV), who have certain sexual behaviors, who are immunosuppressed, or who smoke.⁵ Sexual behaviors associated with cervical cancer include beginning sexual activity at a young age, having multiple male sexual partners, and having a male sexual partner who has had multiple partners. Women at low risk for cancer are those who have two or fewer partners, whose partners use condoms, and who do not smoke.

Pooled data on cervical cancer risk from eight case-control studies found that OC users positive for HPV were more likely to develop cervical cancer.⁷³ Women who had ever used OCs and those who had used OCs for >5 years were 1.5 and 3.4 times, respectively, more likely to develop cervical cancer. This is consistent with older studies that suggest that OC users have an increased risk of developing or dying of cervical cancer. In contrast, a large cohort study conducted in England found no significant increase in deaths due to cervical cancer in women who had ever used OCs.⁷⁴

Epidemiologic comparisons of the prevalence of cervical cancer in OC users versus nonusers often are difficult to interpret because yearly medical examinations (e.g., Pap smears) of OC users result in early detection and treatment of precancerous lesions.⁷⁵ Health care providers may wish to perform Pap smears every 6 months in women who have used OCs for ≥5 years and who are also at a higher risk because of multiple partners or a history of sexually transmitted diseases (STDs).⁴ J.M. should be counseled on the behaviors that put her at risk for cervical cancer and should be encouraged to have a Pap smear annually.

Headache

10. G.R., a 32-year-old woman, comes to the clinic complaining of headaches, which predominantly occur during the 7-day placebo phase of her 28-day cycle of Nordette. The throbbing headaches are preceded by blurred vision, nausea, and vomiting. Aspirin and acetaminophen, which normally relieve her headaches, are ineffective. Lying down in a dark room provides some relief. Her family history is pertinent because her mother and maternal grandmother have migraine headaches. Are these headaches a relative contraindication for the continued use of OCs?

Headache is a common complaint in women taking OCs. They may notice headaches while taking active pills or during the placebo week, due to the withdrawal of estrogen.⁵⁹ Women with migraines may find that their headaches either improve or worsen when OCs are initiated.

Mild headaches may improve over time or if the woman is changed to a pill with less estrogen or progestin. Headaches that occur during the placebo week can be managed by trying Mircette or taking OCs continuously (i.e., skipping placebo pills). Patients with severe headaches should discontinue OCs and should be evaluated by their health care provider.

Ischemic stroke is more likely to occur in OC users with a history of migraines, especially if they smoke.⁷⁶ Women with migraines should use OCs with caution or not at all, particularly if they smoke, are >35 years old, or have other significant medical problems. Clinical experience indicates that women who have increasing migraine attacks with OCs are not likely to improve when the OC is changed to one with a different hormone balance.

G.R.'s symptoms are typical of migraine headache and because she has a family history of migraine headaches, she may need to discontinue OCs and use another method of contraception. Subsequent to a thorough medical evaluation of her headaches, she should be monitored carefully if OCs are to be continued.

Hypertension

11. A.M., an obese 26-year-old Black woman, became hypertensive during all of her pregnancies. She restarted her Lo-Ovral after her last pregnancy and continues to smoke a half-pack of cigarettes per day. Her blood pressure (BP) prior to starting OCs was 126/76 mm Hg. Today, her BP is 146/96 mm Hg. What is the mechanism of OC-induced hypertension? How can OCs be safely used by A.M. despite her history of hypertension during pregnancy?

The underlying mechanisms for OC-induced hypertension may be sodium and water retention and increased renin activity.^{77,78} Hypertension secondary to OCs may develop slowly over 3 to 36 months and may not decline for 3 to 6 months after OC discontinuation.⁹

Women taking the older and more potent oral contraceptives (e.g., OCs with ≥ 50 μg EE) had a two to three times higher incidence of hypertension (BP $>140/90$ mm Hg) than nonusers.⁷⁹⁻⁸¹ Small studies have found systolic BP to increase by 7 to 8 mm Hg and diastolic BP to increase by 6 mm Hg in normotensive or mildly hypertensive women.⁸² Population-based, case-control studies have shown differing results on whether women with hypertension who use OCs are more likely to suffer an MI than nonusers. A small study of adolescent women showed similar systolic and diastolic BPs in users versus nonusers.⁶⁹

In this patient it is reasonable to consider using a 20- μg EE OC such as Alesse/Apri/Levlite or an OC with less progestin and estrogen such as Ortho TriCyclen Lo. The effect of this change in medication on A.M.'s blood pressure should be monitored to determine whether continued use is warranted.

Liver Tumors

12. T.A.'s physician is concerned about the possibility of hepatic tumors. What is the risk of hepatomas in patients using OCs?

The incidence rate of benign liver tumors for women using low-dose OCs is 3.3 per 100,000 users per year compared with 0.1 per 100,000 users per year in nonusers or short-term users.⁸³ The incidence increases after 4 years of use. Although the tumors generally are benign, death can result from intrahepatic or extrahepatic tumor rupture and hemorrhagic shock.^{84,85} Because animal studies suggest that both estrogen and progestin may accelerate abnormal liver cell proliferation, the lowest effective OC dose should be used in all patients.^{83,86} A significant increase in death from liver disease or cancer was not seen in one large cohort study.⁷⁴

Cholestatic jaundice also has been associated with OC use.⁸⁷ T.A. can monitor for signs or symptoms of cholestatic jaundice, since this disorder usually presents as malaise, nausea, anorexia, and pruritus; these usually appear 4 weeks after the initiation of OC use. Discontinuation of the OC results in complete clinical remission within a month.

Thromboembolic Events

13. B.C., a 21-year-old woman, is interested in starting OCs. After taking a complete history, the provider learns that her sister and mother have both had a deep vein thrombosis (DVT). Can OCs contribute to the development of a DVT or pulmonary embolism (PE)? If so, which patients are at the highest risk? Should B.C. start OCs?

OCs contribute to thromboembolic events by several mechanisms. Estrogens increase coagulability and thereby increase the possibility of clot formation. They may increase the serum concentrations of clotting factors VII, X, and XII and decrease the prothrombin time after one to three cycles of use.^{10,63,65,82} Estrogens may also reduce antithrombin III activity and decrease the inhibitory activity of factor X. Long-term OC use is associated with an increased platelet count and increased platelet aggregation similar to that seen late in pregnancy; this is generally thought to be caused by the estrogen component. More recent data showing increased thrombosis rates in users of third-generation progestins (desogestrel and gestodene) suggest that progestin may also have a role in thromboembolism risk.¹⁰

The baseline risk of venous thrombosis is low, at 1 for every 10,000 person-years.¹⁰ The best studies looking at thromboembolism in OC users found that most users have a three- to six-fold increased risk of developing superficial or deep venous thrombosis or PE. Therefore, the risk is still quite low, at approximately 3 to 4 per 10,000 person-years—less than the risk during pregnancy of 6 per 10,000 person-years. Patients requiring emergency major surgery while on OCs are more prone to thromboembolism than nonusers.⁸² The risk of venous thrombosis does not seem to be associated with duration of OC use, past OC use, mild obesity, or cigarette smoking. A greater risk is associated with EE doses >35 μg .

Women with a mutation in clotting factor V (also called factor V Leiden) or a deficiency in protein C, protein S, or antithrombin are more likely to develop a venous thrombosis with OC use than women without a hereditary prothrombotic defect.¹⁰ Women with blood types other than O may also be more susceptible to clotting due to higher levels of factor VIII.

Whether third-generation progestins are associated with a higher risk of venous thromboembolism (VTE) relative to other progestins is controversial.¹⁰ It was believed that the risk of thrombosis with third-generation progestins would be lower than other progestins since they have more beneficial effects on HDL. However, most studies that compared the risk of thrombosis with third-generation progestins to second-generation progestins found that desogestrel and gestodene are associated with a greater VTE risk. Although the risk is increased, the overall rate of thrombosis is still low.

A prospective study from the PHARMO system database in The Netherlands compared the incidence of VTE with the second-generation OC Nordette/Levlen/Levora (2.4/10,000 person-years), the third-generation OC Apri/Desogen/Ortho-Cept, and a gestodene OC that is not available in the United States (9.0/10,000 person-years). In this study, the relative risk for third-generation OC use was 3.5 (95% confidence interval [CI], 1.4 to 8.8). The adjusted relative risk of VTE in women who had used OCs before was 1.7 (95% CI, 0.9 to 3.1).⁸⁹ The relative risk was highest in women <25 years of age who were taking OCs for the first time.

The Contraception Report gave the following advice to practitioners regarding the use of OCs containing a third-generation progestin:⁹⁰

1. Patients already taking a desogestrel-containing OC with no VTE risk factors do not need to change OCs.
2. In new-start patients, take a personal and family history. If no VTE risk factors exist, inform the patient of a possible increased risk with a desogestrel OC.
3. Patients with a personal history of VTE should not start OCs.
4. Patients with a family history of VTE in young first- and second-degree relatives who also have other risk factors such as obesity or immobilization should consider other methods.
5. All patients using OCs should know the VTE warning signs (ACHES; Table 45-6).

The minimal risk of thrombosis associated with OCs in the general population does not justify the cost of routine screening for deficiencies in the coagulation system; however, when a patient has a family history of thrombosis, measurement of antithrombin III, protein C, activated protein C resistance ratio, protein S, anticardiolipin antibodies, prothrombin G mutation, and homocysteine levels should be considered.¹⁰

B.C. should be evaluated for hereditary prothrombotic defects. If any exist, she should avoid OC use. If none exist, she may still wish to consider a method without estrogen but should be educated on the signs and symptoms of thrombosis if she decides to start OCs.

Benefits of Oral Contraceptives

Acne

14. D.S., a 20-year-old woman, has had severe acne since menarche at age 13. She is currently taking no medications but wants to begin OCs. What effect, if any, would oral contraceptives have on her acne? Which OC would you recommend for D.S.?

Depending on the patient, OC use may cause acne to appear, disappear, or significantly improve.^{5,9} Most patients will have improvement in acne with all available OCs, and several brands are FDA approved for this indication. Progestins with

higher androgenic activity may be more likely to increase acne since they stimulate sebaceous glands to produce more sebum. Higher doses of estrogen may decrease acne by suppressing the activity of sebaceous glands, decreasing the production of androgens, and increasing the synthesis of sex hormone binding globulin (SHBG). SHBG binds androgens and thereby diminishes their effects.⁹¹ The triphasic OCs are modestly estrogen-dominant, and these lower-dose contraceptives can significantly reduce the overall incidence of acne. Both desogestrel- and norgestimate-containing OCs are less androgenic, thereby increasing SHBG levels and decreasing acne.⁹²

D.S.'s acne should improve with OC use. Products to consider starting with are OrthoTriCyclen, Estrostep, and Ovcon 35.

Benign Breast Disease

15. A young woman has a family history of fibrocystic breast disease. What influence do OCs have on fibrocystic breast disease?

There appears to be a 50% to 75% reduction in the risk of fibroadenomas, chronic cystic breast disease, and breast biopsies in OC users.⁹ Protection seems directly related to length of use. Because the progestin component may be primarily responsible for this protection, progestin-dominant OCs that contain a less estrogenic progestin such as levonorgestrel are preferred.^{5,9,93} The progestin-only minipill could be of use here, except that its contraceptive effect is not as good as the OCs. In addition, it does not provide endometrial stability and other benefits of OCs such as decreased dysmenorrhea, iron deficiency anemia, acne, and hirsutism.

Dysmenorrhea and Premenstrual Syndrome

16. C.P. has a history of premenstrual syndrome (PMS) and complains of worsened menstrual cramping with an intrauterine device (IUD). What effect on PMS and dysmenorrhea might she expect from OCs?

Dysmenorrhea, or painful menstruation, may be of unknown etiology or may be due to endometriosis or uterine fibroids. Complaints of menstrual pain subsequent to OC therapy may be decreased by >60%.⁹ An OC with decreased estrogenic and increased progestational activity may be the best at relieving dysmenorrhea.

Premenstrual tension has been reported to be reduced 29% in OC users, and other premenstrual symptoms seem to improve as well.^{94,95} Nevertheless, the effect of OCs on PMS symptoms is inconsistent and unpredictable, probably because PMS symptoms are neither consistent nor predictable. There may be augmentation of depression and mood swings by the progestational component. Although the probability of this effect is low with a low-dose product, C.P. should be monitored for changes in her PMS symptoms. (See Chapter 48, Gynecological Disorders, for further discussion of dysmenorrhea and PMS.)

Endometrial Cancer

17. C.P. is hesitant to take OCs because her grandmother, who had been receiving estrogen replacement therapy for 5 years, died of endometrial cancer in 1970. What is the relationship between OCs and endometrial cancer?

Table 45-6 Pill Early Danger Signs (ACHES)

Signals	Possible Problem
Abdominal pain (severe)	Gallbladder disease, hepatic adenoma, blood clot, pancreatitis
Chest pain (severe), shortness of breath, or coughing up blood	Blood clot in lungs or myocardial infarction
Headaches (severe)	Stroke, hypertension, or migraine headache
Eye problems: blurred vision, flashing lights, or blindness	Stroke, hypertension, or temporary vascular problem
Severe leg pain (calf or thigh)	Blood clot in legs

Clinical data suggest that cyclic OCs contain enough progestin to prevent endometrial hyperplasia and to reduce the risk of endometrial cancer by about 50% to 70%.⁷⁶ The protection is directly related to duration of use and may persist for many years after discontinuation of the OC. A meta-analysis of 11 studies showed a 56%, 67%, and 72% reduction in endometrial cancer risk after 4, 8, and 12 years of OC use, respectively.⁹⁶

C.P. should be reassured that OC use will not cause endometrial cancer and will likely reduce her chances of developing this disease. She may want to find out more about her grandmother's cancer, since it may have been due to treating her menopausal symptoms with estrogen alone rather than with estrogen plus a progestin.

Menorrhagia (Heavy Menstrual Bleeding)

18. M.V. has iron deficiency anemia attributed to heavy menses secondary to her past IUD use. What will be the effect of OC use on her iron deficiency anemia?

The total amount of menstrual flow in established OC users is decreased by $\geq 40\%$.⁹⁷⁻⁹⁹ This may reflect the progressive thinning of the endometrium of OC users and the lack of irregular bleeding. Bleeding may be decreased the most by OCs that have a high ratio of progestin to estrogen, since endometrial thinning is maximized.⁵ Another option would be to have the patient take OCs continuously so she has fewer menses.

Ovarian Cancer and Functional Ovarian Cysts

19. C.P. (from Questions 16 and 17) is also concerned about ovarian cysts and cancer. Can OCs cause ovarian problems?

The risk of developing functional ovarian cysts is decreased, pre-existing cysts are more rapidly resolved, and surgery rates for ovarian masses are reduced in women taking OCs.^{97,100,101} This is likely due to reducing ovulation, suppressing androgen production, or increasing progesterone levels.

Each year of OC use decreases the relative risk of developing ovarian cancer by 7% to 9%.¹⁰⁰ The risk reduction continues to be seen in women using OCs for >15 years and persists after OCs are discontinued.

C.P. should be reassured that OC use will decrease, not increase, her likelihood of developing ovarian cancer.

Pelvic Inflammatory Disease and Ectopic Pregnancy

20. M.A., a 20-year-old woman who has several sexual partners, arrives at the emergency department with a temperature of 38.2°C (normal, 37°C) and lower abdominal cramping. Examination is compatible with the diagnosis of pelvic inflammatory disease (PID), based upon her cervical motion tenderness, abdominal pain, and adnexal (ovary and fallopian tube) tenderness. She has been using a Copper-T IUD for contraception for 2 years. Why might OCs be a more suitable contraceptive for M.A.?

Many clinicians prefer to prescribe OCs over other forms of contraception for sexually active young women with multiple sexual partners because PID has been found to be less prevalent with this form of contraception.^{5,102} In one study, OC users were half as likely to develop PID as nonusers.¹⁰³ Although early studies failed to distinguish between gonococ-

cal and nongonococcal PID, the PID protective effects of OCs may depend on the organism. A Swedish study found that OCs protect against both gonococcal and chlamydial PID.¹⁰⁴ In contrast, one report suggested that OCs may promote chlamydial PID; and another concluded that OC users were neither more nor less likely to develop PID.^{105,106} A 1990 case-control study showed protection against symptomatic PID in women infected with chlamydia but not in those infected with gonococcus.¹⁰⁷

Despite the contradictory data, it is logical that the thickening of cervical mucus caused by OCs may prevent bacteria from ascending into the uterus and fallopian tubes, thereby minimizing hospitalizations as well as deaths stemming from PID. The risk of ectopic pregnancy is greater for women who already have had PID, and OC use has been shown to prevent hospitalizations and deaths stemming from ectopic pregnancies.^{108,109}

In view of these data, M.A.'s IUD should be removed and her PID treated. OCs may be initiated if no contraindications are present. Patients and clinicians should be alert for the symptoms of cervicitis or salpingitis in women who are at high risk for STDs.

Other Issues with Oral Contraceptives

Breast Cancer

21. The medical history and physical examination of S.M. are negative for breast disease, except for a history of breast cancer in her maternal grandmother. How will OC use affect S.M.'s risk of breast cancer?

Some studies have suggested an increased risk of breast cancer in young, nulliparous women using OCs with high progestin activity.^{110,111} In addition, the Royal College of General Practitioners' Oral Contraceptive Study in 1981 reported a significant increase in risk for breast cancer in women 30 to 34 years of age who use OCs.¹¹² Another study found an increased risk of breast cancer in women with a first-degree family history of breast cancer who had ever used OCs.¹¹³

In contrast, other studies found no association between current or former OC use and breast cancer.^{74,114} In addition, both the Oxford/Family Planning Association Contraceptive Study in 1977 and the Walnut Creek Contraceptive Drug Study in 1981 found no association between breast cancer and OC use in any age group.¹¹⁵⁻¹¹⁷ The Centers for Disease Control Cancer and Steroid Hormone Study in 1983 reported a relative risk of 0.9 for OC users compared with never-users, despite other risk factors for breast cancer such as early menarche, later age at first birth and menopause, family history of breast cancer, or benign breast disease.¹¹⁸ The ongoing Nurses' Health Study identified 3,383 cases of breast cancer from 1976 to 1992 among 1.6 million person-years of OC use and found that long-term past OC use (10 years), either overall or before a first full-term pregnancy, does not appreciably increase breast cancer risk in women >40 years of age.¹¹⁹

OC users tend to have a greater awareness of breast cancer, examine their breasts more frequently, and are examined by clinicians more often than nonusers. Thus, early detection of breast abnormalities can preclude the progression of these abnormalities into cancerous lesions.¹²⁰ OCs would not be expected to increase the risk of breast cancer in S.M. She should

be instructed to perform monthly self-breast examinations and to return annually for a physical examination by her health care provider.

Depression

22. K.G. is a 24-year-old woman with persistent mild depression. Taking into account her depression, would an OC with high or low estrogen or progestin balance be preferred for K.G.?

Usually patients notice improved mood or premenstrual symptoms when taking an OC.⁵ However, OC-related depression has been attributed to progestin or estrogen excess. Some OC users experience deterioration in mood during the pill-free period. Other causes of depression, such as hypothyroidism or vitamin B₆ deficiency, should also be considered. If depression is severe or of concern, OCs should be discontinued.

On further questioning, K.G. states that she noticed only a minor change in mood, denies suicidal or homicidal ideations, and desires to continue taking OCs. K.G.'s OC should be changed from Nordette to an OC with less estrogenic activity (e.g., Lo-Estrin 1/20), less progestational activity (e.g., Ovcon 25), or both (e.g., Alesse/Levite/Apri) (see Table 45-2). If K.G. found that her depression was worse during the hormone-free week, then changing her to continuous-use OCs may be helpful.

Diabetes

23. R.D., a 33-year-old woman, experienced glucose intolerance during pregnancy that resolved after delivery. She has a father and sister with diabetes. Would an OC be appropriate for R.D.?

Generally, low-dose OCs do not alter glucose tolerance.^{63,65} Results of one controlled, randomized, prospective study showed no adverse effect on carbohydrate or lipid metabolism in women with a history of gestational diabetes after 6 to 13 months of low-dose OC use.¹²¹ Both the users and nonusers showed a significant and similar deterioration in glucose tolerance with an overall prevalence of 14% impaired glucose tolerance and 17% diabetes mellitus. The authors concluded that low-dose OCs could be prescribed safely and that serum lipids and glucose tolerance should be monitored closely, regardless of contraceptive choice.

Women with a history of gestational diabetes and those with a strong family history of diabetes in parents or siblings are at greater risk for OC-induced glucose intolerance.^{5,9,82} OCs have complex effects on carbohydrate metabolism. Progestins decrease and estrogens increase the number of insulin receptors on the cell membrane. Progestins also may alter insulin receptor affinity. The different progestins in OCs have different propensities to induce glucose intolerance. Norgestrel appears to have the greatest insulin-antagonizing activity. Ethynodiol diacetate, norethindrone, norethindrone acetate, desogestrel, and norgestimate have significantly less effect. In general, carbohydrate metabolism is not affected to an important degree in most diabetic women using low-dose OCs.

For R.D., Levlen/Levora/Nordette would be poor choices because they are known to cause glucose intolerance in patients with previous gestational diabetes.¹²² Interestingly, the triphasic levonorgestrel product TriLevlen/Trivora, containing

39% less progestin than the monophasic product, did not alter glucose tolerance, and Alesse/Levite/Apri, which contains 33% less EE, also should not alter glucose tolerance. Lowering the estrogen content of an OC without changing progestin content also has improved glucose tolerance and increased insulin secretion.^{123,124}

For women without diabetes, OC use may protect against developing diabetes. One large prospective, observational study found that White and Black OC users had lower fasting glucose levels and lower odds of diabetes.¹²⁵

R.D. can be started on OCs. However, if she smokes or has other medical problems such as hypertension, nephropathy, retinopathy, or other vascular diseases, OCs should probably be avoided. It seems prudent to put R.D. on an OC with a low dose of estrogen and progesterone and to monitor for any changes in glucose control.

Gallbladder Disease

24. L.S., a 26-year-old woman, arrives at the emergency department with acute epigastric pain accompanied by nausea, vomiting, and diarrhea. She has been taking OCs for 1 year. She is diagnosed as having gallstones. What is the association between gallbladder disease and OC therapy? What would be an appropriate OC for L.S.?

The incidence of cholelithiasis has been reported to increase with OC use. Estrogens and progestins may contribute to bile stasis and cholelithiasis by reducing cholesterol clearance and altering bile acid composition.^{9,126} The incidence of gallbladder disease has been reported to increase during the first year of use but then to decline steadily to a rate lower than that of controls.¹²⁷ In another large study, long-term OC users experienced slightly lower rates of gallbladder disease than nonusers.¹²⁸ Finally, another study found that women who had ever used OCs were not more likely to have symptomatic gallstones, but current and long-term users were. An analysis of 482 women with benign gallbladder disease from the Oxford/Family Planning Association contraception study concluded that it is unlikely that OCs cause gallbladder disease.¹²⁹

The newer OCs with lower progestin and estrogen concentrations should have little effect, if any, on gallstone formation in normal patients. Women who are obese, young, or long-term users of OCs may be the most likely to develop gallstones.

In L.S., it is not known whether OCs were the cause of her gallstones. A history of or the current presence of gallstones is not a contraindication to OC use, so L.S. may continue to use OCs if desired.

Use During Pregnancy and Breastfeeding

25. P.S., a 25-year-old woman, was started on Triphasil 2 months ago because of a history of abnormal menstrual periods. Unknowingly, she was pregnant at that time and continued her OC for two complete cycles. What can you tell P.S. about the possible effects of OC use on her unborn child?

The fact that OCs are classified as pregnancy category X (contraindicated, fetal risks clearly outweigh maternal benefit) is very misleading.¹³⁰ Although an association between OC use and cardiac or limb anomalies had been reported, other studies have not noted a teratogenic effect. Simpson

summarized all available data on contraceptive steroid exposure during pregnancy and concluded that OC use did not substantially increase the risk of anomalies over that expected in other uneventful pregnancies.¹³¹

Clearly, an OC should not be started in someone who is known to be pregnant. However, P.S. should be reassured that the risks to her fetus from the use of a low-dose OC during the first trimester should be minimal.

P.S. may use OCs after she has her baby even if she is breastfeeding, although it may be preferable for her to use a progesterone-only method.^{5,130} For patients without contraindications to OCs, the American Academy of Pediatrics considers OCs to be compatible with breastfeeding.¹³² However, OCs have been reported to decrease milk quantity and quality (see Question 27).¹³⁰ Therefore, many providers suggest avoiding OCs in women who are exclusively breastfeeding. If a postpartum woman would like to start OCs, she should wait to begin them until at least 3 weeks postpartum. By this time, the increased risk of thrombosis that occurs during pregnancy should be reduced to baseline.

CONTRACEPTIVE PATCH AND RING

26. K.H. is a 16-year-old who started taking OCs 3 months ago. She is very concerned about getting pregnant because she has trouble remembering to take her pill each day. She likes all the noncontraceptive benefits of OCs but is wondering if there are dosage forms other than pills. What do you tell her?

Contraceptive Patch

Contraceptive patch users experience about 1 pregnancy per 100 women-years of use (see Table 45-1). The contraceptive patch (Ortho Evra) contains 6 mg norelgestromin and 750 µg EE and delivers, transdermally, 150 µg norelgestromin and 20 µg EE daily into the bloodstream.¹³³ The patch is a 1.75" square with rounded corners and is beige and thin. It is applied once weekly for 3 consecutive weeks, followed by 1 week with no patch. Then this cycle is repeated. Menses should begin during the patch-free week.

The contraceptive patch may be worn on the buttock, abdomen, upper torso, or upper outer arm.¹³³ K.H. should not apply the patch to the same exact spot each month, but rather rotate within or between sites. The patch should not be applied to the breasts. When applying the patch, K.H. should select the application site and be sure it is clean and dry. She should press firmly on the patch for 10 seconds and trace her finger around the edge of the patch to be sure it sticks properly. The patch should stay attached during usual activities, including exercising, swimming, and bathing. If the patch falls off for <24 hours, she should reapply it or apply a new one as soon as possible, and her patch change day will stay the same. No backup contraception is needed. If the patch is off for >24 hours, she should start a new cycle, she will have a new patch change day, and she should use backup contraception for one week.

The patch may be started using the Sunday start or Day 1 start method, and the recommendations for backup contraception are the same as described earlier with OCs.¹³³ If K.H. forgets to start the first patch of a cycle, she should apply it as soon as she remembers. This day will become her new patch change day, and she should use backup contraception for 1

week. If she forgets to change the patch for 1 or 2 days during week 2 or 3, she should apply a new patch as soon as she remembers. This becomes her new patch change day. No backup contraception is needed. If she forgets for >2 days, she should start a new cycle as soon as she remembers. She will need to use backup contraception for 1 week and will have a new patch change day.

Since the patch contains similar hormones to those in OCs, the risks and benefits are thought to be similar. The package insert lists the same contraindications and precautions with the use of the patch as for OCs (see Table 45-4).¹³³ However, since the delivery system and serum levels are different, future studies may find that there are differences in certain risks or benefits between these products. One difference with the patch is efficacy is reduced in users over 90 kg. Therefore, providers may choose to recommend another method for heavier women. The most common side effects reported with the patch are breast tenderness, headache, application site reaction, and nausea.

Contraceptive Ring

The failure rate for the contraceptive ring is one or two pregnancies per 100 woman-years. The contraceptive ring (NuvaRing) delivers 120 µg etonogestrel and 15 µg EE daily through the vaginal mucosa.¹³⁴ The ring is flexible, transparent, and has a diameter of just over 2". The ring is inserted vaginally and kept in place for 3 weeks in a row. After 3 weeks, the ring is removed for 1 week, and then a new ring is inserted.

The ring may be placed anywhere in the vagina, so K.H. does not need to worry about its exact position.¹³⁴ To insert the ring, she should compress it so the opposite sides of the ring are touching, and gently insert it into the vagina. If she feels discomfort with the ring, it has probably not been inserted into the vagina far enough. Most women do not feel the ring once it is in place. To remove the ring, K.H. should grasp the ring between two fingers or hook one finger inside the ring and pull it out. Menses will usually begin within 3 days of removing the ring. If the ring slips out, it should be rinsed with cool water and reinserted. If the ring is out for <3 hours, backup contraception is not needed. If the ring is out for >3 hours, backup contraception should be used for 1 week. If the ring has been left in the vagina for 3 to 4 weeks, the woman should remove it, wait 1 week, then reinsert a new ring. If it has been in place for >4 weeks, the woman should remove it, confirm that she is not pregnant, reinsert a new one, and use backup contraception for 1 week.

The contraceptive ring should be inserted anytime during the first 5 days of the menstrual cycle.¹³⁴ Backup contraception should be used for the first week. When changing from OCs, the woman should insert the ring within 7 days of the last active pill. No backup contraception is needed.

As with the patch, the ring has the same contraindications and precautions as OCs (see Table 45-4).¹³⁴ The most common side effects with the ring are vaginal infections, irritation, and discharge, headache, weight gain, and nausea.

PROGESTERONE-ONLY PILL (MINIPILL)

27. P.K., a 39-year-old woman, plans to breastfeed her infant and begin some type of contraception following her discharge from the hospital. Her past experience with condoms and concurrent spermicidal foams or gels resulted in itching and burn-

ing, and an IUD caused severe cramping and bleeding. She has a strong family history of cardiac disease and smokes two packs of cigarettes a day. What are the advantages of the minipill as a contraceptive method for P.K.?

Advantages

The minipill is devoid of some of the nuisance side effects (see Table 45-4) caused by estrogen (e.g., headaches, chloasma).⁵ More importantly, estrogen-mediated hypertension and clotting factor changes will be avoided in this smoker, who has a strong family history of cardiovascular disease. Confusion with pill taking is minimized since there is no placebo week and all 28 tablets in each pack are the same. Therefore, the missed-dose directions are the same whenever any pill is missed. Minipills also have noncontraceptive benefits, including decreased dysmenorrhea and bleeding. They also may protect against PID and endometrial cancer.

Theoretically, progestin use in the early postpartum period may decrease milk production, since milk production is triggered by the decline in progesterone that occurs after delivery. However, no data have consistently shown this to be a problem in postpartum women.¹³⁰ Once breastfeeding has been established, progestins have not been shown to interfere with the quantity or quality of milk produced by a nursing mother. Thus, an OC containing only progestin is preferred for a patient who plans to breastfeed her infant.

Disadvantages

28. What disadvantages of the minipill should you discuss with P.K.?

The minipills, with a failure rate of 0.5% to 5%, are less effective than OCs (see Table 45-1).⁵ Since minipills must be taken even more regularly than OCs, minipills are not often used in women who are not breastfeeding (see patient instructions below). Some women on minipills consistently have ovulatory cycles, and some shift back and forth between ovulatory and anovulatory cycles. Women who consistently have menses on the minipill are likely to be ovulating and should be advised to use a backup method of contraception or to change to a different method.

Irregular menses, decreased duration and amount of menstrual flow, spotting, or amenorrhea commonly occurs in women taking the minipill.⁵ Because of this, patients often are concerned that they may be pregnant. Women who are exclusively breastfeeding will usually have amenorrhea. The high incidence of irregular menses associated with the minipill may mask underlying pathology. Other side effects reported with minipills include headaches, breast tenderness, mood changes, and nausea.

Minipills should be avoided if there is a personal history of breast cancer or undiagnosed vaginal bleeding. Caution should be exercised when using minipills in women with hepatic disease, certain cardiovascular conditions, a current DVT or PE, or complicated diabetes (see Table 45-4).¹¹

Patient Instructions

29. What instructions should P.K. receive regarding the use of a minipill?

P.K. should begin taking the minipill on the first day of her menses.⁵ Since she is breastfeeding and is less likely to have menses, she can begin taking them immediately postpartum. Alternatively, some providers recommend waiting until 3 to 6 weeks postpartum to begin minipills to minimize complaints of irregular bleeding and to confirm that milk flow is established. Backup contraception is not needed with a Day 1 start. When starting minipills on a day other than the first day of menses, a backup method of contraception should be used for 48 hours.

P.K. should be instructed to take the pill at the exact same time each day. If she is >3 hours late taking a pill, she should take the pill as soon as she remembers and should use backup contraception for 48 hours. This is quite different from the directions for OCs, so this point should be stressed with patients.

LONG-ACTING INJECTIONS: DEPO-PROVERA AND LUNELLE

Depo-Provera

30. A.K., a lactating 35-year-old woman, returns to the gynecology clinic for her second injection of depot medroxyprogesterone acetate (Depo-Provera; DMPA). She is a smoker with a history of thromboembolism. She was given her first injection 3 months ago, immediately postpartum. She is experiencing prolonged intermenstrual bleeding and a 2-lb weight gain. Is this to be expected? What are the benefits and risks of DMPA? How are the side effects managed?

DMPA is given as a 150-mg deep intramuscular injection in the deltoid or gluteus maximus every 11 to 13 weeks.⁵ Since its development in the early 1960s, DMPA has been approved for use in >90 countries and has been used by >30 million women worldwide.¹³⁵ The FDA approved it in 1992. DMPA inhibits ovulation, thickens the cervical mucus, and suppresses endometrial growth, making it a very effective contraceptive.

Advantages

Depo-Provera is a good contraceptive choice for A.K. because she is at risk for estrogenic side effects. She is 35 years old, smokes, is lactating, and has a history of thromboembolism. Among its benefits are a low failure rate of 0.3% (see Table 45-1), ease of use, lack of estrogenic side effects, decreased dysmenorrhea and monthly blood loss, and a reduced risk of endometrial cancer and PID.^{5,136} Other noncontraceptive benefits may include decreasing pain and frequency of sickle cell crises, reduction in seizure frequency in epileptic patients, and a possible reduction in ovarian cancer.^{5,137} Furthermore, contraceptive efficacy is not reduced by the concurrent use of anticonvulsants as is seen with OCs.

Disadvantages

Patients with breast cancer should not use DMPA.¹¹ DMPA should be used with caution in women with undiagnosed vaginal bleeding, certain cardiovascular diseases or multiple risk factors for cerebrovascular disease, or a current DVT or PE (see Table 45-4). Some experts disagree with the Depo-Provera Contraceptive Injection U.S. package insert, which

lists a history of prior thromboembolism as a contraindication, because clotting factors have not been shown to be clinically affected by DMPA.¹³⁸ Some clinicians also begin DMPA immediately postpartum rather than waiting 6 weeks postpartum, as directed by the package insert. Patients started earlier are more likely to report frequent episodes of bleeding or spotting, however.^{139,140}

Estrogen production declines in women using DMPA, so A.K. should be told that DMPA may decrease bone mineral density (BMD).¹⁴¹ Numerous studies have found that women receiving DMPA injection have lower BMD compared with nonusers. Other studies have found that DMPA does not affect BMD. Although there have been reports of stress fractures in DMPA users, no studies to date have documented an increased rate of hip or vertebral fractures in DMPA users.^{142,143} Also, BMD has been shown to recover after discontinuation of the injections.¹⁴⁴

A.K. must understand that DMPA frequently causes irregular bleeding or spotting during the first few months of use or more because estrogen is insufficient to maintain the endometrium. After 1 and 2 years of use, 55% and 68% of women experience amenorrhea, respectively. Amenorrhea leads to discontinuation of DMPA in 13% of patients.¹³⁸ All patients beginning Depo-Provera should be informed that during the first year of use, they might have menstrual changes. If unusually heavy or continuous bleeding occurs, A.K. should be evaluated. A.K. should be counseled and reassured that her intermenstrual bleeding probably will resolve in the next few months. If the bleeding is bothersome to her, a 4- to 21-day course of oral estrogen (e.g., conjugated estrogen 0.625 to 2.5 mg/day) or an OC with 20 µg EE will minimize or eliminate the bleeding.¹² However, the bleeding may recur after discontinuation of the estrogen. Low-dose estrogen may be continued if bleeding recurs. The mean weight gain after 1 year of therapy with DMPA was about 5 lb in two thirds of users. Users typically gain a total of about 8 lb over 2 years, nearly 14 lb over 4 years, and 16.5 lb over 6 years. Other side effects include mood changes, hair loss, and headaches.

Following a 150-mg DMPA injection, conception is delayed approximately 10 months after the last injection in half of users.¹³⁸ The remaining users took longer to become pregnant, with nearly all users becoming pregnant by 18 months.

Lunelle

31. A.K. is concerned about the menstrual changes with DMPA but likes the idea of an injectable method of contraception. Are there any other options for her?

Lunelle contains medroxyprogesterone 25 mg and estradiol cypionate 5 mg and is administered intramuscularly every 28 to 33 days.¹⁴⁵ With this injection, women may experience spotting initially but should have regular menses about 2 to 3 weeks after each injection. The first injection should be given within 5 days of menstrual bleeding, and no backup contraception is needed. Unlike DMPA, ovulation resumes within 2 to 3 months of discontinuing Lunelle. The most common side effects of Lunelle are irregular menses, weight gain (an average of 4 lb in the first year), fluid retention, breast symptoms, nausea, headache, and mood changes.

Lunelle, formerly available in vials and prefilled syringes, encountered manufacturing problems and is no longer marketed because of business reasons. Lunelle has not been available since October 2002, and it is not available as of this writing. Pfizer medical information does not know if it will ever become available again. At this time, A.K. will have to select an alternate method.

SUBDERMAL IMPLANTS

32. A.K. returns to the gynecology clinic on the first day of her flow after missing three consecutive DMPA injections because she cannot remember to come in for her shots and does not like the weight gain and prolonged intermenstrual bleeding that occurred over 6 months. A friend of hers has used Norplant in the past, and she would like to try it. What information should be given to her?

The Norplant System brand of subdermal levonorgestrel implants, approved by the FDA in 1990, consists of a set of six Silastic capsules 2.4 mm wide and 34 mm long that are implanted under the skin in the upper arm.⁵ The set contains a total of 216 mg of levonorgestrel that is released at a constant rate of only 20 to 30 µg/day over 5 years, after which time they are replaced.

Unfortunately, the Norplant System is no longer available. Certain lot numbers of Norplant were recalled in 2000 due to efficacy concerns, and patients were encouraged to use backup contraception. Further research found that the recalled lots did not have reduced efficacy, so backup contraception is no longer required for the affected patients. However, Wyeth does not plan to reintroduce the system. Other implants using one or two rods (versus the six rods for Norplant) are under investigation and may be available in 2004.

INTRAUTERINE DEVICES AND INTRAUTERINE SYSTEMS

Background and Mechanism of Action

33. R.P., a 23-year-old G₀P₀ woman with hydrocephalus, is brought to the gynecology clinic by her mother, S.P., to determine the best method of contraception for her mentally impaired daughter. R.P. is in a monogamous relationship with a mentally impaired partner. According to S.P., R.P. wishes to put off pregnancy for many years, and any method of contraception that necessitates compliance is virtually impossible for the couple. DMPA has been considered but is unacceptable because of the possibility of menstrual irregularities that would upset R.P. R.P. has never heard of IUDs or intrauterine systems (IUSs) before. Counsel her on what is available and how they work.

In the 1960s and 70s, several types of IUDs were available to women in the United States (e.g., Lippes Loop, Saf-T-Coil, Copper 7, Tatum T, Progestasert).¹⁴⁶ The Dalkon Shield IUD was introduced in the United States in 1971. Due to increased susceptibility to PID, with subsequent tubal scarring and infertility, the Shield was removed from the market in 1974. Although the high incidence of PID was not seen with the other types of IUDs, the negative publicity hurt the use of other IUDs. By 1976, the only IUD still available was the Progestasert. The ParaGard IUD was introduced in 1988 and the Mirena IUS in 2000. Progestasert has since been discontinued

and has not been available since 2001. Although the IUDs/IUSs available today are a safe and effective method of contraception, they are still not as popular in the United States (<1% of women are users) as they are worldwide (12% of married women of reproductive age are users).¹⁴⁷

The ParaGard IUD, also known as the Copper-T IUD, has a polyethylene body that is wound with copper wire. Once inserted, the ParaGard may be left in place for 10 years.^{5,148} The Mirena IUS also has a polyethylene body, with a levonorgestrel reservoir in the vertical stem of the T.¹⁴⁹ Mirena is effective for 5 years. The failure rate of ParaGard is 0.6 to 0.8 pregnancies per 100 woman-years compared with 0.1 for Mirena (see Table 45-1). IUDs/IUSs are inserted by a health care provider in their office. The procedure usually takes only a few minutes and does not require sedation. Many providers will recommend that patients take a dose of an NSAID before the insertion visit.

Possible mechanisms of action for ParaGard include prevention of fertilization and implantation and interfering with sperm transport, viability, or number.¹⁴⁸ Mirena is believed to work by thickening the cervical mucus, preventing sperm from entering the uterus, altering the endometrial lining, preventing ovulation, and altering sperm activity.¹⁴⁹

Advantages

34. R.P.'s mother thinks that an IUD/IUS is a good option for her daughter, but R.P. is not sure. What are the advantages of IUDs/IUSs that R.P. should be aware of?

Both the Mirena and ParaGard are both very effective, reversible, long-term methods that are easy to comply with. The ParaGard IUD is a wonderful option for women who desire a nonhormonal method. The Mirena IUS has the advantages of reducing menstrual bleeding and cramping.

Although the initial cost of inserting an IUD/IUS is high (around \$500 for the device and insertion costs), there are no monthly costs to R.P. as there are with other methods. Therefore, women who use an IUD/IUS for over 1 year have an overall lower monthly cost than women who use OCs or the contraceptive ring or patch.

Disadvantages

IUDs/IUSs are contraindicated in women with certain anatomic abnormalities of the uterus, unexplained vaginal bleeding, cervical cancer, and PID or other active genital infection and should be used with caution in women who are HIV positive or are immunosuppressed (see Table 45-4).¹¹ The Mirena IUS should not be used in women with active breast cancer and should be used with caution in women with a current DVT or PE or a history of breast cancer. Breast cancer is hormonally sensitive, and the disease may be worsened by the use of levonorgestrel. Although the serum levels of levonorgestrel are low with the Mirena IUS, the manufacturer currently does not recommend that women with active or past breast cancer use the device.

IUD users are more likely to develop PID than nonusers. For all patients, the greatest risk of PID occurs shortly after insertion.¹⁵⁰ To prevent this from occurring, all patients should be tested for gonorrhea and chlamydia prior to IUD/IUS insertion. Women who are positive for either STD should consider an alternative form of contraception. In addition,

Table 45-7 IUD/IUS Early Danger Signs (PAINS)

Period late (pregnancy) or abnormal spotting or intermenstrual bleeding
Abdominal pain or pain with intercourse
Infection exposure (e.g., gonorrhea) or abnormal vaginal discharge
Not feeling well, fever, chills
String missing, shorter, or longer

IUDs/IUSs should be reserved for women in monogamous relationships or who have strict use of condoms, since these women are least likely to acquire an STD.

If an IUD/IUS user becomes pregnant, the likelihood that the pregnancy is ectopic is higher (i.e., the ratio of ectopic to uterine pregnancies is higher in IUD/IUS users).^{148,149} If a patient using an IUD/IUS becomes pregnant, her risks for spontaneous abortion, sepsis, and premature delivery are increased if the IUD/IUS is left in place.

Approximately 10% to 15% of IUDs are removed because of excessive uterine bleeding, spotting, or pain.^{148,149} Another 2% to 6% of women spontaneously expel their IUD within the first year. Rarely, IUDs/IUSs may become embedded in the endometrium or partially or totally perforate the uterine wall. R.P. should be instructed to look for the warning signs of a possible complication with IUD/IUS use (Table 45-7).

DIAPHRAGM

Mechanism of Action

35. R.C., a 16-year-old G₁P₁ girl who is breastfeeding her 6-week-old infant, will consider only a barrier method of contraception. How do diaphragms prevent pregnancy?

The diaphragm is a soft, latex or silicone rubber cap with a metal spring reinforcing the rim.^{5,12} The device is inserted vaginally and placed over the cervical os to mechanically block access of sperm to the cervix. It is held in place by the spring tension of the rim, vaginal muscle tone, and the pubic bone. Because the diaphragm does not fit tightly enough to be a complete barrier to sperm, spermicidal gel must be placed in the dome prior to use.⁹

The first-year failure rate with diaphragms is 6 to 20 pregnancies per 100 woman-years (see Table 45-1).⁵ R.C. should be counseled that diaphragms are less effective than other available methods. Since breastfeeding offers some protection against pregnancy, breastfeeding women may be the best candidates for the diaphragm.

Types

36. What types of diaphragms are available?

Diaphragms must be properly fitted to be effective. They are made of silicone or latex and are available in different sizes (50 to 95 mm in diameter) and different styles of construction of the circular rim.^{5,12} The coil spring rim diaphragm folds flat and may be used with a diaphragm introducer. These diaphragms are indicated for women with average vaginal muscle tone and for women who can tolerate the sturdy rim and firm spring strength. The rim of the arcing spring rim diaphragm arcs when folded. Most women, even those with lax vaginal muscle tone, can tolerate the firm spring strength of

the arcing spring rim diaphragm. The flat spring rim diaphragm is good for women with firm vaginal muscle tone, because the rim is less firm than the other styles. The wide-seal rim diaphragm (available as an arcing spring or coil spring) has a flexible flange designed to hold spermicide in place and to create a better seal between the diaphragm and vaginal wall.

R.C. would likely be able to tolerate any of the diaphragms. Perhaps she will find that one type is more comfortable than the others when she is fitted for the diaphragm.

Fitting

37. How is a diaphragm size selected?

The goal of fitting a diaphragm is to select the largest rim size that is comfortable for the patient.^{5,12} A diaphragm that is too small may become dislodged during intercourse because vaginal depth increases during sexual arousal. Conversely, a diaphragm that is too large may cause vaginal pressure, abdominal pain or cramping, vaginal ulceration, or recurrent urinary tract infections.

Patient Instructions

38. What instructions should be provided to R.C. concerning the use of a diaphragm?

The diaphragm should not remain in the vagina for >24 hours.^{5,12} Toxic shock syndrome (TSS) has been associated with diaphragm use and women should be alert to its symptoms, which include fever, diarrhea, vomiting, muscle aches, and a sunburn-like rash. Allergic reactions to the latex or spermicides also have been reported.

Prior to insertion, R.C. should inspect the diaphragm for holes or puckering. R.C. should be counseled that the diaphragm should always be inserted before intercourse if contraception is to be maximized; it can be inserted as long as 6 hours before intercourse if necessary. The diaphragm should not be removed for at least 6 hours after intercourse. One teaspoon of spermicidal gel should be placed into the dome of the diaphragm prior to insertion. If intercourse is repeated, a new application of spermicide should be inserted vaginally without removal of the diaphragm.

When the diaphragm is removed, it should be washed with mild soap and water, rinsed and dried, and stored in its plastic container. Talcum or perfumed powders should not be used on the diaphragm because these may damage the diaphragm or harm the vagina or cervix. Oil-based products also may decompose the diaphragm and should not be used. Contraceptive gel, however, may be used if vaginal lubrication is needed. If R.C. gains or loses 10 to 20 lb, has a pregnancy, or has abdominal or pelvic surgery, the fit of her diaphragm should be checked.

CERVICAL CAP

39. R.C. is also interested in the cervical cap. What is it, how well does it work, and what information should be provided to cervical cap users?

The cervical cap is a small, flexible, cuplike device made of latex and designed to fit closely around the base of the

cervix; it is available in 22-, 25-, 28-, and 31-mm internal rim diameter sizes.^{5,12} The cervical cap is less effective in women who have delivered a child, with pregnancy rates of 26 to 40 pregnancies per 100 woman-years in nulliparous women and 9 to 20 pregnancies per 100 woman-years in parous women. Women generally prefer other methods of contraception to cervical caps. In one study, 50% of women discontinued using cervical caps after 6 months, and 50% were pregnant after 2 years of use.¹⁵¹

To use the cervical cap, R.C. should fill the cap about one-third full with spermicidal gel, insert it vaginally, and place it over the cervix.^{5,12} Suction holds it in place. It should be left in place at least 8 hours after intercourse but no longer than 48 hours, according to the manufacturer. Most experts recommend removal after 24 hours because of problems with vaginal odor at 36 to 48 hours and the theoretical risk of TSS.

As with the diaphragm, patients should check the cap for holes before using. Also, R.C. should avoid using oil-based lubricants or medications when using the cervical cap.

CONDOMS

40. J.D. is a 45-year-old woman who is unmarried and has sex infrequently. For this reason, she would like a method to protect against pregnancy as well as STDs. How effective are condoms in preventing pregnancy? What types of condoms are available?

Condoms are an effective method of contraception when used properly. The failure rate with condoms is 3 to 12 pregnancies per 100 woman-years of use (see Table 45-1).^{5,12} The female condom is slightly less effective, with 5 to 21 pregnancies per 100 woman-years. Many different brands of condoms are available in the United States. The brands differ in size, shape, color, material, and the presence or absence of lubricants or spermicide. Most practitioners recommend lubricated condoms with reservoir ends to collect the ejaculate and to prevent breakage.

The most commonly used male condom is made of latex.^{5,12} There are also male condoms made of polyurethane and lambskin, which are recommended for men or women allergic to latex. However, polyurethane condoms are more expensive and harder to find than latex condoms, and lambskin condoms do not offer the same protection against STDs. Female condoms are made of polyurethane.

41. What are the advantages and disadvantages of condoms? How are they used?

Because the pre-ejaculatory secretions may contain sperm, the male condom should be applied before vaginal contact.^{5,12} Female condoms should also be inserted before sexual contact; they may be inserted up to 8 hours before intercourse. Condoms should be used by their expiration date and should not be reused. They should be stored in a cool, dry place, not somewhere they will be exposed to prolonged periods of heat or light.

The chief noncontraceptive benefit of condoms is the prevention of STDs (including gonorrhea, chlamydia, and HIV), and they can be used for vaginal, anal, or oral sex.^{5,12} Condoms are also readily available without a prescription and do not cause systemic side effects like the hormonal methods,

and latex male condoms are inexpensive. However, some complain that condoms reduce sensitivity and spontaneity, and female condoms are more costly (about \$3 each), can be noisy, and can be difficult to insert.¹² Condoms may also break; this is less likely with the female condom. Oil-based products can degrade latex and should be avoided when using male, latex condoms. Oil-based lubricants can be used with female condoms or male polyurethane or lambskin condoms.

When using a male condom, the man or his partner holds the tip of the condom and unrolls it down to the base of the erect penis.^{5,12} The female condom consists of a smaller circular ring at one end (which secures the device around the cervix like a diaphragm) and a larger ring at the other end. The inner ring should be compressed and inserted vaginally as far as it will go, and the larger ring remains outside of the vagina, protecting the external genitalia.

VAGINAL SPERMICIDES

42. J.D. would like to use a spermicide along with condoms. What options does she have, and how effective are spermicides when used alone?

Vaginal spermicides currently are available as gels (jellies), suppositories, foams, and films.^{5,12,152} Most of these products use a nonionic surfactant, nonoxynol-9, as the spermicide; the balance use octoxynol-9. The *in vitro* spermicidal potencies of the various preparations are highest with foam, followed by cream, jelly, and gel, respectively.²⁴⁹ First-year failure rates with these dosage forms range from 6 to 21 failures per 100 woman-years of use (see Table 45-1).

43. What dosage form should J.D. use? How should she be instructed to use a vaginal spermicide? What side effects can be anticipated?

Table 45-8 compares the different spermicidal products.^{5,12,152} The different characteristics of the products can help guide J.D. when selecting a dosage form. Regardless of the dosage form, a new dose of spermicide should be applied before each act of intercourse.

Spermicides may cause genital irritation and in some patients lead to ulceration. For this reason, spermicides have been shown to increase the transmission of STDs, including HIV, gonorrhea, and chlamydia.

EMERGENCY CONTRACEPTION

Emergency Contraceptive Pills

44. B.P., a 24-year-old woman, has just returned home from a vacation in Europe. Her luggage containing her OCs was stolen 2 weeks ago, and she had unprotected midcycle intercourse 34 hours ago. What can be done to prevent an unwanted pregnancy at this time?

Emergency contraception (also known as the morning-after pill) is postcoital contraception¹⁵³ that is useful for women who did not use a contraceptive (e.g., forgot, were assaulted) or whose method failed (e.g., broken condom). Emergency contraceptive pills (ECPs) may reduce the risk of pregnancy by several mechanisms: preventing ovulation, preventing fertilization, or preventing implantation.

Although ECP use is on the rise, many women are not aware that it is available. In a 1998 survey, 686 of 1,000 women aged 18 to 44 had heard of emergency contraception.¹⁵⁴ Only 5% had learned about it from a health care professional, 44% identified the source as a television news program, and another 16% read about it in a magazine. Approximately 12% of obstetrician/gynecologists interviewed in the same survey feared women would use ECPs for routine contraception, and another 11% stated that they had moral or religious objections to emergency contraception.

Available Emergency Contraceptive Pills

ESTROGEN AND PROGESTIN EMERGENCY CONTRACEPTIVE PILLS

One option for patients is to use regular OCs for emergency contraception. The Yuzpe regimen of emergency contraception uses commercially available OCs to deliver 0.5 mg levonorgestrel or 1 mg norgestrel and 100 µg EE per dose.¹⁵⁵ Patients are instructed to take two doses 12 hours apart. Table 45-9 shows which OCs may be used and how many tablets need to be taken per dose.^{152,156,157} It is very important to counsel patients about which pills to take, since the tablet color and number differ depending on the brand chosen. This makes this method less desirable than Preven and Plan B (discussed below).

The Preven Emergency Contraceptive Kit, which contains four blue tablets (each containing 0.25 mg levonorgestrel and

Table 45-8 Comparison of Vaginal Spermicides

Formulation	Brand Name Examples	How to Use	Onset of Action	Duration of Action
Gel	Conceptrol, Gynol II	Fill applicator, insert applicator vaginally as far as it will comfortably go, press plunger of applicator to deposit spermicide near the cervix.	Immediate	1 hr
Film	VCF	Fold film in half, fold over finger, use finger to insert as far as it will comfortably go.	15 min	3 hr
Foam	Delfen, Koromex, VCF	Shake foam canister, fill applicator, insert applicator vaginally as far as it will comfortably go, press plunger of applicator to deposit spermicide near the cervix.	Immediate	1 hr
Suppository	Conceptrol, Encare	Unwrap, use finger to insert as far as it will comfortably go.	15 min	1 hr

Table 45-9 Oral Contraceptive Pills That May Be Used As Emergency Contraception

Brand	Number of Tablets per Dose	Color
Alesse	5	Pink
Aviane	5	Orange
Cryselle	4	White
Enpresse	4	Orange
Lessina	5	Pink
Levlen	4	Light-orange
Levlite	5	Pink
Levora	4	White
Lo-Ovral	4	White
Low-Ogestrel	4	White
Nordette	4	Light-orange
Ogestrel	2	White
Ovral	2	White
Ovrette	20	Yellow
Plan B	1	White
Portia	4	Pink
Preven	2	Blue
Tri-Levlen	4	Yellow
Triphasil	4	Yellow
Trivora	4	Pink

50 µg EE), a pregnancy test, and an instruction book, is a good alternative to using OCs. Patients are instructed first to read the instruction book, then to use the pregnancy test; if the pregnancy test is negative, they should take two tablets as soon as possible and two more tablets exactly 12 hours later.

Estrogen and progestin ECPs have been shown to reduce the incidence of pregnancy by about 75%.¹⁵³ The reduction in pregnancy is greatest when used within 24 hours after unprotected intercourse.

PROGESTIN EMERGENCY CONTRACEPTIVE PILLS

Plan B is a progestin-only ECP. The Plan B pack consists of two white levonorgestrel 0.75-mg tablets and patient instructions.^{152,155,156} One tablet is taken as soon as possible and the second is taken 12 hours later. Progestin ECPs have been shown to be more effective than estrogen and progestin

ECPs.¹⁵⁷ They reduce the average risk of pregnancy by 89% after a single act of intercourse when taken within 72 hours. In the first 24 hours after intercourse, progestin ECPs can prevent 95% of expected pregnancies.

The progesterone-only pill, Ovrette, may also be used for emergency contraception.¹⁵³ However, this product is rarely used, since the patient would need to take 20 pills per dose to get the proper amount of progestin.

Patient Instructions

ECPs are most effective when taken as soon as possible after intercourse; therefore, treatment should not be delayed.^{153,156,157} Although the FDA-approved indication for Preven and Plan B is for use within 72 hours after intercourse, ECPs have been shown to be effective when the first dose is taken within 5 days of unprotected sex.^{158,159} The most common side effects with ECPs are nausea and vomiting. Gastrointestinal adverse effects are more likely with the estrogen and progestin ECPs than with the progestin ECPs. B.P. should be instructed that if she vomits within 1 hour of taking either dose of medication, the dose should be repeated. Providers often prescribe an antiemetic such as prochlorperazine or meclizine that patients can take 30 to 60 minutes before each dose of ECP to prevent nausea or vomiting.¹⁵³

B.P.'s menses may come early or late, but she should take a pregnancy test if her menses does not come within 3 weeks of taking ECPs.

Patients may call the Emergency Contraception Hotline (1-888-NOT-2-Late or 1-888-668-2528) to find a provider near them who will prescribe ECPs. Patients may also find information about ECP at the Emergency Contraception website (www.not-2-late.com).

IUDs for Emergency Contraception

The copper IUD is also an effective method of emergency contraception when inserted within 5 days of unprotected sex.¹³ Since some women are not good candidates for IUDs (see discussion above) and IUDs must be inserted by a health care provider, they are not used as regularly for emergency contraception. The biggest advantage of using an IUD for emergency contraception is that it provides continued contraception for the patient.

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