CHAPTER 82

Contraception

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KEY CONCEPTS

1. The attitude of both the patient and the sexual partner toward various contraceptive methods, the reliability of the patient in using the method correctly (which may affect the effectiveness of the method), and the patient's ability to pay must be considered carefully when selecting a contraceptive method.
2. Patient-specific factors (e.g., frequency of intercourse, age, smoking status, and concomitant diseases, conditions, or medications) that may prove to be a consideration or precaution for use of a specific method must be evaluated when selecting a contraceptive method.
3. Adverse effects or difficulties using the chosen method should be monitored carefully and managed in consideration of patient-specific factors.
4. Accurate and timely counseling on the optimal use of the contraceptive method and strategies for minimizing sexually transmitted diseases must be provided to all patients when contraceptive pharmacotherapy is initiated and on an ongoing basis.
5. Certain oral contraceptives in high doses can be used as emergency contraception to prevent pregnancy after unprotected intercourse.

Unintended pregnancy is a significant public health problem with economic, health, personal, and social consequences. In the United States, approximately 62 million women are of childbearing age (15–44 years), and approximately six million become pregnant each year.[1] The most recent data reveal that 31% of pregnancies are unintended, with the highest rates occurring in women aged 25 to 44 years (38%).[1] About half of all unintended pregnancies end in abortion, and half also occurred in sexually active couples who claimed they used some method of contraception.[2] If the goal of contraception—for pregnancies to be planned and desired—is to be realized, education on the use and efficacy of contraceptive methods must be improved.

ETIOLOGY AND PATHOPHYSIOLOGY

Comprehension of the hormonal regulation of the normal menstrual cycle is essential to understanding contraception in women (Fig. 82–1).

Learning objectives, review questions, and other resources can be found at **www.pharmacotherapyonline.com.**

The cycle of menstruation begins with menarche, usually around age 12 years, and continues to occur in nonpregnant women until menopause, usually around age 50 years.[3,4] The cycle includes the vaginal discharge of sloughed endometrium called *menses* or *menstrual flow*. The menstrual cycle comprises three phases: follicular (or preovulatory), ovulatory, and luteal (or postovulatory).

THE MENSTRUAL CYCLE

The first day of menses is referred to as *day 1 of the menstrual cycle* and marks the beginning of the follicular phase.[3,4] The follicular phase continues until ovulation, which typically occurs on day 14. The time after ovulation is referred to as the *luteal phase,* which lasts until the beginning of the next menstrual cycle. The median menstrual cycle length is 28 days, but it can range from 21 to 40 days. Generally, variation in length is greatest in the follicular phase, particularly in the years immediately after menarche and before menopause.[4]

The menstrual cycle is influenced by the hormonal relationships among the hypothalamus, anterior pituitary, and ovaries.[3] In response to epinephrine and norepinephrine stimulation, the hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile fashion every 60 to 90 minutes.[3,4] These GnRH bursts stimulate the anterior pituitary to secrete bursts of gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). The gonadotropins FSH and LH direct events in the ovarian follicles that result in the production of a fertile ovum.

Follicular Phase

In the first 4 days of the menstrual cycle, FSH levels rise and allow the recruitment of a small group of follicles for continued growth and development (see Fig. 82–1).[3,4] Between days 5 and 7, one follicle becomes dominant and later ruptures, releasing the oocyte. The dominant follicle develops increasing amounts of estradiol and inhibin, which cause a negative feedback on the hypothalamic secretion of GnRH and pituitary secretion of FSH, causing atresia of the remaining follicles recruited during the cycle.

Once the follicle has received FSH stimulation, it must receive continued FSH stimulation or it will die.[3,4] Gonadotropin-dependent growth allows the follicle to enlarge, produce other layers of receptors for FSH and LH, and synthesize estradiol, progesterone, and androgen. Estradiol serves to stop the menstrual flow from the previous cycle, thickening the endometrial lining of the uterus to prepare it for embryonic implantation. Estrogen is responsible for increased production of thin, watery cervical mucus, which will enhance sperm transport during fertilization. FSH regulates the aromatase enzymes that convert androgens to estrogens in the follicle. If a follicle has insufficient aromatase, androgen will accumulate, and the follicle will not survive. Therefore, follicles with the most FSH stimulation have the lowest ratios of androgen to estrogen.

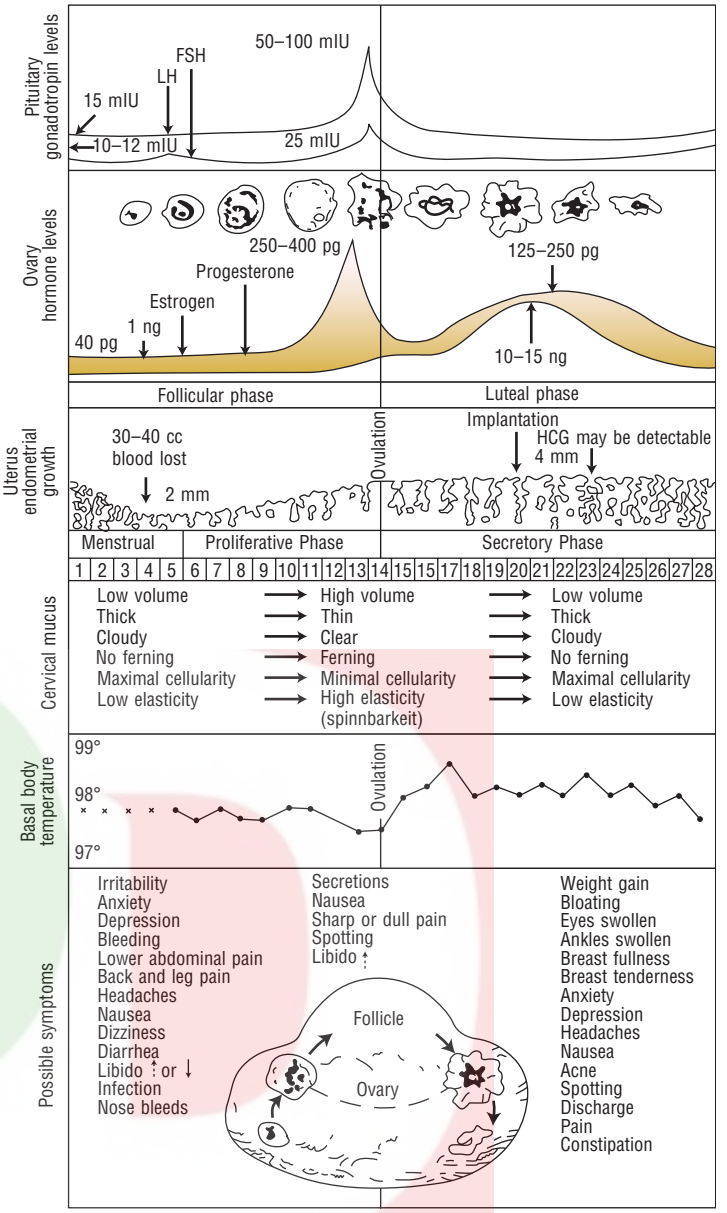

FIGURE 82-1. Menstrual cycle events, idealized 28-day cycle. (FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin, LH, luteinizing hormone.) *(From Hatcher et al.[3] This figure may be reproduced at no cost to the reader.)*

Ovulation

When estradiol levels remain elevated for a sustained period of time (200 pg for at least 50 hours), the pituitary releases a midcycle LH surge (see Fig. 82–1).[3,4] This LH surge stimulates the final stages of follicular maturation and ovulation (follicular rupture and release of the oocyte). On average, ovulation occurs 24 to 36 hours after the estradiol peak and 10 to 16 hours after the LH peak. The LH surge, which occurs 28 to 32 hours before a follicle ruptures, is the most clinically useful predictor of approaching ovulation. After ovulation, the oocyte is released and travels to the fallopian tube, where it can be fertilized and transported to the uterus for embryonic implantation. Conception is most successful when intercourse takes place from 2 days before ovulation to the day of ovulation.

Luteal Phase

After rupture of the follicle and release of the ovum, the remaining luteinized follicles become the corpus luteum, which synthesizes androgen, estrogen, and progesterone (see Fig. 82–1).[3,4] Progesterone helps to maintain the endometrial lining, which sustains the implanted embryo and maintains the pregnancy. It also inhibits GnRH and gonadotropin release, preventing the development of new follicles. If pregnancy occurs, human chorionic gonadotropin (hCG) prevents regression of the corpus luteum and stimulates continued production of estrogen and progesterone secretion to maintain the pregnancy until the placenta is able to fulfill this role (usually 6–8 weeks' gestation).

If fertilization or implantation does not occur, the corpus luteum degenerates, and progesterone production declines.[3,4] The life span of the corpus luteum depends on the continuous presence of small amounts of LH, and its average duration of function is 9 to 11 days. As progesterone levels decline, endometrial shedding (menstruation) occurs, and a new menstrual cycle begins. At the end of the luteal phase, when estrogen and progesterone levels are low, FSH levels start to rise, and follicular recruitment for the next cycle begins.

EPIDEMIOLOGY

Contraception generally implies the prevention of pregnancy following sexual intercourse by inhibiting viable sperm from coming into contact with a mature ovum (i.e., methods that act as barriers or prevent ovulation) or by preventing a fertilized ovum from

implanting successfully in the endometrium (i.e., mechanisms that create an unfavorable uterine environment).

Commonly used methods of reversible contraception include oral, transdermal, and vaginal ring contraceptives, injectable and implantable progestins, intrauterine devices (IUDs), condoms, spermicides, diaphragms, cervical caps, sponges, withdrawal, and periodic abstinence.[3–5] These methods differ in their relative effectiveness, safety, and patient acceptability.

The actual effectiveness of any contraceptive method is difficult to determine because many factors affect contraceptive failure. A failure in patients who use the contraceptive agent properly is considered a method failure or perfect-use failure. User failure or typical use failure takes into account the user's ability to follow directions correctly and consistently.[3,4] In a survey of women who had abortions in 2000 to 2001, 46% had not used a contraceptive method in the month they conceived owing to a perceived low risk of pregnancy (33%) and concerns about the use of contraceptives (32%).[6] The male condom was the most commonly used method (28%), with inconsistent use the cited cause of pregnancy in 49% of cases. Oral contraceptives (OCs) were used by 14% of women, 76% of whom reported inconsistent use resulting in pregnancy.[6]

CLINICAL PRESENTATION

For many young women, a major reason for visiting a clinician is to obtain contraception. Clinicians may use this opportunity to provide health maintenance/disease prevention by counseling about reproductive health and sexually transmitted diseases (STDs). Most health maintenance annual visits should include assessment of and counseling about reproductive health. Traditionally, hormonal contraception is provided subsequent to clinical breast and pelvic examinations. However, the need for the physical examination may delay access to contraception, resulting in unintended pregnancies and other health risks. In addition, requiring the breast and pelvic examinations prior to prescription of hormonal contraception reinforces the incorrect perception that these methods of pregnancy prevention are harmful or dangerous. Therefore, the American College of Obstetrics and Gynecology (ACOG) and other national organizations allow provision of hormonal contraception after a simple medical history and blood pressure measurement.[7] Other preventive measures, such as pelvic and breast examinations, provision of the human papillomavirus vaccine, screening for cervical neoplasia, and counseling for prevention of STDs, can be accomplished during routine annual office visits.[8–10]

TREATMENT

DESIRED OUTCOME

The obvious goal of treatment with all methods of contraception is to prevent pregnancy. However, many health benefits are associated with contraceptive methods, including prevention of STDs (with condoms), improvements in menstrual cycle regularity (with hormonal contraceptives), prevention of malignancies and other health conditions (with OCs), and management of perimenopause.[3]

NONPHARMACOLOGIC THERAPY

Periodic Abstinence

1 2 Highly motivated couples may use the abstinence (rhythm) method of contraception, avoiding sexual intercourse during the days of the menstrual cycle when conception is likely to occur. These women rely on physiologic changes, such as basal body temperature and cervical mucus, during each cycle to determine the fertile period. The major reasons for the lack of acceptance are the relatively high pregnancy rates among users and the need to avoid intercourse for several days during each menstrual cycle. To overcome these drawbacks, many women use barrier methods or spermicides during the fertile period.[3,4]

Barrier Techniques

1 2 The effectiveness of barrier methods and spermicides depends almost exclusively on a couple's motivation to use them consistently and correctly.[3,4] These methods include condoms, diaphragms, cervical caps, and sponges (Table 82–1). A major disadvantage is higher failure rates than with most hormonal contraceptives; thus, provision of counseling and an advanced prescription for emergency contraception (EC) are recommended for all patients using barrier methods as their primary means of contraception.

Condoms are devices that create a mechanical barrier, preventing direct contact of the vagina with semen, genital lesions and discharges, and infectious secretions.[3,4] Most condoms in the United States are made of latex rubber, which is impermeable to viruses. A small proportion (5%) are made from young lamb intestine, which is not impermeable to viruses. Condoms are used worldwide as protection from STDs. When condoms are used in conjunction with any other barrier method, their effectiveness theoretically approaches 98%. Spillage of semen or perforation and tearing of the condom can occur, but proper use minimizes these problems.[4] Mineral oil–based vaginal drug formulations (e.g., Cleocin vaginal cream, Premarin vaginal cream, Vagistat 1, Femstat, and Monistat Vaginal suppositories), lotions, or lubricants can decrease the barrier strength of latex by 90% in just 60 seconds, thus making water-soluble lubricants (e.g., Astroglide, K-Y Jelly) preferable.[4] Condoms with spermicides are no longer recommended at all because they provide no additional protection against pregnancy or STDs and may increase vulnerability to human immunodeficiency virus (HIV) infection.[4]

The female condom (Reality) is a prelubricated, soft, loose-fitting polyurethane sheath, closed at one end, with flexible rings at both ends.[3,4] Properly positioned, the ring at the closed end covers the cervix, and the sheath lines the walls of the vagina. The outer ring remains outside the vagina, covering the labia; this may make the female condom more effective than the male condom in preventing transmission of STDs because it protects the labia from contact with the base of the penis. However, the pregnancy rate is reported to be 21% in the first year of use.

The diaphragm, a reusable dome-shaped rubber cap with a flexible rim that is inserted vaginally, fits over the cervix in order to decrease access of sperm to the ovum. The diaphragm requires a prescription from a physician who has fitted the patient for the correct size.[3,4] Its effectiveness depends on its function as a barrier and on the spermicidal cream or jelly placed in the diaphragm before insertion. The diaphragm may be inserted up to 6 hours before intercourse and must be left in place for at least 6 hours afterward. With subsequent acts of intercourse, the diaphragm should be left in place, and a condom should be used for additional protection.[3] Users of diaphragms appear to have a lower incidence of cervical neoplasia, which may be attributed to the adjunctive spermicide and the diaphragm's barrier effect against the human papillomavirus.

The cervical cap is a soft, deep cup with a firm round rim that is smaller than a diaphragm and fits over the cervix like a thimble.[3,4] Currently, two latex-free cervical caps are available by prescription in the United States: the FemCap and the Lea's Shield.[3] The FemCap is available in three sizes and should be filled with spermicide prior to insertion.[3,4] It is held in place against the cervix until the cap is removed. The Lea's Shield is available in only one size and is held in place by the vaginal wall; therefore, cervical size is not a factor.[3] Both caps can be inserted 6 hours prior to intercourse and remain in place for multiple episodes of intercourse without adding more spermicide.

TABLE 82-1 Comparison of Methods of Nonhormonal Contraception

Method	Absolute Contraindications	Advantages	Disadvantages	Percent of Women with Pregnancy[a]	
				Perfect Use	*Typical Use*
Condoms, male	Allergy to latex or rubber	Inexpensive STD protection, including HIV (latex only)	High user failure rate Poor acceptance Possibility of breakage Efficacy decreased by oil-based lubricants Possible allergic reactions to latex in either partner	2	15
Condoms, female (Reality)	Allergy to polyurethane History of TSS	Can be inserted just before intercourse or ahead of time STD protection, including HIV	High user failure rate Dislike ring hanging outside vagina Cumbersome	5	21
Diaphragm with spermicide	Allergy to latex, rubber, or spermicide Recurrent UTIs History of TSS Abnormal gynecologic anatomy	Low cost Decreased incidence of cervical neoplasia Some protection against STDs	High user failure rate Decreased efficacy with increased frequency of intercourse Increased incidence of vaginal yeast UTIs, TSS Efficacy affected by oil-based lubricants Cervical irritation	6	16
Cervical cap (FemCap, Leah's Shield)	Allergy to spermicide History of TSS Abnormal gynecologic anatomy Abnormal Papanicolaou smear	Low cost Latex-free Some protection against STDs FemCap reusable for up to 2 years	High user failure rate Decreased efficacy with parity Cannot be used during menses	9	16[b]
Spermicides alone	Allergy to spermicide	Inexpensive	High user failure rate Must be reapplied before each act of intercourse May enhance HIV transmission No protection against STDs	18	29
Sponge (Today)	Allergy to spermicide Recurrent UTIs History of TSS Abnormal gynecologic anatomy	Inexpensive	High user failure rate Decreased efficacy with parity Cannot be used during menses No protection against STDs	9	16

HIV, human immunodeficiency virus; STD, sexually transmitted disease; TSS, toxic shock syndrome; UTI, urinary tract infection.
[a]Failure rates in the United States during first year of use.
[b]Failure rate with FemCap reported to be 29% per package insert.
Data from Hatcher et al.[3,4] and Dickey.[5]

They should not be worn for more than 48 hours at a time to reduce the risk of toxic shock syndrome. Failure rates are higher than with other methods, perhaps due to difficulty in fitting the cap. Some studies have shown an increased risk of cervical dysplasia, so users must have a repeat Papanicolaou (Pap) smear 3 months after starting to use a cervical cap. Followup data showed no increase in dysplasia at 1 year.[3]

PHARMACOLOGIC THERAPY

Spermicides

1 2 Spermicides, most of which contain nonoxynol-9, are chemical surfactants that destroy sperm cell walls and act as barriers that prevent sperm from entering the cervical os.[4] They are available as creams, films, foams, gels, suppositories, sponges, and tablets.[3,4] Unfortunately, spermicides offer no protection against STDs. In fact, when used frequently (more than two times per day), spermicides containing nonoxynol-9 may increase the risk of transmission of HIV by causing small disruptions in the vaginal epithelium.[11,12] The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) do not promote products containing nonoxynol-9 for protection against STDs. Women at high risk for HIV infection or who are HIV infected should not use spermicides.[3,13]

Spermicide-Implanted Barrier Techniques

1 2 The vaginal contraceptive sponge (Today) is pillow shaped and contains 1 g of the spermicide nonoxynol-9.[4] It has a concave dimple on one side (to fit over the cervix and decrease the risk of dislodgement during intercourse) and a loop on the other side (to facilitate removal). After being moistened with tap water, the sponge is inserted into the vagina up to 6 hours before intercourse. The sponge provides protection for 24 hours, regardless of the frequency of intercourse during this time. After intercourse, the sponge must be left in place for at least 6 hours before removal. Sponges should not be left in place for more than 24 to 30 hours in order to reduce the risk of toxic shock syndrome. After use, sponges should be discarded (they are not effective for reuse). The sponge comes in one size and is available over the counter (OTC).[4]

Hormonal Contraception

Hormonal contraceptives contain either a combination of estrogen and progestin or a progestin alone. OC preparations first became available in the 1960s, but options have expanded to include a transdermal patch, a vaginal contraceptive ring, and long-acting injectable, implantable, and intrauterine contraceptives.

Components Combined hormonal contraceptives (CHCs) work primarily before fertilization to prevent conception. Progestins provide most of the contraceptive effect, by thickening cervical mucus to prevent sperm penetration, slowing tubal motility and delaying sperm transport, and inducing endometrial atrophy. Progestins block the LH surge, therefore inhibiting ovulation. Estrogens suppress FSH release from the pituitary, which may contribute to blocking the LH surge and preventing ovulation. However, the primary role of estrogen in hormonal contraceptives is to stabilize the endometrial lining and provide cycle control.[3–5]

Estrogens. Two synthetic estrogens found in hormonal contraceptives available in the United States, ethinyl estradiol (EE) and mestranol, differ only by the presence of a methyl group attached to

mestranol at the C-3 site. Mestranol, which must be converted by the liver to ethinyl estradiol before it is pharmacologically active, is estimated to be 50% less potent than EE.[3–5] Most combined OCs contain estrogen at doses of 20 to 50 mcg of EE, and the transdermal patch releases approximately 20 mcg of EE daily. The contraceptive ring produces half the serum concentration of EE derived from a 30-mcg OC.[4]

Progestins. Progestins currently used in OCs include desogestrel, drospirenone, ethynodiol diacetate, norgestimate, norethindrone, norethindrone acetate, norethynodrel, norgestrel, and levonorgestrel, the active isomer of norgestrel. The transdermal patch contains norelgestromin, the active metabolite of norgestimate. The vaginal ring contains etonogestrel, the metabolite of desogestrel.[4,5]

Progestins vary in their progestational activity and differ with respect to inherent estrogenic, antiestrogenic, and androgenic effects.[3–5] Estrogenic and antiestrogenic properties are secondary to the extent of progestins' metabolism to estrogenic substances, whereas androgenic activity results from the structural similarity of the progestin to testosterone (receptor binding and activity) and the ability to affect free testosterone concentrations through impact on sex hormone-binding globulin, a major carrier protein for testosterone.[5]

Considerations with Combined Hormonal Contraceptive Use

1 When selecting a CHC, clinicians are challenged by the many formulations, weighing benefits and evaluating potential risks associated with their use. The clinician also must determine if the form of contraception fits the patient's lifestyle and if the patient will be compliant. As previously stated, a complete medical examination and Pap smear are not necessary before a CHC is prescribed. A medical history and blood pressure measurement should be obtained before a patient begins using CHC, and the benefits, adverse effects, and risks should be discussed.[3–5,14,15,16] For example, OCs are associated with numerous noncontraceptive benefits, including relief from menstruation-related problems (e.g., decreased menstrual cramps, decreased ovulatory pain [mittelschmerz], and decreased menstrual blood loss), improvement in menstrual regularity, increased hemoglobin concentrations, and an improvement in acne. Women who take combination OCs have a reduced risk of ovarian and endometrial cancer, which is detectable within 1 year and persists for years after discontinuation. Combination OCs reduce the risk of ovarian cysts, ectopic pregnancy, pelvic inflammatory disease, and benign breast disease. The CHC transdermal patch is convenient because it is applied only once weekly, and it may be associated with less breast discomfort and dysmenorrhea than OCs. The CHC vaginal ring also has the advantage of convenience, being inserted for 3 weeks at a time.

2 3 Adverse effects may hinder compliance and therefore efficacy, so they should be discussed prior to initiating a hormonal contraceptive agent (Table 82–2). Estrogen excess can cause nausea and bloating, and low-dose estrogen CHCs can cause early or midcycle breakthrough bleeding and spotting. Progestins may be associated with fatigue and changes in mood. Low-dose progestin CHCs may cause late-cycle breakthrough bleeding and spotting. Androgenic activity derived from progestins may cause increased appetite and acne.[3–5] The CHC vaginal ring may be uncomfortable and cause some vaginal discharge.

The main safety concern about the use of CHC is their lack of protection against STDs. Because of their high efficacy in preventing pregnancy, patients may choose not to use condoms, which do protect against STDs. In addition to public health awareness, at every office visit clinicians must encourage their sexually active patients to use condoms for prevention of STDs. OCs have an extensive history of safety concerns, which traditionally were related to high-dose estrogen in early pills. To replace the traditional absolute and relative contraindications to the use of OCs, the WHO developed a graded list of precautions for clinicians to consider when they are initiating OCs and other methods of CHC (Table 82–3).[4,13] For specific clarifications and explanations, please refer to the complete WHO document.[13]

TABLE 82-2 Adverse Effects of Combined Hormonal Contraception and Management[a]

Adverse Effects	Management
Estrogen excess	
Nausea, breast tenderness, headaches, cyclic weight gain due to fluid retention	Decrease estrogen content in CHC Consider progestin-only methods or IUD
Dysmenorrhea, menorrhagia, uterine fibroid growth	Decrease estrogen content in CHC Consider extended-cycle or continuous regimen OC Consider progestin-only methods or IUD NSAIDs for dysmenorrhea
Estrogen deficiency	
Vasomotor symptoms, nervousness, decreased libido	Increase estrogen content in CHC
Early-cycle (days 1–9) breakthrough bleeding and spotting	Increase estrogen content in CHC
Absence of withdrawal bleeding (amenorrhea)	Exclude pregnancy Increase estrogen content in CHC if menses is desired Continue current CHC if amenorrhea acceptable
Progestin excess	
Increased appetite, weight gain, bloating, constipation	Decrease progestin content in CHC
Acne, oily skin, hirsutism	Decrease progestin content in CHC Choose less androgenic progestin in CHC
Depression, fatigue, irritability	Decrease progestin content in CHC
Progestin deficiency	
Dysmenorrhea, menorrhagia	Increase progestin content in CHC Consider extended-cycle or continuous regimen OC Consider progestin-only methods or IUD NSAIDs for dysmenorrhea
Late-cycle (days 10–21) breakthrough bleeding and spotting	Increase progestin content in CHC

CHC, combined hormonal contraceptive; IUD, intrauterine device; NSAID, nonsteroidal antiinflammatory drug; OC, oral contraceptive.

[a]CHC regimens should be continued for at least 3 months before adjustments are made based on adverse effects.

Data from Hatcher et al.[3,4] and Dickey.[5]

In addition to the WHO precautions, the ACOG provides information for clinicians to use when selecting CHCs for women with coexisting medical conditions.[16] Overall, the health risks associated with pregnancy, the specific health risks associated with CHCs, and the noncontraceptive benefits of CHCs should be factored into risk-to-benefit considerations.

Women Older Than 35 Years. Generally, CHCs containing less than 50 mcg EE are an acceptable form of contraception for nonsmoking women up to the time of menopause. Population-based case-control studies have not demonstrated an increased risk of myocardial infarction (MI) and stroke in healthy nonsmoking women older than 35 years using low-dose OCs. As women approach the perimenopausal stage, CHCs may confer a benefit with respect to bone mineral density (BMD), reduction in vasomotor symptoms, and reduced risk of endometrial and ovarian cancer. However, these benefits must be weighed against the risk of cardiovascular disease in women with risk factors. If women choose to use hormone therapy, they should switch from CHCs to hormone therapy in the perimenopausal period.[4,16,17]

Smoking. In early studies, OCs with 50 mcg EE or more were associated with MI in women who smoked cigarettes.[4,14,16,17] United States case-control studies have found that both nonsmoking and

TABLE 82-3 World Health Organization Precautions in the Provision of Combined Hormonal Contraceptives (CHCs)

Category 4: Refrain from providing CHCs for women with the following diagnoses

- Thrombophlebitis or thromboembolic disorder, or a history of these conditions
- Cerebrovascular disease, coronary artery disease, peripheral vascular disease
- Valvular heart disease with thrombogenic complications (e.g., pulmonary hypertension, atrial fibrillation, history of endocarditis)
- Diabetes with vascular involvement (e.g., nephropathy, retinopathy, neuropathy, other vascular disease or diabetes >20 years' duration)
- Migraine headaches with focal aura
- Migraine headaches without aura in women ≥35 years old should discontinue CHC
- Uncontrolled hypertension (≥160 mm Hg systolic or ≥90 mm Hg diastolic)
- Major surgery with prolonged immobilization
- Thrombogenic mutations (e.g., factor V Leiden, protein C or S deficiency, antithrombin III deficiency, prothrombin deficiency)
- Breast cancer
- Acute or chronic hepatocellular disease with abnormal liver function, cirrhosis, hepatic adenomas, or hepatic carcinomas
- Age >35 years and currently smoking ≥15 cigarettes per day
- Known or suspected pregnancy
- Breast-feeding women <6 weeks postpartum

Category 3: Conditions may be adversely impacted by CHCs, and the risks generally outweigh the benefits; providers should exercise caution if combined CHCs are used in these situations and carefully monitor for adverse effects

- Multiple risk factors for arterial cardiovascular disease
- Known hyperlipidemia
- Migraine headache without aura in women ≥35 years old
- History of hypertension (systolic 140–159 mm Hg or diastolic 90–99 mm Hg)
- History of cancer, but no evidence of current disease for 5 years
- Cirrhosis, mild and compensated
- Symptomatic gallbladder disease
- Cholestatic jaundice with prior pill use
- Age >35 years and currently smoking <15 cigarettes per day
- Postpartum <21 days, not breast-feeding
- Breast-feeding women 6 weeks to 6 months postpartum
- Commonly used drugs that induce liver enzymes (rifampin, phenytoin, carbamazepine, barbiturates, primidone, topiramate) and reduce efficacy of CHC

Category 2: Some conditions may trigger potential concerns with CHCs, but benefits usually outweigh risks

- Family history of thromboembolism
- Superficial thrombophlebitis
- Uncomplicated valvular heart disease
- Diabetes without vascular disease
- Sickle cell disease
- Migraine headaches without aura in women <35 years old
- Nonmigrainous headaches at any age should discontinue CHC
- Hypertension during pregnancy, resolved postpartum
- Major surgery without prolonged immobilization
- Gallbladder disease (symptomatic and treated by cholecystectomy or asymptomatic)
- Cholestatic jaundice of pregnancy
- Undiagnosed breast mass
- Undiagnosed abnormal genital bleeding
- Cervical intraepithelial neoplasia or cervical cancer
- Obesity (body mass index ≥30 kg/m^2)
- Age <35 years and currently smoking
- Breastfeeding women ≥6 months postpartum
- Age ≥40 years
- Drugs that may induce metabolism of CHC and reduce efficacy (griseofulvin, antiretroviral therapy)

Category 1: Do not restrict use of combined oral contraceptives for the following conditions

- Varicose veins
- History of gestational diabetes
- Nonmigrainous headaches
- Thyroid disease
- Thalassemia
- Iron deficiency anemia
- Depression
- Epilepsy
- Infectious diseases (HIV, schistosomiasis, tuberculosis, malaria)
- Minor surgery without immobilization
- Benign ovarian tumors
- Endometriosis
- Irregular or heavy vaginal bleeding, severe dysmenorrhea
- Sexually transmitted diseases
- Uterine fibroids
- Pelvic inflammatory disease
- Endometrial cancer
- Ovarian cancer
- History of pelvic surgery
- Trophoblast disease
- History of ectopic pregnancy
- Postabortion
- Postpartum women ≥21 weeks, not breast-feeding
- Menarche to 40 years of age
- Drug interactions with antibiotics other than rifampin and griseofulvin

CHC, combined hormonal contraception; HIV, human immunodeficiency virus.
Data from Hatcher et al.,[3,4] Dickey,[5] World Health Organization,[13] Roddey et al.,[14] and Petitti.[16]

smoking women, regardless of age, taking OCs with less than 50 mcg EE did not have an increased risk of MI or stroke. However, these studies included few women older than 35 years who were smokers. European studies, with a higher population of older smoking women, demonstrated an increased risk of MI in this population. Therefore, practitioners should prescribe CHC with caution, if at all, to women older than 35 years who smoke. The WHO precautions further state that smoking 15 or more cigarettes per day by women in this age group is a contraindication to CHC, and that the risks generally outweigh the benefits of CHC in those who smoke fewer than 15 cigarettes per day.[13] Progestin-only contraceptive methods should be considered for women in this group.

Hypertension. CHCs, even those containing less than 35 mcg of estrogen, can cause small increases (i.e., 6–8 mm Hg) in blood pressure.[4,14,16,17] This has been documented in both normotensive and mildly hypertensive women given a 30-mcg EE OC. In case-control studies of women with hypertension, OCs have been associated with an increased risk of MI and stroke. Use of low-dose CHC is acceptable in women younger than 35 years with well-controlled and frequently monitored hypertension. If a CHC-related increase in blood pressure occurs, discontinuing the CHC usually restores blood pressure to pretreatment values within 3 to 6 months.[4] Hypertensive women who have end-organ vascular disease or who smoke should not use CHCs. Women with hypertension who are taking potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or aldosterone antagonists may have increased serum potassium concentrations if they are also using an OC-containing drospirenone (e.g., Yasmin), which has antialdosterone properties.[4] Progestin-only pills and depot medroxyprogesterone acetate (DMPA) have not been shown to increase blood pressure or increase the risk of vascular events in normotensive or hypertensive women and therefore are choices for women with hypertension.

Dyslipidemia. Generally, synthetic progestins adversely affect lipid metabolism by decreasing high-density lipoprotein (HDL) and increasing low-density lipoprotein (LDL).[4,16,17] Estrogens tend to have more beneficial effects by enhancing removal of LDL and increasing HDL levels. Estrogens also may moderately increase triglycerides. As a net result, most low-dose CHCs have no significant impact on HDL, LDL, triglycerides, or total cholesterol. CHCs containing more androgenic progestins (e.g., levonorgestrel) may result

in lower HDL levels in some patients. Although the lipid effects of CHCs theoretically can influence cardiovascular risk, the mechanism of increased cardiovascular disease in CHC users is believed to be due to thromboembolic and thrombotic changes, not atherosclerosis. Women with controlled dyslipidemia can use low-dose CHCs, although periodic fasting lipid profiles are recommended. Women with uncontrolled dyslipidemia (LDL >160 mg/dL, HDL <35 mg/dL, triglycerides >250 mg/dL) and additional risk factors (e.g., coronary artery disease, diabetes, hypertension, smoking, or positive family history) should use an alternative method of contraception.

Diabetes. Any effect of CHCs on carbohydrate and lipid metabolism is thought to be due to the progestin component.[4,17] However, with the exception of some levonorgestrel-containing products, formulations containing low doses of progestins do not significantly alter insulin, glucose, or glucagon release after a glucose load in healthy women or in those with a history of gestational diabetes. The new progestins are believed to have little, if any, effect on carbohydrate metabolism. CHCs do not appear to alter the hemoglobin A_{1c} values or accelerate the development of microvascular complications in women with type 1 diabetes. In the Nurses' Health Study, women who used OCs did not demonstrate any increased risk of developing type 2 diabetes.[17] Therefore, nonsmoking women younger than 35 years with diabetes but no associated vascular disease can safely use CHCs. Diabetic women with vascular disease (e.g., nephropathy, retinopathy, neuropathy, or other vascular disease or diabetes of more than 20 years' duration) should not use CHCs. Copper and progestin-releasing IUDs have not been associated with impaired metabolic control in women with uncomplicated diabetes.

Migraine Headaches. Women in their reproductive years frequently experience headaches, primarily tension headaches. Women with migraine headaches (with and without aura) may experience a decreased or an increased frequency of migraine headaches when using CHCs.[4,14,16,17] Headaches may even occur during the hormone-free interval (during menses). Most studies have demonstrated a higher risk of stroke in women experiencing migraine with aura compared to women with simple migraines (without aura). In population-based studies, the risk of stroke in women with migraines has been elevated twofold to threefold. However, given the low absolute risk of stroke in young women (age <35 years), the ACOG recommends considering CHCs in healthy, nonsmoking women with migraine headaches if they do not have focal neurologic signs.[16] Women of any age who have migraine with aura should not use CHC. Women who develop migraines (with or without aura) while receiving CHC should discontinue use immediately. Progestin-only, intrauterine, or barrier contraceptives should be considered in these patients.

Breast Cancer. Worldwide epidemiologic data from 54 studies in 25 countries (many of which studied high-dose OCs) were collected to assess the relationship between OCs and breast cancer.[17] Overall, investigators noted a small increased risk of breast cancer associated with current or recent use, but OCs did not further increase risk in women with a history of benign breast disease or a family history of breast cancer. A more recent U.S.–based case-control study found no association between overall breast cancer and current or past OC use.[17] This study also found no association between DMPA and breast cancer. Although some studies have found differences in risk of breast cancer based on the presence of *BRCA1* and *BRCA2* mutations, the most recent cohort study found no association with low-dose OCs and the presence of either mutation. Therefore, the choice to use CHCs should not be affected by the presence of benign breast disease or a family history of breast cancer with either mutation. The WHO precautions state that women with a recent personal history of breast cancer should not use CHCs, but that CHCs can be considered in women without evidence of disease for 5 years.[13]

Thromboembolism. Estrogens increase hepatic production of factor VII, factor X, and fibrinogen in the coagulation cascade, therefore increasing the risk of thromboembolic events (e.g., deep-vein thrombosis, pulmonary embolism). These risks are increased in women who have underlying hypercoagulable states (e.g., deficiencies in antithrombin III, protein C, and protein S; factor V Leiden mutations, prothrombin G2010 A mutations) or who have acquired conditions (e.g., obesity, pregnancy, immobility, trauma, surgery, and certain malignancies) that predispose them to coagulation abnormalities.[4,14,16,17] In U.S. case-control studies, the risk of venous thromboembolism (VTE) in women currently using low-dose OCs (<50 mcg EE with norethindrone or levonorgestrel) was four times the risk in nonusers.[4,16,17] However, this risk is less than the risk of thromboembolic events incurred during pregnancy. OCs containing desogestrel have been associated with a 1.7 to 19 times higher risk of VTE than OCs containing levonorgestrel. Some clinicians argue that this difference reflects preferential prescribing of the newer, and perceived safer, progestin products for women at greater risk for VTE. Estrogen exposure in women using transdermal CHC may be greater than that in women taking OCs or using the vaginal contraceptive ring, but the absolute risk of VTE in this population is unknown. Therefore, CHCs are contraindicated in women with a history of thromboembolic events and in those at risk due to prolonged immobilization with major surgery unless they are currently taking anticoagulants. Women with familial coagulopathies are at particular risk during pregnancy, given the risk of VTE and of fetal exposure to warfarin. CHCs reduce menstrual blood loss and are safe for use by women with appropriate anticoagulation. DMPA and levonorgestrel IUDs are also recommended for this population. EC has not been associated with an increased risk of thromboembolic events.

Obesity. As the proportion of women who are obese (body mass index [BMI] >30 mg/kg^2) has increased, the issue of contraception in this population has become more important. Obese women (weight >90 kg) taking OCs or using transdermal contraceptives are at increased risk for contraceptive failure compared to women with a normal BMI.[4,17] These women who use CHCs also are at increased risk of VTE. Because increased pregnancy rates have not been documented in obese women using DMPA as the method of contraception, this or intrauterine methods of contraception should be considered. Given that the intrauterine levonorgestrel system improves dysfunctional uterine bleeding, a particular problem in obese women, and that DMPA may increase irregular bleeding patterns, the levonorgestrel IUD may be preferred for this population.

Systemic Lupus Erythematosus. Contraception is important in women with systemic lupus erythematosus (SLE) because the risks associated with pregnancy are high in this population. Historically, clinicians have thought that CHCs exacerbated the symptoms of SLE.[4,17,18] However, randomized controlled trials have shown that OCs do not increase the risk of flare among women with stable SLE and without antiphospholipid/anticardiolipin antibodies. Because 25% of women with SLE who become pregnant choose to terminate the pregnancy, effective contraception is essential for these patients. CHCs should be avoided in women with SLE and antiphospholipid antibodies or vascular complications; progestin-only contraceptives can be used in this situation.

Sickle Cell Disease. Two controlled trials have demonstrated a reduction in risk of vasoocclusive crises in women with sickle cell disease using DMPA as the method of contraception.[17] Theoretical concerns about the effects of CHCs on platelet activation and red cell deformity, for example, led clinicians to avoid their use in women with sickle cell disease. Because pregnancy carries such a

high risk in this population, contraception with DMPA should be considered.

Oral Contraceptives 1 2 When OCs are used correctly, their effectiveness approaches that of surgical sterilization.[3–5] With perfect use, their efficacy is greater than 99%, but with typical use, up to 8% of women may experience unintended pregnancy.[4] The low-dose combination OCs currently available are modifications of the original products introduced in 1960, containing significantly less estrogen and progestin than the earlier pills.[3–5,14] High-dose formulations were associated with vascular and embolic events, cancers, and significant side effects, but reductions in estrogen and progestin doses have been associated with fewer complications.

Monophasic OCs contain the same amounts of estrogen and progestin for 21 days, followed by 7 days of placebo pills (Table 82–4). Biphasic and triphasic pills contain variable amounts of estrogen and progestin for 21 days, also followed by a 7-day placebo phase. Over the past decade, combination multiphasic formulations have further lowered the total monthly hormonal dose without clearly demonstrating any significant clinical differences.[3,4,14] Monophasic, biphasic, and triphasic OCs attempted to reduce breakthrough bleeding and other side effects, but reviews from the Cochrane Library found no important differences in bleeding patterns based on phasic composition.[19,20]

Extended-cycle pills and continuous combination regimens are new developments that may offer some benefits for patients in terms of side effects. Extended-cycle OCs increase the number of hormone-containing pills from 21 to 84 days, followed by a 7-day placebo phase, resulting in four menstrual cycles per year. One unique product provides hormone-containing pills daily throughout the year.[15] Continuous combination regimens provide OCs for 21 days, then very-low-dose estrogen and progestin for an additional 4 to 7 days (during the traditional placebo phase).

OCs containing newer progestins (e.g., desogestrel, drospirenone, gestodene, and norgestimate) are sometimes referred to as *third-generation* OCs. These progestins are potent progestational agents that appear to have no estrogenic effects and are less androgenic compared with levonorgestrel on a weight basis. Therefore, these agents are thought to have improved side-effect profiles, such as improving mild to moderate acne.[3–5] Drospirenone also has antimineralocorticoid and antialdosterone activities, which may result in less weight gain compared to use of OCs containing levonorgestrel.[3–5] Unfortunately, few clinical trials have compared OCs and sample sizes are small, so the actual relevance of these differences in progestational selectivity and lower androgenic activity remains unknown. For example, a review by the Cochrane Library concluded that there was no evidence supporting a causal association between combination OCs or combination skin patches and weight gain.[21] Table 82–4 lists available OCs products by brand name and specifies hormonal composition.

Also introduced in 1960, the progestin-only "minipills" (28 days of active hormone per cycle) still are available.[3–5,14] Progestin-only pills tend to be less effective than combination OCs and are associated with irregular and unpredictable menstrual bleeding.[3–5] Minipills must be taken every day of the menstrual cycle at approximately the same time to maintain contraceptive efficacy. If a progestin-only pill is taken more than 3 hours late, patients should use a backup method of contraception for 48 hours.[4] Because minipills may not block ovulation (nearly 40% of women continue to ovulate normally), the risk of ectopic pregnancy is higher with their use than with use of other hormonal contraceptives.

Initiating an Oral Contraceptive. 4 Historically, women were instructed to initiate OCs at some point after the next menstrual period occurred, several weeks after childbirth, or after a breast-feeding infant was weaned.[21] However, these recommendations to delay initiation of contraception resulted in many unintended pregnancies. This practice began in an effort to avoid exposing an unknown pregnancy to hormones. Because a large body of evidence shows that combined estrogens and progestins do not cause birth defects, delaying initiation of OCs is unnecessary.

In the "quick start" method for initiating OCs, the patient takes the first pill on the day of her office visit (after a negative urine pregnancy test).[3,4,22] Women should be instructed to use a second method of contraception for at least 7 days and informed that the menstrual period will be delayed until completion of the active pills in the current OC pill pack. The quick start method has been shown to be more successful in getting women to start OCs and to continue using OCs through the third cycle of use. No evidence shows increased bleeding irregularities with this method of OC initiation.

In the first-day start method, women take the first pill on the first day of the next menstrual cycle.[3,4,22] The Sunday start method was the most common method of initiating OCs for years. Women started OCs on the first Sunday after starting the menstrual cycle. Sunday start methods result in "period-free" weekends but may affect compliance if obtaining refills on weekends is difficult.

In the postpartum phase, there is concern about use of OCs because of the mother's hypercoagulability and the effects on lactation. The WHO precautions state that, in the first 21 days postpartum (when the risk of thrombosis is higher), estrogen-containing hormonal contraceptives should be avoided if possible (Table 82–3).[13] If contraception is required during this period, progestin-only pills and IUDs (progesterone or copper) are acceptable choices. Although a review by the Cochrane Library indicated that existing randomized, controlled trials were insufficient to establish an effect of CHC, if any, on milk quality and quantity, the WHO recommends that women who are breast-feeding avoid CHC in the first 6 weeks postpartum.[13,23] WHO precautions cite concerns about hormonal exposure in the newborn and diminished quality and quantity of breast milk due to early exposure to CHCs. Progestin-only pills do not adversely affect milk production, so they can be used after 6 weeks postpartum. Once effective lactation has been established, particularly in women who are not exclusively breast-feeding, estrogen-containing hormonal contraceptives can be safely used.

Choice of Oral Contraceptive. 1 2 Because all combined OCs are similarly effective in preventing pregnancy, the initial choice is based on the hormonal content and dose, preferred pattern of pill use, and coexisting medical conditions (Table 82–3). In women without coexisting medical conditions, an OC containing 35 mcg or less of EE and less than 0.5 mg of norethindrone is recommended (Table 82–4).[5] This strategy is based on evidence that complications and side effects from CHC (i.e., thromboembolic events, stroke, or MI) result from excessive hormonal content.[3–5,14] Adolescents, underweight women (<110 lb [50 kg]), women older than 35 years, and those who are perimenopausal may have fewer side effects with OCs containing 20 to 25 mcg of EE. Risk of noncompliance with OCs is greater in women taking OCs containing less than 35 mcg of EE and thus should be considered, particularly in adolescents. Women weighing more than 160 lb (72.7 kg) may have higher contraceptive failure rates with low-dose OCs and may benefit from pills containing 35–50 mcg of EE. Women with regular heavy menses initially may benefit from a 50-mcg EE OC as well because of their higher endometrial activity. On the other hand, women with regular light menses can be started on 20-mcg EE OCs. Women with oily skin, acne, and hirsutism should be given low androgenic OCs.[5]

Conventional regimens (21 days of active pills, 7 days of placebo) provide predictable menses. Because monophasic OCs may be easier to take, easier to identify and manage side effects, and easier to manipulate to alter the timing of the menstrual cycle, they are preferred over conventional biphasic or triphasic OCs.[3–5] Extended-cycle OCs either eliminate the menstrual cycle or result in only four

TABLE 82-4 Composition of Commonly Prescribed Oral Contraceptives[a]

Product	Estrogen	Micrograms[b]	Progestin	Milligrams[b]	Spotting and Breakthrough Bleeding
50 mcg estrogen					
Necon, Nelova, Norethin, Norinyl, Ortho-Novum 1/50	Mestranol	50	Norethindrone	1	10.6
Norlestrin 1/50	Ethinyl estradiol	50	Norethindrone acetate	1	13.6
Ovcon 50	Ethinyl estradiol	50	Norethindrone	1	11.9
Ovral, Ogestrel	Ethinyl estradiol	50	Norgestrel	0.5	4.5
Demulen 50, Zovia 1/50	Ethinyl estradiol	50	Ethynodiol diacetate	1	13.9
Sub-50 mcg estrogen monophasic					
Alesse, Aviana, Lessina, Levlite	Ethinyl estradiol	20	Levonorgestrel	0.1	26.5
Brevicon, Modicon, Necon, Nortrel 0.5/30	Ethinyl estradiol	35	Norethindrone	0.5	24.6
Demulen, Zovia 1/35	Ethinyl estradiol	37.4	Ethynodiol diacetate	1	37.4
Apri, Desogen, Ortho-Cept	Ethinyl estradiol	30	Desogestrel	0.15	13.1
Levlen, Levora, Nordette, Portia	Ethinyl estradiol	30	Levonorgestrel	0.15	14
Loestrin 1/20 (check)	Ethinyl estradiol	20	Norethindrone acetate	1	29.7
Microgestin 1/20 (check)	Ethinyl estradiol	20	Norethindrone acetate	1	29.7
Loestrin, Microgestin 1.5/30	Ethinyl estradiol	30	Norethindrone acetate	1.5	25.2
Cryselle, Lo-Ovral, Low-Ogestrel	Ethinyl estradiol	30	Norgestrel	0.3	9.6
Necon, Nelova, Norinyl, Norethin, Nortrel, Ortho-Novum 1/35	Ethinyl estradiol	35	Norethindrone	1	14.7
Ortho-Cyclen, Sprintec	Ethinyl estradiol	35	Norgestimate	0.25	14.3
Ovcon-35	Ethinyl estradiol	35	Norethindrone	0.4	11
Yasmin	Ethinyl estradiol	30	Drospirenone	3	14.5
Sub-50 mcg estrogen monophasic extended cycle					
Loestrin-24 FE[c]	Ethinyl estradiol	20	Norethindrone	1	
Lybrel	Ethinyl estradiol	20	Levonorgestrel	0.09	52[e]
Seasonale[d]	Ethinyl estradiol	30	Levonorgestrel	0.15	58.5%[e]
YAZ[c]	Ethinyl estradiol	20	Drospirenone	3	
Sub-50 mcg estrogen multiphasic					
Cyclessa	Ethinyl estradiol	25 (7)	Desogestrel	0.1 (7)	11.1
		25 (7)		0.125 (7)	
		25 (7)		0.15 (7)	
Estrostep	Ethinyl estradiol	20 (5)	Norethindrone acetate	1 (5)	21.7
	Ethinyl estradiol	30 (7)	Norethindrone acetate	1 (7)	
	Ethinyl estradiol	35 (9)	Norethindrone acetate	1 (9)	
Kariva, Mircette	Ethinyl estradiol	20 (21)	Desogestrel	0.15 (21)	19.7
	Ethinyl estradiol	10 (5)	Desogestrel		
Necon, Nelova, Ortho-Novum 10/11	Ethinyl estradiol	35 (10)	Norethindrone	0.5 (10)	17.6
	Ethinyl estradiol	35 (11)	Norethindrone	1 (11)	
Nortrel, Ortho-Novum 7/7/7	Ethinyl estradiol	35 (7)	Norethindrone	0.5 (7)	14.5
	Ethinyl estradiol	35 (7)	Norethindrone	0.75 (7)	
	Ethinyl estradiol	35 (7)	Norethindrone	1 (7)	
Ortho Tri-Cyclen	Ethinyl estradiol	35 (7)	Norgestimate	0.18 (7)	17.7
	Ethinyl estradiol	35 (7)	Norgestimate	0.215 (7)	
	Ethinyl estradiol	35 (7)	Norgestimate	0.25 (7)	
Ortho Tri-Cyclen LO	Ethinyl estradiol	25 (7)	Norgestimate	0.18 (7)	11.5
	Ethinyl estradiol	25 (7)	Norgestimate	0.215 (7)	
	Ethinyl estradiol	25 (7)	Norgestimate	0.25 (7)	
Tri-Norinyl	Ethinyl estradiol	35 (7)	Norethindrone	0.5 (7)	25.5
	Ethinyl estradiol	35 (9)	Norethindrone	1 (9)	
	Ethinyl estradiol	35 (5)	Norethindrone	0.5 (5)	
Sub-50 mcg estrogen multiphasic extended cycle					
Seasonique	Ethinyl estradiol	30 (84)	Levonorgestrel	0.15 (84)	42.5[e]
	Ethinyl estradiol	10 (7)	Levonorgestrel	0.15 (7)	
Progestin only					
Camila, Errin, Micronor, Nor-QD	Ethinyl estradiol	–	Norethindrone	0.35	42.3
Ovrette	Ethinyl estradiol	–	Norgestrel	0.075	34.9

[a]28-day regimens (21-day active pills, then 7-day pill-free interval) unless otherwise noted.
[b]Number in parentheses refers to the number of days the dose is received in multiphasic oral contraceptives.
[c]28-day regimen (24-day active pills, then 4-day pill-free interval).
[d]91-day regimen (84-day active pills, then 7-day pill-free interval).
[e]Percent reporting after 6–12 months of use.
Data from Hatcher et al.,[3,4] Dickey,[5] and Anonymous.[14]

menstrual cycles per year, so they may be associated with less dysmenorrhea and menstrual migraines. Commercially available extended-cycle OCs are available, or monophasic 28 day OCs can be cycled by skipping the 7-day placebo phase for two to three cycles (sometimes referred to as *bicycling* and *tricycling*). With continued use of extended-cycle OCs for 1 year, no significant changes in blood pressure, weight, or hemoglobin compared with cyclic users have been noted. However, long-term studies have not been per-

formed to assess the risk of cancer, VTE, or changes in fertility. Continuous regimens provide a shortened pill-free interval, from the traditional 7 days to 2 to 4 days. These regimens may be beneficial for women with dysmenorrhea and menstrual migraines.

Coexisting medical conditions and their impact on CHC use have been previously addressed. Women with migraine headaches, history of thromboembolic disease, heart disease, cerebrovascular disease, SLE with vascular disease, and hypertriglyceridemia are good candidates for progestin-only methods (pills, DMPA, and the levonorgestrel intrauterine system). Women older than 35 years who are smokers or are obese, or who have hypertension or vascular disease should use progesterone-only methods.[13,17]

Managing Oral Contraceptive Side Effects. 3 Many symptoms occurring with early OC use (e.g., nausea, bloating, breakthrough bleeding) improve spontaneously by the third cycle of use after adjusting to the altered hormone levels.[3–5] However, 59% to 81% of women who stopped OCs in one study did so because of the side effects. Therefore, patient education and early reevaluation (i.e., within 3–6 months) are necessary to identify and manage adverse effects, in an effort to improve compliance and prevent unintentional pregnancies. A list of OC-related side effects and their management is given in Table 82–2.

If the patient has symptoms related to OC use, it is necessary to determine if the symptom indicates the presence or potential development of a serious illness (Table 82–5).[4,5] Patients should be instructed to immediately discontinue CHCs if they experience warning signs, sometimes described as ACHES (abdominal pain, chest pain, headaches, eye problems, and severe leg pain).[4]

CLINICAL CONTROVERSY

There is a widely held belief that antibiotics reduce the efficacy of OCs, increasing the risk of pregnancy. However, few data support this drug interaction with most antibiotics, with the exception of rifampin. Because of this potential risk and considering the fact that OCs are not 100% effective, many practitioners still counsel patients about this issue. The Council on Scientific Affairs at the American Medical Association recommends that women be informed about the small risk of interactions with antibiotics and, if desired, provided with additional nonhormonal contraceptive agents.

Managing Oral Contraceptive Drug Interactions. 3 The effectiveness of an OC is sometimes limited by drug interactions that interfere with gastrointestinal absorption, increase intestinal motility by altering gut bacteriologic flora, and alter the metabolism, excretion, or binding of the OC (Table 82–6).[4,17,24] The lower the dose of hormone in the OC, the greater the risk that a drug interaction will compromise its efficacy. Women should be instructed to use an alternative method of contraception (e.g., condoms) if there is a possibility of a drug interacting altering the efficacy of the OC.[4] Although less well documented, these recommendations generally also apply to patients receiving transdermal and vaginal CHC products.

TABLE 82-5 Serious Symptoms That May Be Associated with Combined Hormonal Contraception

Serious Symptoms	Possible Underlying Problem
Blurred vision, diplopia, flashing lights, blindness, papilledema	Stroke, hypertension, temporary vascular problem of many possible sites, retinal artery thrombosis
Numbness, weakness, tingling in extremities, slurred speech	Hemorrhagic or thrombotic stroke
Migraine headaches	Vascular spasm, stroke
Breast mass, pain, or swelling	Breast cancer
Chest pain (radiating to left arm or neck), shortness of breath, coughing up blood	Pulmonary embolism, myocardial infarction
Abdominal pain, hepatic mass or tenderness, jaundice, pruritus	Gallbladder disease, hepatic adenoma, pancreatitis, thrombosis of abdominal artery or vein
Excessive spotting, breakthrough bleeding	Endometrial, cervical, or vaginal cancer
Severe leg pain (calf, thigh), tenderness, swelling, warmth	Deep-vein thrombosis

Data from Hatcher et al.[4] and Dickey.[5]

TABLE 82-6 Interactions of Oral Contraceptives with Other Drugs

Interacting Drugs	Outcome and Recommendation
Anticonvulsants (barbiturates, including phenobarbital and primidone; carbamazepine; felbamate; phenytoin; topiramate; vigabatrin)	Decreased contraceptive effect Use OCs containing 50 mcg ethinyl estradiol and a second method of contraception or IUD
Griseofulvin (Fulvicin, Grifulvin V, and others)	Possible decreased contraceptive effect Use second method of contraception
Nonnucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine)	Possible decreased contraceptive effect Use IUD
Protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir)	Increased or decreased contraceptive effect Use IUD
Rifampin	Decreased contraceptive effect Use second method of contraception or alternate method (IUD) if concomitant use is long term

IUD, intrauterine device; OC, oral contraceptives.
Data from Hatcher et al.,[4] World Health Organization,[13] ACOG Practice Bulletin,[17] Dickenson et al.,[24] and Archer and Archer.[25]

Several reviews of the interaction between antibiotics and OCs have documented a true pharmacokinetic interaction with rifampin in which the efficacy of OCs is impaired. Pharmacokinetic studies of other antibiotics have not shown any consistent interaction, but case reports of individual patients have shown a reduction in EE levels when OCs are taken with tetracyclines and penicillin derivatives.[24,25] The ACOG states that ampicillin, doxycycline, fluconazole, metronidazole, miconazole, fluoroquinolones, and tetracyclines do not decrease steroid levels in women taking OCs.[17] The Council on Scientific Affairs at the American Medical Association recommends that women taking rifampin should be counseled about the risk of OC failure and advised to use an additional nonhormonal contraceptive agent during the course of rifampin therapy. The council also recommends that women be informed about the small risk of interactions with other antibiotics, and, if desired, appropriate additional nonhormonal contraceptive agents should be considered. In addition, women who develop breakthrough bleeding during concomitant use of antibiotics and OCs (and other CHCs) should be advised to use an alternate method of contraception during the period of concomitant use.[24]

Women receiving anticonvulsants for a seizure disorder require special attention with regard to hormonal contraception. Some anticonvulsants (mainly phenobarbital, carbamazepine, phenytoin) induce the metabolism of estrogen and progestin, inducing breakthrough bleeding and potentially reducing contraceptive efficacy. In addition, some anticonvulsants (i.e., phenytoin) are known teratogens. Use of condoms in conjunction with high-estrogen OCs or IUDs can be considered for these women.[17]

Patient Instructions with Oral Contraceptives. 4 Many women who take OCs are poorly informed about the proper use of these medications. The patient first should be given the package insert that accompanies all estrogen products and instructed to read it carefully. The written information in the package insert should be

supplemented with verbal information describing the way the medication works (primarily by thickening cervical mucus to prevent sperm penetration), both common and serious side effects, and management of side effects (Table 82–4). Although several transient self-limiting side effects often occur, the patient should be aware of the danger signals that require immediate medical attention (Table 82–5). The benefits and risks should be discussed in terms that the patient can understand, including the fact that OCs provide no physical barrier to the transmission of STDs, including HIV. Detailed instructions on when to start taking the OC, such as the "Quick Start" method, should be provided. Patients should be told the importance of routine daily administration to ensure consistent plasma concentrations and improve compliance, and specific instructions should be given regarding what to do if a pill is missed (Table 82–7). Use of an additional contraceptive method is advisable if the patient misses taking a pill or experiences severe diarrhea or vomiting for several days. Important drug interactions should be discussed. The patient taking combination OCs should expect her menses to start within 1 to 3 days after taking the last active pill. She should start another pack of pills immediately after finishing a 28-day pack (no days between) or 1 week after finishing the previous 21-day pack, even if her menses is not completed.[3–5]

Discontinuing Oral Contraceptives and Return of Fertility. The average delay in ovulation after discontinuing OCs is 1 to 2 weeks, but delayed ovulation is more common in women with a history of irregular menses. Post-OC amenorrhea rarely lasts 6 months.[3–5] Traditionally, women are counseled to allow two to three normal menstrual periods before becoming pregnant to permit the reestablishment of menses and ovulation. However, in several large cohort and case-control studies, infants conceived in the first month after discontinuation of an OC had no greater chance of miscarriage or being born with a birth defect than those born in the general population.

TABLE 82-7 Recommendations for Missed Oral Contraceptive Doses

Number of Pills Missed	Week in Which Pills Were Missed	Recommendation	Use of 7-Day Back Up Method
1	1	Take two pills as soon as possible Finish the pill pack Use emergency contraception if necessary	Yes
1	2–3	Take two pills as soon as possible Finish the pill pack	No
1	4	Skip placebo pills Finish the pill pack	No
2–4	1	Take two pills as soon as possible[a] Finish the pill pack Use emergency contraception if necessary	Yes
2–4	2	Take two pills as soon as possible[a] Finish the pill pack Use emergency contraception if necessary	Yes
2–4	3	Start a new pill pack[a]	No
2–4	4	Skip placebo pills Finish the pill pack	No
5	Any	Take two pills as soon as possible Start a new pill pack Use emergency contraception if necessary	Yes

[a]Alternative recommendation is to take one of the missed pills every 12 hours until caught up, then continue the rest of the pill pack.
Data from Hatcher et al.[3,4] and Dickey.[5]

Transdermal Contraceptives 1 2 A CHC is available as a transdermal patch (Ortho Evra), which includes 0.75 mg of EE and 6 mg of norelgestromin, the active metabolite of norgestimate.[3–5] Comparative trials have shown the transdermal patch to be as effective as combined OCs in patients weighing less than 90 kg (198 pounds). Of the 15 pregnancies reported in the clinical trials, five were among women weighing more than 198 lb (90 kg); therefore, this product is not recommended as a first-line option for these women.[3,4,26] Some patients experience application-site reactions, but other side effects are similar to those experienced with OCs (e.g., breast discomfort, headache, and nausea).

3 A warning from the manufacturer states that women using the patch are exposed to approximately 60% more estrogen than from a typical OC containing 35 mcg of EE, due to the transdermal system eliminating first-pass metabolism. Whether this increased estrogen exposure leads to increased cardiovascular or thromboembolic events is unclear. The Ortho Evra package insert provides preliminary data indicating a higher incidence of thromboembolic events with the patch.[26] Another case-control study compared the patch to a 35-mcg norgestimate-containing OC and found no significant difference in thromboembolism occurrence.[27] Currently, the Food and Drug Administration (FDA) is monitoring this risk because more consistent data are needed.

The patch should be applied to the abdomen, buttocks, upper torso, or upper arm at the beginning of the menstrual cycle and replaced every week for 3 weeks (the fourth week is patch-free).[3,4] The patch releases estrogen and progestin for 9 days. If the woman forgets to change her patch or restarts the active patches after the ninth day, a backup method should be used for 7 days. Approximately 5% of patches will need to be replaced because they become partly detached or fall off altogether, so single replacements are available. If the patch is detached for more than 24 hours, a new 4-week cycle should be restarted and backup method used for 7 days.[3,4] Users have demonstrated greater compliance with the patch than with an OC, but whether this results in reduced pregnancy rates remains to be seen.[28] The benefits of compliance must be weighed against of the risk of increased estrogen exposure and possibility of thromboembolic events.

Vaginal Rings 1 2 The vaginal ring containing EE and etonogestrel (NuvaRing) currently is the only product available using vaginal delivery for hormonal contraception.[29] It is a 54-mm flexible ring, 4 mm in thickness.[3] Over a 3-week period, the ring releases approximately 15 mcg/day of EE and 120 mcg/day of etonogestrel. Comparative trials have shown the vaginal ring to be as effective as combined OCs. On the first cycle of use, the ring should be inserted on or before the fifth day of the menstrual cycle, remain in place for 3 weeks, then removed for 1 week to allow for withdrawal bleeding. The new ring should be inserted on the same day of the week as it was during the last cycle, similar to starting a new OC pack on the same day of the week. A second method of contraception should be used if the ring has been expelled accidentally for more than 3 hours.[3,29]

3 Side effects, precautions, and contraindications for use of the hormonal ring are similar to those for all CHCs. The most commonly reported reasons for discontinuation of use were device-related issues, such as foreign-body sensation, device expulsion, and vaginal symptoms. Cycle control with the vaginal ring appears to be as good as or better than with combined OCs, with a low incidence of breakthrough bleeding and spotting after the second cycle of use, presumably due to increased compliance and release of steady levels of estrogen and progestin.[29,30] Patient acceptability of the delivery system has been studied, and the majority of women do not complain of discomfort in general or during intercourse.[31]

The ring should be inserted vaginally. In contrast to diaphragms and cervical caps, precise placement is not an issue because the estrogen and progestin are absorbed anywhere in the vagina.

Women should be in a comfortable position, and compress the ring between the thumb and index finger and push it into the vagina. There is no danger of inserting the ring too far because the cervix will prevent it from traveling up the genital tract. Removal of the ring is performed in a similar manner; pulling it out with the thumb and index finger, and discarding into the foil patch (the ring should not be flushed down the toilet).[29] Patients should be discouraged from douching, but other vaginal products, including antifungal creams and spermicides, can be used.[3,4,29]

Long-Acting Injectable and Implantable Contraceptives Steroid hormones provide long-term contraception when injected or implanted into the skin. Progestins are used in existing injectable and implantable contraceptives.[3–5] Sustained progestin exposure blocks the LH surge, thus preventing ovulation. Should ovulation occur, progestins reduce ovum motility in the fallopian tubes. Even if fertilization occurs, progestins thin the endometrium, reducing the chance of implantation. Progestins also thicken the cervical mucus, producing a barrier to sperm penetration. These long-acting methods of contraception do not provide any protection from STDs.

1 2 Women who particularly benefit from progestin-only methods are those who are breast-feeding, those who are intolerant to estrogens (i.e., have a history of estrogen-related headache, breast tenderness, or nausea), and those with concomitant medical conditions in which estrogen is not recommended (Table 82–3). Additionally, injectable and implantable contraceptives are beneficial for women with compliance issues. Pregnancy failure rates with long-acting progestin contraceptives are comparable to the rates with female sterilization.[3–5] Reports have stated an increased risk of ectopic pregnancies while using progestin-only methods, but no evidence supports this finding with use of recent injectable and implantable products.

Injectable Progestins. 1 2 Medroxyprogesterone acetate is similar in structure to naturally occurring progesterone. DMPA 150 mg (Depo-Provera) is administered by deep intramuscular injection in the gluteal or deltoid muscle within 5 days of onset of menstrual bleeding and inhibits ovulation for more than 3 months.[32] Additionally, a new formulation approved by the FDA contains 104 mg of DMPA (Depo-SubQ Provera 104), which is injected subcutaneously into the abdomen or thigh.[33] With perfect use, the efficacy of DMPA is more than 99%; however, with typical use, 3% of women experience unintended pregnancy.[4] Although these injections may inhibit ovulation for up to 14 weeks, the dose should be repeated every 3 months (12 weeks) to ensure continuous contraception. The manufacturer recommends excluding pregnancy in women with a lapse of 13 or more weeks between injections for the intramuscular formulation or 14 or more weeks between injections for the subcutaneous formulation. Depo-Provera is available as a 150 mg/mL injection vial or prefilled syringe and Depo-SubQ Provera 104 is available as a prefilled syringe.[32,33]

Although no adverse effects have been documented in infants exposed to DMPA through breast milk, the manufacturer recommends not initiating DMPA until 6 weeks postpartum in breast-feeding women. Women who are not breast-feeding but require contraception can receive DMPA immediately postpartum.[13,32] Women with sickle cell disease are good candidates for DMPA, as studies have demonstrated a reduction in sickle cell pain crises in women using DMPA.[13] In addition, women with seizure disorders may experience fewer seizures when taking DMPA for contraception.[4] The subcutaneous DMPA formulation has been FDA approved for treatment of endometriosis-associated pain.[33] The incidence of *Candida* vulvovaginitis, ectopic pregnancy, and pelvic inflammatory disease, as well as endometrial and ovarian cancer, is decreased in women using DMPA for contraception compared with women using no contraception.[3,32]

Because return of fertility may be delayed after discontinuation of DMPA, it should not be recommended to women desiring pregnancy in the near future. The median time to conception from the first omitted dose is 10 months. Sixty-eight percent of women will be able to conceive within 12 months, 83% within 15 months, and 93% within 18 months of the last injection.[32,33]

3 Menstrual irregularities, including irregular, unpredictable spotting or, more rarely, continuous heavy bleeding, are the most frequent adverse effects of both formulations of DMPA. In some cases, bleeding is severe enough to cause a significant drop in hemoglobin. Women who cannot tolerate prolonged bleeding may benefit from a short course of estrogen (e.g., 7 days of 2-mg estradiol or 1.25-mg conjugated estrogen given orally).[3,4] The incidence of irregular bleeding decreases from 30% in the first year to 10% thereafter. After 12 months of therapy with either formulation, 55% of women report amenorrhea, with the incidence increasing to 68% after 2 years.[32,33] Bleeding patterns after 1 year of the subcutaneous formulation have not been established.[33,34]

Other adverse effects, including breast tenderness, weight gain, and depression, occur less commonly (<5%). However, data suggest that DMPA may actually improve depression, and use of DMPA in women with depression may be appropriate with close monitoring.[13] Weight gain averages 1 kg annually and may not resolve until 6 to 8 months after the last injection.[32,33]

CLINICAL CONTROVERSY

Both formulations of DMPA have a black box warning that addresses the association between DMPA use and decreased BMD, specifically in adolescent and young women. The clinical significance of this finding is unknown, and current evidence suggests osteoporosis or fractures do not occur more frequently in women who use DMPA. Many clinicians have adopted the policy, recommended by the manufacturer, of dual-energy x-ray absorptiometry (DXA) studies to monitor BMD. In contrast, WHO and ACOG guidelines recommend against the use of DXA in short- and long-term DMPA users due to the limited clinical utility of monitoring BMD in this population.

Concern has been raised over DMPA use and the development of osteoporosis because DMPA suppresses ovarian production of estradiol and has been associated with a reduction in BMD.[4,17] However, DMPA has not been associated with the development of osteoporosis or fractures, and discontinuation of DMPA results in return to baseline BMD values within 12 to 30 months. In 2004, the FDA added a black box warning to DMPA, recommending continued use of more than 2 years only if other contraceptive methods were inappropriate.[17,32,33] However, current data do not provide a clear rationale for this time limit, as evidence suggests the rate of BMD loss may slow after 1 to 2 years of DMPA use.[35]

Many clinicians have adopted the policy, recommended by the manufacturer, of DXA studies to monitor BMD in DMPA users. Bone loss with DMPA can be prevented by providing supplemental estrogen (0.625-mg conjugated equine estrogen daily or 5-mg intramuscular estradiol cypionate), but because reductions in BMD have not been linked to the development of osteoporosis, the utility of this finding is questionable. In addition, most women use DMPA because they are unable to use estrogen-containing contraceptives, or adolescents use DMPA because of compliance issues. The WHO does not recommend a restriction on the use of DMPA in women aged 18 to 45 years and states that the benefits of use outweigh the potential risks.[36] Appropriate counseling regarding prevention of osteoporosis should be provided for women using DMPA, including the use of 1,200 to 1,500 mg of elemental calcium plus 400

international units of vitamin D and a regular regimen of weight-bearing exercise.[3]

Subdermal Progestin Implants. 1 2 Norplant, developed by the Population Council, was the first subdermal progestin implant approved for use in the United States in 1990.[4] The Norplant contraceptive system was a set of six implantable, nonbiodegradable, soft silicone rubber capsules, each filled with 36-mg crystalline levonorgestrel, that provided continuous contraception for up to 5 years. Although extremely effective, Norplant was removed from the U.S. market in 2003 due to difficulty with insertion and removal.

Implanon is the progestin implant currently available in the United States.[37] Implanon is a single 4-cm-long implant, containing 68 mg of etonogestrel, that is placed under the skin of the upper arm using a preloaded inserter.[37,38] Implanon releases etonogestrel at a rate of 60 mcg daily for the first month, then decreases to an average of 30 mcg daily at the end of the 3 years of recommended use. Etonogestrel suppresses ovulation in 97% of cycles. When ovulation is not suppressed, etonogestrel still is effective as the progestin thickens the cervical mucus and produces an atrophic endometrium. With perfect use, efficacy approaches 100% but may be reduced in women weighing more than 130% of their ideal body weight. Because only one rod is used, the difficulties experienced with insertion and removal of Norplant hopefully will be avoided.

4 The etonogestrel implant should be inserted between days 1 and 5 of the menstrual cycle in women who have not previously used hormonal contraception.[37,38] Women currently taking OCs can have the implant inserted within 7 days after taking the last active OC tablet. Women currently taking progestin-only pills should have the implant inserted without skipping any days, on the same day that the progestin-only IUD is removed, or on the day that the DMPA injection is due. After removal, fertility returns within 30 days.

3 The major adverse effect associated with Implanon is irregular menstrual bleeding, which led to discontinuation of the implant in 11% of patients in clinical trials.[37,38] Like the bleeding pattern seen with other progestins, some women (22%) became amenorrheic with continued use, but many continued to have prolonged bleeding and spotting (18%) and frequent bleeding (7%). Other adverse effects include headache, vaginitis, weight gain, acne, and breast and abdominal pain. Implanon does not appear to affect BMD. Concomitant administration of drugs that induce hepatic enzymes (Table 82–6) may decrease the efficacy of etonogestrel, necessitating use of a different method of contraception while these potentially interacting drugs are used. Implanon is contraindicated in women who are pregnant or have active liver disease, a history of thromboembolic events, or a history of breast cancer.

Implanon is a unique implantable contraceptive agent that provides enhanced compliance and prolonged efficacy. Therefore, it may be a good choice for women with a history of noncompliance, who do not plan to have children for at least 3 years, and who have estrogen-related adverse effects or contraindications. Because fertility returns soon after removal and Implanon does not affect bone health, it may be preferred over DMPA. Women should be counseled about the risk of irregular bleeding patterns so that patients will not request early removal of Implanon.

Intrauterine Devices

1 2 The low-grade intrauterine inflammation and increased prostaglandin formation caused by IUDs and endometrial suppression caused specifically by the progestin-releasing IUD appear to be primarily spermicidal, although interference with implantation is a backup mechanism.[3,4,39] Efficacy rates with IUDs are greater than 99% with both perfect and typical use.[4] Although increasing in popularity, the IUD still has several contraindications. The risk of pelvic inflammatory disease among IUD users ranges from 1% to 2.5%. Because the increased risk of infection appears to be related to introduction of bacteria into the genital tract during IUD insertion, the risk is highest during the first 20 days after the procedure.[40] Ideal patients for IUD use include nulligravid women who are monogamous and are not at risk for STDs or pelvic inflammatory disease. Two IUDs currently are marketed in the United States; all are T-shaped and are medicated, one with copper (ParaGard) and one with levonorgestrel (Mirena).[3,4]

3 ParaGard provides better contraceptive effectiveness than previous copper devices and can be left in place for 10 years.[3,4] A disadvantage of ParaGard is increased menstrual blood flow and dysmenorrhea; average monthly blood loss among users increased by 35% in clinical trials. Initially, Mirena releases 20 mcg of levonorgestrel daily, but release decreases to 10 mcg daily over the 5 years of use.[3,4,39] Systemically absorbed levonorgestrel is minimal and considerably less than with OCs. However, the levonorgestrel IUD produces its effects locally via suppression of the endometrium, causing a reduction in menstrual blood loss. In contrast to the copper IUD, menstrual flow in users of the levonorgestrel IUD is decreased, and development of amenorrhea has been observed in 20% of users in the first year and 60% in the fifth year. A disadvantage of the levonorgestrel IUD is increased spotting in the first 6 months of use, and women should be counseled that the spotting will decline gradually over time.[3,4,39]

IUDs should be considered because they require no compliance once inserted and result in immediate return of fertility once removed. The levonorgestrel IUD is a good choice for women with menorrhagia or dysmenorrhea because of its benefits with regard to menstrual blood loss. IUDs, in general, are an alternative for women who cannot tolerate estrogen-containing contraceptive agents.

CLINICAL CONTROVERSY

Pharmacists who refuse to fill valid prescriptions for emergency contraception have been highly publicized in the media. Position statements published by the American Pharmaceutical Association and American College of Clinical Pharmacy support pharmacists' rights to decline filling a valid prescription if doing so conflicts with moral, ethical, or religious beliefs. However, it is the pharmacists' professional responsibility to refer the patient to another pharmacist who will fill the prescription in a timely, confidential, and nonjudgmental manner so that no harm is caused to the patient.

Emergency Contraception

5 EC is used to prevent unwanted pregnancy after unprotected sexual intercourse (e.g., condom breakage, diaphragm dislodging, or sexual assault). Higher doses of combined estrogen and progestin or progestin-only containing products can be used.[3–5] Insertion of copper IUD is an option, although it is not an FDA approved or a widely used method of EC. Exact mechanisms of action of oral EC are being studied and vary according to the product used. EC may prevent the fertilized egg from implanting into the endometrium; however, studies contradict this potential mechanism. Additional mechanisms include impaired sperm transport and corpus luteum function. Pregnancy occurs when the fertilized egg is implanted into the endometrial lining. After intercourse, implantation of the fertilized egg typically takes approximately 5 days. Oral EC will not disrupt the fertilized egg after implantation has occurred.[40,41] Currently, one progestin-containing pill is approved and marketed specifically for EC in the United States. Commercially available OCs in specific dosages can be used as an alternative.[3–5,41]

Plan B is the only product specifically approved for EC and is the regimen of choice. It contains two white tablets, each containing

0.75 mg of levonorgestrel. The first dose is taken within 72 hours of unprotected intercourse (although the sooner, the more effective); the second dose is taken 12 hours later.[3–5,41–43] One study found that 1.5 mg of levonorgestrel (two tablets of Plan B) taken as a single dose was as effective as taking the doses 12 hours apart and did not cause an increased incidence of adverse effects. Although this single-dose regimen is not FDA approved, it is a reasonable option, especially in women who may not be compliant with the two-dose regimen.[41,44] Plan B was approved by the FDA in 2006 for OTC sales to women 18 years of age or older. A prescription is required for patients aged 17 years and younger. It is sold only in pharmacies and must be stocked behind the counter. Patients must provide proof of age prior to purchasing the product. The manufacturer is continuing its efforts in gaining OTC status for provision to minors.[45]

Despite the availability of Plan B, use of regular combined contraceptives for EC (i.e., Yuzpe method) still is permissible, although some studies suggest that they may not be as effective and may be associated with more adverse effects.[41,42] Specifically, the FDA has declared the following regimens containing the progestins norgestrel and levonorgestrel safe and effective methods of EC: Ovral (two tablets per dose); Nordette, Levlen, Levora, Lo/Ovral, Triphasil, Tri-Levlen, or Trivora (four tablets per dose); and Alesse or Levlite (five tablets per dose).[3–5,41] Additionally, regular progestin-only pills can be used as EC, but many tablets must be taken (i.e., Ovrette, 20 tablets per dose).[3,4,41] Patients should be counseled to take the appropriate number of tablets as soon as possible after unprotected sexual intercourse and to repeat the dose in 12 hours.

The efficacy of all EC regimens declines if they begin more than 72 hours after intercourse.[3,4,41] However, one study suggests that EC may still be effective when used up to 120 hours after intercourse and should be considered in some women when use is delayed.[41,46] It is recommended that women have an advanced prescription on hand to maximize the effectiveness of EC.

Common adverse effects include nausea, vomiting, and irregular bleeding. Nausea and vomiting occur significantly less when Plan B is administered. If the Yuzpe method is prescribed, antiemetics given 1 hour before the dose is taken may be warranted. Many women will experience irregular bleeding regardless of which EC method is used, with the menstrual period usually occurring 1 week before or after the expected time. No current data regarding the safety of repeated use EC are available, but current consensus suggests the risks are low, and women can receive multiple regimens if warranted. Pharmacists have a key role in providing patient counseling regarding EC. Appropriate counseling should be provided regarding timing of the dose, common adverse effects, and use of a regular contraceptive method (backup barrier methods should be used after EC for at least 7 days).[41]

PHARMACOECONOMIC CONSIDERATIONS

More than half of all pregnancies in the United States are unintended.[4] Not all unintended pregnancies are unwanted; many are just "mistimed." Nevertheless, the United States has a higher rate of induced abortions than most other industrialized western nations. Whatever method is used, preventing unintended pregnancy is highly cost effective. With regard to the acquisition cost of reversible contraception, spermicides alone are the least expensive method, followed by use of spermicides with condoms. The diaphragm and cervical cap (with spermicide) are midrange in cost; the female condom is slightly more expensive than the other female barrier methods. Injectable and implantable methods (Depo-Provera, Implanon, ParaGard, Mirena) carry a higher initial cost that can be prohibitive for some women, and the annual cost is greater if the products are removed prior to their expiration. OCs, the contraceptive patch, and the vaginal ring are the most expensive forms of reversible contraception. These cost estimates are based on the assumption of 100 acts of intercourse annually. However, with regard to direct medical costs (e.g., method use, side effects, and unintended pregnancies) over 5 years, IUDs, vasectomy, Depo-Provera, and now Implanon are the most cost effective. OCs are more cost effective than methods with high failure rates (e.g., barrier methods, spermicides, withdrawal, and periodic abstinence), but even these methods are more cost effective than no method.[47]

EVALUATION OF THERAPEUTIC OUTCOMES

4 Patients should receive both verbal and written instructions on the chosen method of contraception. Followup appointments can increase compliance, allow time for the patient to ask questions, and provide opportunities to address other health maintenance issues (e.g., self-breast examination, Pap smears, human papillomavirus vaccines, STD risk).[4]

At least annual blood pressure monitoring is recommended for all users of CHC. When a patient with a history of glucose intolerance or overt diabetes mellitus begins or discontinues the use of CHC, glucose levels must be monitored closely for deterioration of the condition. Contraceptive users should receive at least annual (more frequent if they are at risk for STDs) cytologic screening. Women should undergo annual examination for clinical problems possibly relating to the CHC (e.g., breakthrough bleeding, amenorrhea, weight gain, and acne).

Women using Implanon should be monitored annually for menstrual cycle disturbances, weight gain, local inflammation or infection at the implant site, acne, breast tenderness, headaches, and hair loss. Women using DMPA should be asked at 3-month followup visits about weight gain, menstrual cycle disturbances, and STD risks. Patients taking DMPA should be weighed, undergo blood pressure checks, and receive annual examinations as indicated based on the patient's age.

Choosing a contraceptive method most suited to the patient's needs will reduce significantly the chance of unintended pregnancy. A medical and sexual history and a thorough physical examination are essential when evaluating the various methods available. Understanding the risks and precautions associated with the methods available is essential for both patients and clinicians.

ABBREVIATIONS

ACOG: American College of Obstetrics and Gynecology
BMD: bone mineral density
BMI: body mass index
CDC: Centers for Disease Control and Prevention
CHC: combined hormonal contraception
DMPA: depot medroxyprogesterone acetate
DXA: dual-energy x-ray absorptiometry
EC: emergency contraception
EE: ethinyl estradiol
FDA: Food and Drug Administration
FSH: follicle-stimulating hormone
GnRH: gonadotropin-releasing hormone
hCG: human chorionic gonadotropin
HDL: high-density lipoprotein
HIV: human immunodeficiency virus
IUD: intrauterine device
LDL: low-density lipoprotein