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Contraceptive Technology

Eighteenth Revised Edition

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Combined Hormonal Contraceptive Methods

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- More than 100 million women throughout the world currently rely on oral contraceptives (OCs). In the United States, more than 80% of women born since 1945 have used OCs at some time in their lives, compared to 95% of French women and 4% of Japanese women. In Canada, 70% of pill users over the age of 35 have been taking OCs for more than 10 years.[1]
- OCs effectively prevent pregnancy. Of 1,000 women taking pills perfectly, only 3 will become pregnant within a year. Of 1,000 typical users initiating OC use, 80 women (8%) will become pregnant in the first year of use. However, failure rates as high as 10% to 20% have been reported.[2] Women on pills may find it reassuring to use a back-up contraceptive consistently.
- Dual protection with both condoms and any combined hormonal contraceptive will provide some protection against infection as well as excellent protection against an unintended pregnancy. A woman who misses hormonal pills, or is late starting a new cycle of pills, should consider using a back-up contraceptive until she has taken 7 consecutive pills. Emergency contraceptive pills are also an option for any woman who has missed one or more pills.
- The newer combined hormonal methods—the monthly vaginal ring and weekly patches—were developed to combine the effectiveness and noncontraceptive benefits of combined pills with longer acting delivery systems in order to reduce the demands placed by daily administration of pills.

Forty years ago, "the pill" transformed family planning by providing women with an effective method to control their own fertility for the first time in history. Over the years, the doses of the sex steroids in oral contraceptive (OC) preparations have decreased, which increased both their safety and their acceptability. In addition, numerous noncontraceptive benefits have been identified with both short- and long-term OC use.

Newer hormonal methods—the once-a-month vaginal contraceptive ring and the once-a-week transdermal contraceptive patch—are now available and combine the obvious attractiveness of OCs with longer-acting delivery systems to reduce the demands imposed by daily administration.

This chapter describes combined hormonal contraceptives: methods that contain both estrogen and progestin. Because all of these methods share the same mechanisms of action, the chapter begins with a discussion of how sex steroids influence the reproductive cycle. The effectiveness and cost sections compare OCs, the patch, and the ring. Following these reviews, each combined hormonal method is presented in detail.

MECHANISMS OF ACTION

Combined hormonal contraceptives work primarily as a contraceptive, acting before fertilization. The progestins in all combined hormonal contraceptives provide most of the birth control activity:

- Thicken cervical mucus to prevent sperm penetration into the woman's upper genital tract
- Block the luteinizing hormone (LH) surge and thus inhibit ovulation. Although there are no precise statistics concerning the occurrence of "escape ovulation" in oral contraceptive users, the incidence in earlier higher dose pills was estimated in 1980 to be around 2%.[3] Breakthrough ovulation is probably higher in current lower dose pills. In a study of 20 mcg pills, progesterone levels indicative of luteinization and ovulation were found in 2 of 24 women (8.3%).[4]
- Inhibit capacitation of the sperm, which limits the sperm's ability to fertilize the egg
- Slow tubal motility, which may delay sperm transport

Some progestin effects additionally alter the environment that would be required for embryogenesis to proceed:

- Disrupt transport of the fertilized ovum
- Induce endometrial atrophy, change underlying vascular function and structure and alter the metalloproteinase content in the endometrium

Estrogen is included in combined hormonal methods primarily to provide better cycle control (see below), but it may also boost contraceptive efficacy. Pharmacologic doses of estrogen from combined hormonal contraceptives decrease follicle-stimulating hormone (FSH) release from the pituitary, which may aid in suppressing the LH surge and thus in blocking ovulation (contraception). Estrogen at high doses may induce localized edema in the endometrial lining, which, in turn, may reduce the probability of implantation (interception); however, the clinical significance of this impact is not clear.

HORMONES IN COMBINED HORMONAL CONTRACEPTIVES

Estrogens

Only two estrogenic compounds are used in hormonal contraceptives available in the United States: ethinyl estradiol (EE) and mestranol. The patch, ring, and virtually all modern OC formulations contain EE. Mestranol, which must be metabolized into EE by the liver, is found only in a few 50 mcg pills. (Because 50 mcg of mestranol is equivalent to 35 to 40 mcg of EE, avoid using 50 mcg mestranol-containing pills when high-dose estrogen pills are needed.) The patch and vaginal ring also release EE. Only the combined injection (Lunelle), which is no longer on the market, used a different estrogen (see Chapter 24, Future Methods).

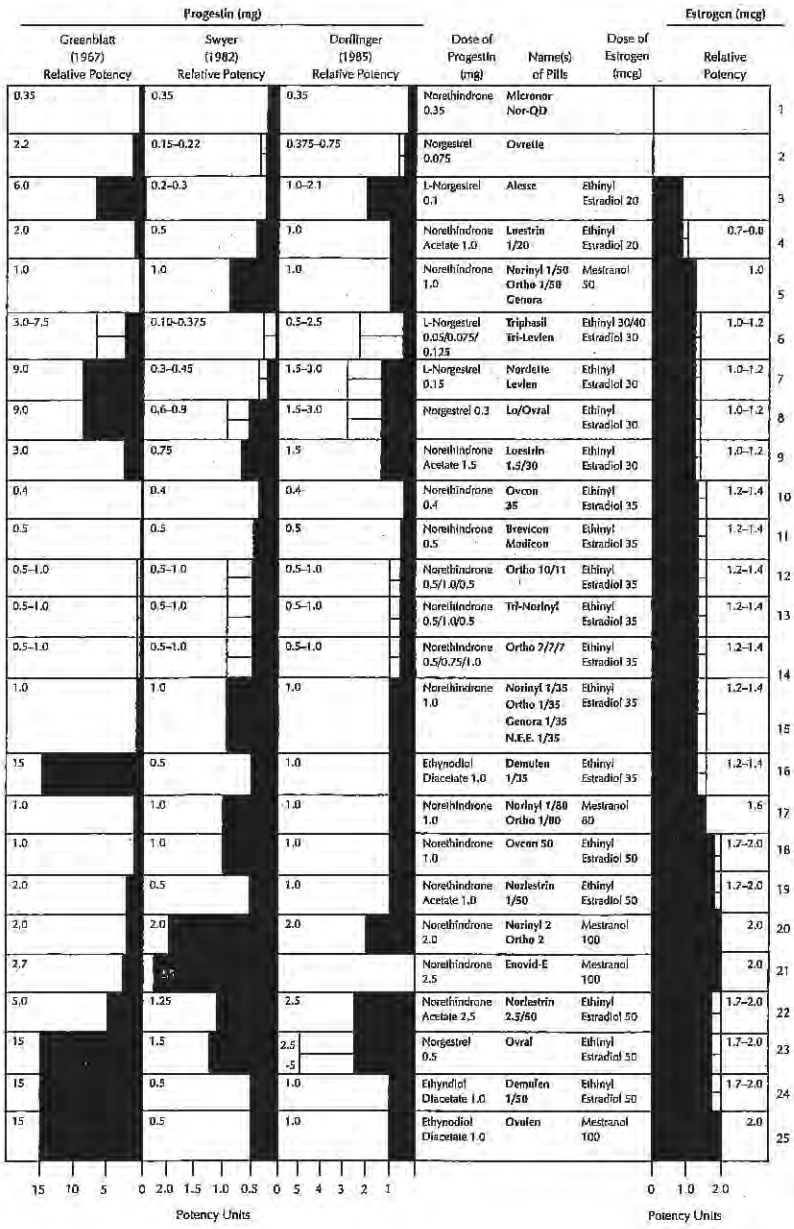
Doses of estrogen in active OCs vary from 20 to 50 mcg per day (see Figure 19-1 for a sample of pills). The transdermal contraceptive patch releases about 20 mcg EE into circulation each day. The vaginal contraceptive ring has serum levels of 15 mcg/cc of EE, or about half the circulating levels associated with that of a comparable 30 mcg OC.[5]

Progestins

In order to maintain adequate serum concentrations of progestogenic activity for daily administration, an array of progestins was developed. There are currently nine different progestins available in OCs and three other progestins in the other combined hormonal systems. The power of a particular progestin results not only from its intrinsic potency, but also from the dose that is used. Each compound has a different potency and a different balance between progesterone activity and any residual androgenicity.

In OCs, the androgen-derived compounds include norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, norethynodrel, desogestrel, and norgestimate. OCs containing the last two are sometimes called "third-generation pills." (Other androgen-derived compounds, such as gestodene, are not available in the United States.) One new OC contains a new class of compound: drospirenone, derived from the antihypertensive compound spironolactone. Drospirenone has both anti-androgenic and anti-mineralocorticoid activity. Doses of progestins in OCs vary from 0.15 to 1 mg (see Figure 19-1).

The patch contains norelgestromin, the primary active metabolite of norgestimate, the progestin found in three OCs: Ortho-Cyclen, Ortho Tri-Cyclen, and Ortho Tri-Cyclen LO. About 150 mcg of norelgestromin is released into the circulatory system each day. The ring releases 120 mcg a day of etonogestrel, the metabolite of the progestin desogestrel found in Cyclessa and Mircette OCs. Because the bioavailability of the progestins in the patch and the vaginal ring is higher than that of OC progestins, a lower dose can produce similar serum levels. Lower doses are effective.



	Greenblatt (1967) Relative Potency	Swyer (1982) Relative Potency	Dorflinger (1985) Relative Potency	Dose of Progestin (mg)	Name(s) of Pills	Dose of Estrogen (mcg)	Relative Potency	
1	0.35	0.35	0.35	Norethindrone 0.35	Micronor Nor-QD			
2	2.2	0.15–0.22	0.375–0.75	Norgestrel 0.075	Ovrette			
3	6.0	0.2–0.3	1.0–2.1	L-Norgestrel 0.1	Alesse	Ethinyl Estradiol 20		
4	2.0	0.5	1.0	Norethindrone Acetate 1.0	Loestrin 1/20	Ethinyl Estradiol 20	0.7–0.8	
5	1.0	1.0	1.0	Norethindrone 1.0	Norinyl 1/50 Ortho 1/50 Genora	Mestranol 50	1.0	
6	3.0–7.5	0.10–0.375	0.5–2.5	L-Norgestrel 0.05/0.075/ 0.125	Triphasil Tri-Levlen	Ethinyl 30/40 Estradiol 30	1.0–1.2	
7	9.0	0.3–0.45	1.5–3.0	L-Norgestrel 0.15	Nordette Levlen	Ethinyl Estradiol 30	1.0–1.2	
8	9.0	0.6–0.9	1.5–3.0	Norgestrel 0.3	Lo/Ovral	Ethinyl Estradiol 30	1.0–1.2	
9	3.0	0.75	1.5	Norethindrone Acetate 1.5	Loestrin 1.5/30	Ethinyl Estradiol 30	1.0–1.2	
10	0.4	0.4	0.4	Norethindrone 0.4	Ovcon 35	Ethinyl Estradiol 35	1.2–1.4	
11	0.5	0.5	0.5	Norethindrone 0.5	Brevicon Modicon	Ethinyl Estradiol 35	1.2–1.4	
12	0.5–1.0	0.5–1.0	0.5–1.0	Norethindrone 0.5/1.0/0.5	Ortho 10/11	Ethinyl Estradiol 35	1.2–1.4	
13	0.5–1.0	0.5–1.0	0.5–1.0	Norethindrone 0.5/1.0/0.5	Tri-Norinyl	Ethinyl Estradiol 35	1.2–1.4	
14	0.5–1.0	0.5–1.0	0.5–1.0	Norethindrone 0.5/0.75/1.0	Ortho 7/7/7	Ethinyl Estradiol 35	1.2–1.4	
15	1.0	1.0	1.0	Norethindrone 1.0	Norinyl 1/35 Ortho 1/35 Genora 1/35 N.E.E. 1/35	Ethinyl Estradiol 35	1.2–1.4	
16	15	0.5	1.0	Ethynodiol Diacetate 1.0	Demulen 1/35	Ethinyl Estradiol 35	1.2–1.4	
17	1.0	1.0	1.0	Norethindrone 1.0	Norinyl 1/80 Ortho 1/80	Mestranol 80	1.6	
18	1.0	1.0	1.0	Norethindrone 1.0	Ovcon 50	Ethinyl Estradiol 50	1.7–2.0	
19	2.0	0.5	1.0	Norethindrone Acetate 1.0	Nuelestrin 1/50	Ethinyl Estradiol 50	1.7–2.0	
20	2.0	2.0	2.0	Norethindrone 2.0	Norinyl 2 Ortho 2	Mestranol 100	2.0	
21	2.7	2.5		Norethindrone 2.5	Enovid-E	Mestranol 100	2.0	
22	5.0	1.25	2.5	Norethindrone Acetate 2.5	Norlestrin 2.5/50	Ethinyl Estradiol 50	1.7–2.0	
23	15	1.5	2.5 -5	Norgestrel 0.5	Ovral	Ethinyl Estradiol 50	1.7–2.0	
24	15	0.5	1.0	Ethynodiol Diacetate 1.0	Demulen 1/50	Ethinyl Estradiol 50	1.7–2.0	
25	15	0.5	1.0	Ethynodiol Diacetate 1.0	Ovulen	Mestranol 100	2.0	

Potency Units: 15 10 5 0 | 2.0 1.5 1.0 0.5 0 | 5 4 3 2 1

Potency Units: 0 1.0 2.0

Sources: Dorflinger (1985); Greenblatt (1967); Swyer (1982); Heinen (1971).

Figure 19-1 Relative potency of estrogens and progestins in selected oral contraceptives reflecting the debate about the strength of the progestins

EFFECTIVENESS

In general, combined OCs, patches, and vaginal rings belong in the second tier of contraceptive effectiveness, having higher failure rates than IUDs, implants, and injections.

Oral Contraceptives

Among women who use OCs correctly and consistently, not missing any pills and following instructions perfectly, only about 3 in 1,000 (0.3%) are expected to become pregnant within the first year. (See Table 19-1.) The first-year failure rates among typical users as observed in real world use are estimated to be 8% (see Chapter 9, The Essentials of Contraception). This means that 1 woman in 12 will become pregnant in the first year of OC use. Among these typical users, pill-taking mistakes that increase the length of the hormone-free interval are particularly likely to lead to failures. The conventional 7-day pill-free interval may also play an important role in the pill's failures. Ultrasound studies have demonstrated that by the 7th placebo pill day, 23% of women can have ovarian follicles that measure at least 10 mm in diameter.[6] If a woman misses pills early in her pack of pills, it may be much more difficult to suppress ovulation and protect against pregnancy during that cycle. Thus, OCs may be made more effective by eliminating or shortening the pill-free interval (see Starting The Pill section). Confusing this picture, however, is a recent small-scale study showing that initiation of pills early in the cycle did not reduce the risk of ovulation.[7] Larger scale studies are underway to answer this question.

Many pregnancies occur when women discontinue OCs, fail to begin another method of contraception and, therefore, have unprotected intercourse. Studies show that 11% of women discontinue their pills in the first month of use, and 19% of those who discontinue fail to adopt a new method.[8] By 6 months, 28% of pill users have stopped the pill; by one year, that percentage approaches 33% to 50%.[9] Quite disturbingly, 42% of women who discontinued OC use did so *without* consulting their clinicians. Because of these concerns, women starting the pill should also be given a second method they can implement on their own should they discontinue pill use before returning for follow-up. Instruct women in as much detail about their second method as you do their pills, and encourage them to practice using it. Also, provide new-start OC patients with a packet of or prescription for emergency contraception (Plan B) or, at a minimum, inform her about its availability.

Recently, one retrospective study has suggested that heavier women may experience higher failure rates than do lighter women.[10] The greatest difference in failure rates was seen in the use of pills with less than 35 mcg EE, with which heavier women were noted to have 4.5 (1.4 - 14.4) times higher pregnancy rates (6.8% vs. 1.8%) than did lighter women. These

results have not yet been substantiated by any other studies. Consensus is that it is not prudent to prescribe higher dose pills based on these preliminary data because of the increased risk of thrombosis with high doses of estrogen.[11] Heavier women who used extended cycles of OCs had no increase in pregnancy risk.[12]

Transdermal Patch and Contraceptive Ring

The patch and the vaginal ring have not been in use long enough to permit precise measurements of typical-use failure rates. In comparative trials, the failure rates for patches, vaginal rings, and OCs were low[13,14] and roughly equivalent. Successful utilization rates were statistically higher with the longer acting agents than with the pills that were taken daily. Overall, women who used the patch or vaginal ring were more likely to use their methods correctly and consistently for 13 cycles than were OC users.[15,16] These observations suggest that, in routine practice, the newer long-acting delivery systems may be associated with lower typical-use pregnancy rates than are the pills. However, since this tantalizing possibility has not yet been demonstrated, the authors have decided to quote the same typical failure rates for the pill, the patch, and the vaginal ring (see Chapter 9, The Essentials of Contraception).

One group of potential patch users deserves special counseling. Heavier women, weighing >198 lbs, comprised 3% of the study population but experienced 30% of all the pregnancies in the clinical trial.[17] This decrease in efficacy does not preclude use of the patch by heavier women but does suggest that these women may benefit from additional counseling,[18] including recommending back-up contraception.

Table 19-1 First-year probability of pregnancy* for women using combined hormonal contraceptives compared with other hormonal contraceptives

Method	% of Women Experiencing an Unintended Pregnancy Within the First Year of Use		% of Women Continuing Use at One Year
	Typical Use	Perfect Use	
Combined pill and minipill	8	0.3	68
Evra Patch and Nuva Ring	8**	0.3	68
Depo-Provera	3	0.3	56
IUD			
Paragard (Copper T)	0.8	0.6	78
Mirena (LNG-IUS)	0.1	0.1	81

* See Table 9-2 for pregnancy year failure rates of all methods.
** No data available; assumed to be same as combined oral contraceptives.

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%. (See Chapter 12 for more information.)

COST

Health department family planning programs in Washington State have paid much less for OCs than for other hormonal contraceptives. In 2001, they reported paying $1.35 per cycle of combined pills, just over one third of the cost of Depo-Provera. In Washington, the discounted cost of OCs to health departments is about 1/20th of the price charged to a private pharmacy chain.[19] The cost of the pills to women paying full price at pharmacies varies somewhat but is becoming higher all the time, ranging from $15 to $50 or even higher per cycle. Generic brands are typically less expensive. Usually, pills cost from $30 to $35 per cycle, one ring costs $40, and a pack of 3 patches (one cycle) costs $42. This means women paying full price pay $390 to $455 per year out of pocket for OCs, just over $500 for the ring and about $550 for the patch. Women whose contraceptives are covered by insurance have to pay a co-pay each month. Purchase of OCs from the Internet, when 3 cycles are bought at a time, can reduce the price to under $20 per cycle with delivery charges extra. Some women travel to Mexico to purchase pills over-the-counter for as little as $3 to $5 per cycle.

ORAL CONTRACEPTIVES

OCs are safe and effective for the vast majority of reproductive-aged women. They are the most extensively studied medications in the history of medicine. Over 80% of U.S. women born after 1945 have used the pill at some time.[1] In the United States, OCs are available only by prescription; in some other countries, they are available over the counter. The keys to successful and safe OC use are selection of appropriate OC candidates, patient motivation, and effective counseling.

Oral Contraceptive Formulations

OCs are available in either monophasic or multiphasic packaging:

- **Monophasic formulations.** Each active pill contains the same doses of the estrogen and progestin.
- **Multiphasic formulations.** The amounts of hormones in the active pills can vary throughout the cycle.
  - — Biphasic pills have 2 different combinations of estrogen and progestin in the pills.
  - — Triphasic formulations have 3 different combinations. Sometimes the progestin content increases in stepwise progression during the cycle, but some other formulations may also alter the amounts of estrogen given during the cycle. One formulation (Estrostep) holds the progestin dose constant and increases the estrogen content in tablets late in the cycle.

Most pill packs contain 21 active (hormone containing) pills with or without 7 placebo pills (21-pill packs versus 28-pill packs). However, one

brand (Mircette) includes 21 active pills, 2 placebo pills and 5 pills with 10 mcg EE each. Another preparation (Seasonale) has 84 active pills followed by 7 placebo pills, which reduces the number of withdrawal bleeds to 4 episodes a year. Under development are preparations containing 24 active pills and 4 placebo pills per pack.

ADVANTAGES AND INDICATIONS

Many women harbor profound misinformation about the safety and utility of OCs. A 2000 survey revealed that 41% of those interviewed believed the pill was associated with significant health hazards.[20] However, OCs have numerous attractive features:

General Advantages

1. **Effectiveness.** When taken correctly and consistently, OCs are very effective contraceptives that give women control over their own fertility.
2. **Safety.** Through prudent selection of users (see below), OCs are safer for a woman's health than are pregnancy and delivery. Recent large-scale studies show that OC use does not increase the risk of death among non-smokers.[21]
3. **An option throughout the reproductive years.** Healthy women can safely use OCs throughout their reproductive lives. Age itself is not a reason to avoid OCs. The noncontraceptive benefits of the pill meet the varying needs of women of all ages. Young women may benefit from reduction in severe dysmenorrhea and acne, while at the other end reproductive life, perimenopausal women may benefit from cycle control and hot flash reduction provided by OCs.
4. **Rapid reversibility.** On average, women who stop taking OCs have only a 2-week delay in return of ovulation. Some women (<3%) have a slower return to fertility—the so-called "post-pill amenorrhea"—that is diagnosed 6 months after stopping the pills. Women need to understand that OC use neither hastens nor delays the onset of menopause.

Contraceptive health benefits

1. **Reduction of maternal deaths.** The CDC calculated that there were 11.8 pregnancy-related deaths per 100,000 live births in the last decade of the 20th century, but that there was significant under-reporting.[22] Embolism, hemorrhage, and pregnancy-induced hypertension were the 3 leading causes of death. Considering that nearly half the pregnancies in this country are unintended, prevention of those pregnancies could significantly decrease maternal deaths.

2. **Reduction of ectopic pregnancies.** OCs reduce the risk of ectopic pregnancy by over 90%.[23–25] At least one in 80 pregnancies in the United States is an ectopic pregnancy, the leading cause of maternal death in the first trimester. The CDC reports that 25 women died of ectopic pregnancy in 1992.

Menstrually-related health benefits

1. **Decreased dysmenorrhea.** OCs significantly decrease menstrual cramps and pain. Although the original studies used high-dose formulations, even low-dose formulations help when given in the conventional cyclic fashion.[26] OC use reduces the incidence of all degrees of dysmenorrhea by 60%.[27] Severe dysmenorrhea was reduced by almost 90%.[28] In a randomized clinical trial, low-dose OC users reported fewer absences from school and work and used less pain relief medicine than placebo users. More significant relief of symptoms can be achieved by continuous or extended use, which eliminates withdrawal periods for prolonged periods of time.

2. **Decreased menstrual blood loss.** OCs decrease the number of days of bleeding and the amount of blood women lose each cycle. In women with menorrhagia, high-dose OC use reduced blood loss by 53%.[29] In more recent studies with low dose OCs (30 mcg EE), menstrual blood loss and duration of flow were also decreased.[30] Overall, a 38% to 49% reduction in menstrual blood loss was seen in another study with a 30 mcg EE preparation.[31,32] In addition, nearly 50% of women experience a reduction in duration of menstrual bleeding with OC use.[33] Decreased menstrual blood loss reduces a woman's risk for iron deficiency anemia. If women use any of the extended cycle options, the number of withdrawal bleeds decreases, enhancing these benefits even more.

3. **Reduction in menstrually-related PMS symptoms.** OCs can reduce menstrually-related PMS symptoms such as mastalgia, bloating, cramping, and pain. Drospirenone-containing pills have also been shown to improve symptoms of water retention, negative affect, and increased appetite associated with menses.[34,35]

4. **Decreased anovulatory bleeding.** Low-dose OC use was associated with a more than 80% improvement in dysfunctional uterine bleeding in a randomized, double blind, placebo-controlled study.[36]

5. **Mittelschmerz relief.** By preventing ovulation, OCs can eliminate the midcycle pain some women experience with ovarian follicle swelling and oocyte extrusion.

6. **Fewer ovarian cyst problems.** Because OCs suppress ovulation, they reduce the risk of hemorrhagic corpora luteal cysts, a condition which can require surgery. Because OCs decrease stimulation of the ovaries by FSH and LH, the incidence of other functional ovarian cysts among women using high-dose OCs was also reduced. Low-dose and multiphasic formulations may help reduce postovulatory cysts;[37,38] however, they do not protect against follicular cyst formation.[39,40]

7. **Improvement in menstrual migraines.** Menstrual migraines are caused by estrogen withdrawal. Cyclic OC use may worsen the intensity of a woman's migraine during her menses; on the other hand, menstrual migraine symptoms may be prevented if she takes active pills every day continuously. (See the section on Headaches, in Managing Side Effects.)

General health benefits

1. **Endometrial and ovarian cancer risk reductions.** When compared with women who have never used OCs, OC users are 40% less likely to develop epithelial ovarian cancer.[41] Ten years or more of use of all monophasic formulations reduces a woman's risk of developing such cancers by 80%.[42] This protection lasts for up to two decades beyond the time the woman takes her last OC.[42,43] Studies that focus on the newer lower dose formulations (<35 mcg EE) have found similar protection levels[43] even in women genetically at higher risk for developing ovarian cancer (BRCA1 mutation cancers).[43,44] Formulations with high doses of progestins protected more than twice as well as OCs with a lower dose of progestins.[45] Women with a family history of ovarian cancer enjoy a greater benefit of ovarian cancer risk reduction than women with no family history.[46] Women with first-degree relatives with ovarian cancer who use OCs for 4 years had a 90% reduction in ovarian cancer risk.[47] One study found that increased duration of OC use did not reduce further the risk of ovarian cancer in BRCA1 or BRCA2 mutation carriers and cautioned against routine use of OCs for chemoprevention.[48] On the other hand, current information has led some to suggest that OCs should be offered to women at high risk for ovarian cancer even if contraceptive benefit is not required.[49]

   OC use for at least 12 months reduces a woman's risk of developing endometrial cancer by about 40%.[50] That risk reduction is increased to 80% in women who use OCs for at least a decade.[41] This protection also endures for up to 20 years after OC discontinuation.[51]

2. **Decreased risk of benign breast conditions.** OC users are less likely to develop fibrocystic breast changes, cysts, or fibroadenoma and are less likely to experience progression of those breast

conditions.[52] In one case-controlled study with over 500 women, the risk of benign breast conditions was lower in the OC users, and significantly less in women who started OC use before their first full-term pregnancy.[53] Women who have hyperplasia with atypia are a notable exception; OC use does not confer any protection to these women.[54]

3. **Improvement of androgen sensitivity or androgen-excess conditions** (e.g., polycystic ovary syndrome). In prospective, randomized, placebo-controlled, double-blind trials, women who use OCs have been shown to have a reduction in the numbers and size of acne lesions.[55,56] Dutch surveys reported that OC use reduced the prevalence of acne by over two-thirds.[57] Only 2 formulations have received FDA approval for treatment of mild to moderate acne (OrthoTri-Cyclen and Estrostep), but other formulations with little or no androgenicity and relatively high estrogenicity increase sex hormone binding globulin (SHBG), which is understood to be the main mechanism for OC use in acne treatment. Women with excessive facial or body hair (hirsutism) have reduction in the hair shaft diameter with OC use.[58,59]

4. **Reduced risk of hospitalization for gonorrheal PID.** The risk of cervical gonorrhea infection spreading into the uterus (endometritis), fallopian tubes (salpingitis) or other pelvic organs (PID) is reduced. In studies conducted in the 1980s, when fewer women with PID were treated on an outpatient basis, the risk of hospitalization for PID was reduced by 50% to 60% in current users after 12 months of use.[61] The exact mechanism of this protection is not known. It may be due to thickened cervical mucus blocking sperm penetration, atrophy of the endometrium (fewer days of bleeding), and/or reduction of movement of pathogens into the tube. Similar reductions are not seen in the risk of chlamydial PID.[60]

5. **Suppression of endometriosis.** Current or recent OC use is associated with a lower incidence of symptomatic endometriosis, especially among parous women (see Chapter 6, Menstrual Problems and Common Gynecologic Concerns).[62] The risk of endometrioma was found to be significantly reduced in current OC users over age 25.[63] OCs reduce menstrual flow and presumably decrease retrograde menses, which is generally believed to contribute to endometriosis. Women who have endometriosis can be treated with extended or continuous use of strong progestogenic OCs to induce pseudo-decidualization of the endometriotic implants and to reduce symptoms during use.[64] Such treatment is not curative, however; the implants undergo atrophy during treatment but remain ready for reactivation when OCs are stopped.[65]

6. **Decrease risk of iron deficiency anemia.** By reducing menstrual blood loss, women increase their hemoglobin and ferritin

levels.[66] This benefit is especially important for women with sickle cell anemia or Von Willebrand's disease, women using anticoagulants or anticonvulsants, and women with fibroids or other causes of primary or secondary menorrhagia (see Chapter 6, Menstrual Problems and Common Gynecologic Concerns).

7. **Treatment of hot flashes and other hormonal fluctuation symptoms** in perimenopausal women.[67,68] (See Chapter 5 on Menopause for more discussion.)

Other potential health benefits

1. **Reduced risk of developing rheumatoid arthritis** (RA). Although early studies suggested that OC use was associated with a reduced risk of RA, there is still controversy about this benefit. One meta-analysis suggested that instead of protecting against the condition, OC use slowed progression of RA,[69] and a later metaanalysis found no protective effect.[70]

2. **Reduced risk of uterine fibroids.** OC users have fewer fibroids, especially with long-term use,[71] but use early in life may increase risk.[72] OCs may control menorrhagia due to uterine myoma. In fact, in many settings, women with moderate-sized fibroids must fail to respond to medical management for menorrhagia (usually with OCs) before they can be considered for surgery.

3. **Reduced risk of fractures.** The impact OC use has on the risk for fracture is still under question. Studies have shown a lower risk for postmenopausal hip fractures,[73] increased bone mineral density (BMD) especially in the lumbar spine,[74] and a slight reduction in osteoporosis.[75] However, one prospective study reported an increased risk of osteoporosis.[76] A comprehensive review of 13 studies of low-dose OCs use found 9 studies showed favorable impact on BMD, and 4 were neutral.[77] If there is a benefit, it may only be in at-risk women with low estrogen levels. OC use increases BMD in young women with hypothalamic amenorrhea.[78] OC use in women with osteopenia due to anorexia nervosa is not sufficient to protect bone, but when added to anabolic agents such as insulin growth factor (IGF), OC use significantly improves that agent's effectiveness.[79] OC use modulates the negative impact of smoking in young women and improves BMD in young women with irregular menses.[80]

4. **Favorable impact on lipids.** EE increases HDL cholesterol and reduces LDL cholesterol. Progestins diminish the magnitude of this favorable impact; the more androgenic formulations have a more pronounced negative effect. Although triglyceride levels increase somewhat with estrogen-containing contraception, there is little concern because those remnants are not atherogenic. However, estrogen-containing contraceptives should be avoided

if their use will be anticipated to raise triglyceride levels to 500 mg/dl and place the woman at risk for pancreatitis.

5. **Improved lung mechanics.**[81]
6. **Possible reduced risk for colorectal cancer.**[82]
7. **Influence on sexual enjoyment.** OC use may increase sexual pleasuring, either by increasing libido (less concern about pregnancy) or increasing lubrication. On the other hand, some OC users report decreased libido and more vaginal dryness.
8. **Fewer episodes of seizures, porphyria, and asthma.** These conditions may worsen during a woman's menses. Continuous use of OCs can prevent these problems for months at a time.
9. **Vitamin fortification.** Iron has been added to some placebo pills at the end of the cycle. Work is underway to add 400 mcg of folic acid to both active and placebo pills. Iron deficiency is associated with anemia, and maternal folic acid deficiency contributes to neural tube defects in offspring.

INDICATIONS

Considering the wide range of benefits OCs offer, their use can be particularly attractive for women who desire reversible contraception and have hormone-related problems. It should be noted that OCs might be beneficial in treatment of some of the following conditions (after underlying pathology has been ruled out), even if the woman is not at risk for pregnancy:

- Heavy, painful, irregular menstrual bleeding, or menorrhagia (dysmenorrhea, oligomenorrhea)
- Dysfunctional uterine bleeding
- Recurrent luteal phase ovarian cysts
- Family history of ovarian cancer
- Personal risk for endometrial cancer
- Acne or hirsutism
- Polycystic ovary syndrome (PCOS)

In addition, extended use OC may be particularly helpful for women with

- Premenstrual symptoms (PMS)
- Endometriosis
- Mentally challenged women whose monthly menstruations terrify them and provide a hygiene challenge to their caregivers.
- Anemia due to menorrhagia
- Dysmenorrhea

Finally, OCs with levonorgestrel or norgestrel may be used for emergency contraception. New studies suggest that OCs with norethindrone may be used for emergency contraception if the more effective formulations are not available (see Chapter 12 on Emergency Contraception).[83]

DISADVANTAGES AND HEALTH COMPLICATIONS

Inform women that OC use may be associated with some disadvantages, many of which can be overcome or managed. Consult the section on Managing Side Effects. Some disadvantages are also discussed in the section on Special Issues.

General Disadvantages

1. **Daily administration.** Inconsistent or incorrect use of OCs reduces protection from the risk of pregnancy and increases the incidence of side effects, such as breakthrough bleeding.
2. **Expense and access.** In many states, insurance plans are not required to cover contraception, so women must pay for their OCs. Often, women are required to return to pharmacies each month to purchase another package. The mismatch between calendar months with 30 to 31 days and pill packs with only 28 pills can present challenges in use.
3. **Need for storage and ready access.** Adolescent women or women whose partners do not want them to use contraception may not have a place to hide their pills. Practitioners need to confirm that the patient's plans for storage are realistic (school lockers are not an answer) and guide them to more private contraceptive methods, if needed. Homeless women and women who travel extensively may have difficulty storing their pill packs.
4. **No protection against STIs.** Women at risk for STIs may use OCs, but they should be advised to reduce their risk for infection by confining their activity to mutually monogamous, uninfected partners, or by using condoms with every act of coitus.

Health Complications

1. **Myocardial infarction (MI).** A pivotal U.S. study showed that low-dose OCs (<50mcg EE) do not significantly increase the risk of MI or stroke in healthy, non-smoking women.[84] Compared to never-users, current users as a group had a relative risk of 1.3 for MI; most of the increased risk was seen in women with known risk factors. A second study supported those findings.[85] Recent metaanalysis of the literature demonstrated that overall current use of OCs increased the risk of MI by 2.48 times. Pills with 20 mcg EE did not increase the risk of MI.[86] Large increases, by

factors of 7 to more than 100, have been observed in the relative risk (RR) of MI and ischemic stroke among OC users who also smoke or have hypertension.[87] The attributable risk of death from cardiovascular disease from low-dose OC use is 0.06 per 100,000 nonsmokers age 15 to 34 and 3.0 per 100,000 nonsmokers aged 35 to 44. However, the risk of death attributable to OC use by low-risk women of any age is less than their risk of mortality from pregnancy.[88]

In an interesting analysis of those data, it was observed that nearly 75% of cases of MI could be attributed to smoking.[89] The third-generation OCs showed no increase in the risk of MIs, but the second-generation formulations apparently doubled the risk.[86] The increase in heart attacks seen with use of combined hormonal contraceptives is due to arterial thrombosis caused by estrogen. This is why women with underlying atherosclerotic coronary vessel damage from smoking, hypertension, and hyperlipidemia are more vulnerable. The effect is reversible. After women stop taking the pill, their risks for MI return to baseline. Once women over age 40 have stopped smoking for 3 to 12 months, they may be candidates for OC use if they have no other contraindications. Women with risk factors for MI may still be candidates for progestin-only methods.

2. **Stroke in high-risk women.** In 2002, a World Health Organization (WHO) panel found no significant increased risk of ischemic or hemorrhagic stroke among nonsmoking women with no history of migraine headaches who use low-dose (<35 mcg EE) OCs,[90] as did a subsequent study.[91] However, OC users who smoke or are hypertensive have a three-fold risk of hemorrhagic stroke compared to those who do not have those risk factors. WHO studies found a significant increase in the risk of ischemic stroke, but not hemorrhagic stroke, among OC users who experienced migraine with aura (odds ratio 3.0, CI 1.3–11.3) and a nonsignificant increase in OC users who reported migraine without aura (OR 3.0, CI 0.7–148) (see Headache section in Managing Side Effects, below).[92] The WHO panel stated that migraineurs with aura have a higher risk of stroke than those without aura, but no study had sufficient proof to examine risk of stroke by type of migraine.[93] There is no difference between second- and third-generation formulations.[94] OC patient package inserts state that the relative risk of hemorrhagic stroke associated with OC use is reported to be 1.2 for non-smokers, 7.6 for smokers, and 25.7 for severe hypertensives. The risk is also greater in older women.[95]

3. **Venous thromboembolism** (VTE). VTE can develop in different organ systems and present with different symptoms as listed on Table 19-2. The rate of thrombosis is 4 to 5 for every 100,000 reproductive-age women, 12 to 20 for low-dose OC users, and 48

Table 19-2 Circulatory diseases attributable to pills

Diagnosis	Location of Pathology	Symptoms
Thrombophlebitis	Lower leg	Calf pains, swelling, heat or tenderness
Thrombophlebitis	Thigh	Pain, heat, or redness
Pulmonary embolism	Lung	Cough, including coughing up blood, chest pain; shortness of breath
Myocardial infarction	Heart	Chest pain, left arm and shoulder pain, shortness of breath, weakness
Thrombotic stroke	Brain	Headache, weakness or numbness, visual problem, sudden intellectual impairment
Hemorrhagic stroke, including subarachnoid hemorrhage	Brain	Headache, weakness or numbness, visual problem, sudden intellectual impairment
Retinal vein thrombosis	Eye	Headache, complete or partial loss of vision
Mesenteric vein thrombosis	Intestines	Abdominal pain, vomiting, weakness
Pelvic vein thrombosis	Pelvis	Lower abdominal pain, cramps

Source: Stewart F, et al. (1987).

to 60 for pregnant women.[96,97] Pills with 35 mcg EE are associated with a lower risk of VTE than are 50 mg formulations.[98–100] The risk for VTE is highest in the first 1 to 2 years of OC use and then decreases over time. The effects are reversible. Past use of OCs is not associated with increased risk. Smoking does not add to the risk.

Estrogen increases liver production of a variety of clot promoting factors (such as factor VII, factor VIII, factor X and fibrinogen), decreases the production of clot lysing factors (such as antithrombin III and protein S), and increases platelet activity. Progestins alone have no impact on the clotting system, but when combined with estrogen they generally temper estrogen's actions or maintain neutrality. In the mid 1990s, international studies indicated that pills containing the progestins desogestrel and gestodene (not available in the United States) may be associated with higher rates of thrombosis than the formulations containing levonorgestrel and norgestrel.[98–100] U.S. labeling reflects these findings. Since then, it has been shown that there were confounding factors such as duration of use, selection bias (healthy user effect), and detection biases that may have influenced those study outcomes. Norgestimate was not included in the early international studies but was implicated in a subsequent transnational study.[101] Because the new compound, drospirenone,

has antiandrogenic effects, it may also allow fuller expression of estrogen's thrombotic impact.[102,103]

In most healthy women, estrogen and progestin together have no clinically significant impact on the coagulation system. Risk factors that place a woman at increased risk for venous thrombosis include obesity, previous venous compromise, and immobilization. However, the increase in VTE risk seen with OC use is most frequently due to inherited disorders such as factor V Leiden mutation or Protein S and C synthesis disorders. The factor V Leiden mutation explains 30% of all deep venous thromboses. In the United States, it is estimated that 5.3% of Caucasians, 2.2% of Hispanics, 1.2% of Blacks and Native Americans, and 0.5% of Asians carry Leiden mutations. Caucasians have a common genetic mutation in prothrombin, which affects 0.7% to 4% of that population.[104] Heterozygous factor V Leiden mutation carriers have thrombotic risk 6 to 8 times higher (24 to 40/100,000), and homozygous carriers have risk about 10 times greater than in the general population. When a carrier uses OCs, her VTE risk rises to 120 to 150/100,000 a year.[105] (For further discussion, see section on Patient Selection.)

4. **Hypertension.** OCs increase circulating levels of angiotensin II. Some women are very sensitive to angiotensin II levels, which can increase both their diastolic and systolic blood pressure readings. Both estrogen and progestin enhance aldosterone activity, which results in fluid retention, which, in turn, also contributes to an increase in blood pressure. The vast majority of women who use OCs will have no significant increase in either diastolic or systolic blood pressure measurements, although a 3 to 5 mm rise is not uncommon. However, 1% to 3% of women who use modern, low-dose OCs will, over time, experience increases in their blood pressure readings, which, if attributable to OC use, will normalize within 3 months of stopping estrogen-containing contraceptives. The women whose readings do not return to normal should undergo a standard work-up, although most will be found to have essential hypertension. Some women may need to begin antihypertensive agents as well as discontinuing OCs.

5. **Glucose tolerance and diabetes.** OCs currently available in the United States do not adversely affect carbohydrate metabolism.[106] Older OC formulations with high doses of sex steroids had a more profound impact on glucose tolerance and in some instances resulted in hyperglycemia with hyperinsulinemia. In the CARDIA study, current use of OCs was associated with lower glucose levels and perhaps with a lower odds ratio of diabetes.[107] Concerns have been raised about OC use in women at risk for developing diabetes because progesterone is a competitive inhibitor of the insulin

receptor and estrogen influences the release of insulin from the pancreatic islet cells and decreases insulin sensitivity.[108] High-risk women, such as those with a history of gestational diabetes who used OCs with low progestin content (Ovcon-35), had no higher risk of developing glucose intolerance or overt diabetes than the controls who used non-hormonal methods when both groups were studied for up to 7 years.[109]

6. **Gallbladder disease.** Recent studies of low-dose OCs do not show the increased risk of cholelithiasis and cholecystitis associated earlier with high-dose OCs. However, it may still be possible that low-dose OCs accelerate the development of symptomatic gallbladder disease in women with preexisting stones or sludge. OCs do not increase the risk of gallbladder cancer.[110]

7. **Cholestatic jaundice.** The active transport of bile can be impaired by high-dose combined hormonal contraceptives, resulting in cholestatic jaundice with pruritus. This condition reverses with discontinuation of hormones. The incidence in the general population using low-dose formulations is not known but is assumed to be very rare.

8. **Hepatic neoplasms.** Benign liver tumors have been associated with the use of high-dose OCs, especially long-term use. Focal nodular hyperplasia may be increased nearly 3-fold in OC users.[111] Adenomas are the most significant, since they can cause rupture of the liver capsule, extensive intraperitoneal hemorrhage, and even death. Women may or may not have abdominal pain with adenomas; their liver function tests are usually normal. Palpate the liver edge as part of the annual physical exam. If the liver is enlarged or tender, discontinue hormonal contraception and evaluate with MRI or CT tests; ultrasound is not reliable. Tumor regression is expected after stopping OCs.

   Hepatocellular carcinoma risk is not increased with OC use.[112] Use of hormonal contraception by high-risk women (with chronic hepatitis B virus) did not appear to increase the risk of hepatitis cellular carcinoma beyond their baseline elevated risk.

9. **Chlamydia/HIV.** Women who use OCs are at increased risk for acquiring chlamydia cervicitis.[113,114] In a study of Kenyan professional sex workers, users of OCs had an increased risk (hazard ratio 1.8, C1.1–2.9) of becoming infected with chlamydia when compared with women using no contraceptives.[115]

   OCs influence transcription of natural antimicrobials in the human endometrium, which might increase a woman's vulnerability to upper-tract chlamydia or HIV infection.[116] Although a recent study shows that OCs thicken the vaginal epithelium,[117]

hormonal contraception might increase a woman's vulnerability to HIV infection by reducing its barrier protection, by increasing the number or permissiveness of susceptible cells, or by directly affecting viral expression.[118] Clearly, all women at risk for STIs should limit their sexual activity to one uninfected, monogamous partner or, at a minimum, use latex or polyurethane condoms with every sexual act.

10. **Melanoma.** A pooled analysis of 10 case-controlled studies involving nearly 2,400 cases of melanoma revealed no correlation between OC use and the development of melanoma. No effect of duration of use or current use was observed.[119] However, it is recommended that women with a history of melanoma refrain from getting pregnant or using hormonal contraception for at least 3 years after their original therapy, since the risk of recurrence is highest at this time.

11. **Leiomyoma** (uterine fibroids) contain both estrogen and progesterone receptors. Since fibroids often shrink after menopause, when estrogen levels decrease, it has been suggested that estrogen-containing contraceptives might increase the growth of these benign uterine tumors. However, clinical studies with low-dose OCs have found no impact on the risk of developing new fibroids or increasing the size of pre-existing fibroids.[120–122] In fact, OCs are often used to control excessive menstrual bleeding caused by fibroids.

12. **Cervical dysplasia and cervical carcinoma.** OC users have a statistically significant higher risk of developing cervical dysplasia compared to women who use no method of contraception or who rely on tubal ligation. Cervical dysplasia and cervical carcinoma are caused by the human papillomavirus (HPV), especially HPV 16 and 18. OC users may have more unprotected intercourse with multiple partners. However, combined hormonal methods cause eversion of the cervical os, which not only increases metaplasia in nulliparous women but exposes those vulnerable metaplastic cells to HPV. OC use may be associated with artifacts that mimic ASC-US (glycogen vacuoles create perinuclear halos in OC users) on liquid-based cytology tests. Reflex HPV testing will demonstrate that two-thirds of those women have no virus.[123]

    OC users do not need to have cervical cytology testing more frequently than required by their other risk factors. Similarly, they do not need to be tested with more sensitive cytologic modalities because they use OCs.

    Women who use OCs for more than 5 years and who are infected with HPV have a 3- to 4-fold increased risk for in situ and invasive

smokers (>15 cigarettes/day) over age 35 should avoid estrogen-containing methods, according to product labeling. Many clinicians will not provide combined pills for women over the age of 35 if they smoke at all. (See discussion on Smokers in section on Special Populations.)

Combined hormonal contraceptives should not be used by women with an increased propensity to form blood clots, polycythemia vera, or a personal history of thrombosis, stroke or heart attack, advanced diabetes, labile hypertension, estrogen sensitive malignancies (such as breast cancer), active liver problems, and migraines with focal neurologic symptoms. Although the relative risk of thrombosis is greatly increased in women who have factor V Leiden mutations, routine screening for these rare mutations is not recommended prior to prescribing estrogen-containing contraceptives. However, it may be very appropriate to test (not screen) women who have a strong family history of multiple, unexplained clots in many family members, especially at a young age. Table 19-3 lists conditions from pill package labeling that are listed as contraindications.

PRECAUTIONS

To guide family planning programs, WHO has developed a more comprehensive list of precautions in providing combined hormonal contraceptives, which are summarized in Table 19-4.[130] Use of hormonal contraception by women who have medical conditions are ranked into four different categories. Category 4 conditions preclude the use of combined hormonal contraceptives. Conditions in Category 3 may be adversely impacted by combined hormonal contraceptives, and the risks generally outweigh the benefits. Providers should exercise caution if these agents are used and carefully monitor these OC users for adverse effects. The WHO recognized in its Category 2 that some conditions may trigger potential concerns with hormonal contraceptives, but the benefits of contraceptive use with these conditions usually outweigh the risks. Category 1 conditions raise no concerns about OC use, and OC use should not be restricted.

PROVIDING ORAL CONTRACEPTIVES

Explore the patient's medical and reproductive health history and her family history to ensure that she has no reason to avoid using combined hormonal contraception (see Tables 19-3 and 19-4 on WHO Medical Eligibility Criteria). Discuss the potential noncontraceptive benefits and examine all her lifestyle issues to ensure that she has a secure plan for where to keep her pill pack and can realistically expect to take a pill a day. Anticipatory counseling about safety concerns can reduce later discontinuation. Determine if she wants to have monthly withdrawal bleeding

or if she would prefer less frequent bleeding episodes. Ask if she has any other complaints that need to be addressed at this visit. In particular, find out if she needs any STI testing or if she needs emergency contraception now or may need it in the future. Advise her to follow safer sex practices.

Measure the woman's blood pressure. It may be prudent to do a breast examination, but a pelvic examination is *not* needed for an asymptomatic woman prior to initiating OCs,[131,132] even if the woman has not had a recent Pap smear. STI screening, if needed, can be urine-based. No other screening tests are routinely needed unless her history or blood pressure indicate a need for further assessment.[133]

Table 19-3 Medical conditions precluding OC use, as listed in pill package inserts (PPI)

There are specific medical conditions that indicate a woman should not use OCs. The FDA-approved pill package inserts (PPI) list a somewhat different set of medical conditions that preclude OC use than do the WHO medical eligibility criteria. Below is the FDA-approved package insert list of medical conditions that indicate OCs "should not be used." The category assigned in the WHO medical eligibility criteria (Table 19-4) is included in the adjacent column.

Medical Conditions Precluding OC Use (PPI)	WHO Category
• Thrombophlebitis or thromboembolic disorder	4
• Past history of deep vein thrombosis or thromboembolic disorders	4
• Cerebrovascular or coronary artery disease	4
• Valvular heart disease with thrombogenic complications	4
• Uncontrolled hypertension	4
• Diabetes with vascular involvement	3/4
• Headaches with focal aura	4
• Major surgery with prolonged immobilization	4
• Breast cancer	4
• Carcinoma of the endometrium	1
• Other known or suspected estrogen-dependent neoplasia	Not discussed
• Undiagnosed abnormal genital bleeding	2
• Cholestatic jaundice of pregnancy	2
— Jaundice with prior pill use	3
• Acute or chronic hepatocellular disease with abnormal liver function, hepatic adenomas, or hepatic carcinomas	4
• Known or suspected pregnancy	"Not applicable"
• Hypersensitivity to any component of the product	Not discussed

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004

LOW-DOSE COMBINED ORAL CONTRACEPTIVES (COCs) <35 mcg of ethinylestradiol	COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to reduce the risk of STI/HIV.
CONDITION	**CATEGORY** I = Initiation C = Continuation
PERSONAL CHARACTERISTICS AND REPRODUCTIVE HISTORY	
PREGNANCY	NA
AGE	
a) Menarche to <40 years	1
b) ≥ 40 years	2
PARITY	
a) Nulliparous	1
b) Parous	1
BREASTFEEDING	
a) < 6 weeks postpartum	4
b) ≥ 6 weeks to <6 months postpartum (primarily breastfeeding)	3
c) ≥ 6 months postpartum	2
POSTPARTUM (in non-breastfeeding women)	
a) <21 days	3
b) ≥ 21 days	1
POST-ABORTION	
a) First trimester	1*
b) Second trimester	1
c) Immediate post-septic abortion	1
PAST ECTOPIC PREGNANCY	1
HISTORY OF PELVIC SURGERY (including Caesarean section)	1
SMOKING	
a) Age <35 years	2*
b) Age ≥ 35 years	
(i) < 15 cigarettes/day	3*
(ii) ≥ 15 cigarettes/day	4*

(continued)

* For more detailed clarifications, consult the WHO website.

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
OBESITY	
≥ 30 kg/m^2 body mass index (BMI)	2
CARDIOVASCULAR DISEASE	
MULTIPLE RISK FACTORS FOR ARTERIAL CARDIOVASCULAR DISEASE (such as older age, smoking, diabetes and hypertension)	3/4*
HYPERTENSION	
a) History of hypertension, where blood pressure CANNOT be evaluated (including hypertension during pregnancy)	3*
b) Adequately controlled hypertension, where blood pressure CAN be evaluated	3*
c) Elevated blood pressure levels (properly taken measurements)	
(i) systolic 140–159 or diastolic 90–99	3
(ii) systolic ≥160 or diastolic ≥100	4
d) Vascular disease	4
HISTORY OF HIGH BLOOD PRESSURE DURING PREGNANCY (where current blood pressure is measurable and normal)	2
DEEP VENOUS THROMBOSIS (DVT)/ PULMONARY EMBOLISM (PE)	
a) History of DVT/PE	4
b) Current DVT/PE	4
c) Family history of DVT/PE (first-degree relatives)	2
d) Major surgery	
(i) with prolonged immobilization	4
(ii) without prolonged immobilization	2
e) Minor surgery without immobilization	1
KNOWN THROMBOGENIC MUTATIONS (e.g., Factor V Leiden, prothrombin, protein S, protein C, and antithrombin deficiency)	4*

(continued)

* For more detailed clarifications, consult the WHO website.

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation	
SUPERFICIAL VENOUS THROMBOSIS		
a) Varicose veins	1	
b) Superficial thrombophlebitis	2	
CURRENT AND HISTORY OF ISCHAEMIC HEART DISEASE	4	
STROKE (history of cerebrovascular accident)	4	
KNOWN HYPERLIPIDAEMIAS (screening is *not* necessary for safe use of contraceptive)	2/3*	
VALVULAR HEART DISEASE		
a) Uncomplicated	2	
b) Complicated (pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis)	4	
NEUROLOGIC CONDITIONS		
HEADACHES	**I**	**C**
a) Non migrainous (mild or severe)	1*	2*
b) Migraine		
(i) without aura		
Age < 35	2*	3*
Age ≥ 35	3*	4*
(ii) with aura (at any age)	4*	4*
EPILEPSY	1*	
DEPRESSIVE DISORDERS	1*	

(continued)

* For more detailed clarifications, consult the WHO website.

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
REPRODUCTIVE TRACT INFECTIONS AND DISORDERS	
VAGINAL BLEEDING PATTERNS	
a) Irregular pattern *without* heavy bleeding	1
b) Heavy or prolonged bleeding (includes regular and irregular patterns)	1*
UNEXPLAINED VAGINAL BLEEDING (suspicious for serious condition)	
Before evaluation	2*
ENDOMETRIOSIS	1
BENIGN OVARIAN TUMOURS (including cysts)	1
SEVERE DYSMENORRHOEA	1
TROPHOBLAST DISEASE	
a) Benign gestational trophoblastic disease	1
b) Malignant gestational trophoblastic disease	1
CERVICAL ECTROPION	1
CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)	2
CERVICAL CANCER (awaiting treatment)	2
BREAST DISEASE	
a) Undiagnosed mass	2*
b) Benign breast disease	1
c) Family history of cancer	1
d) Cancer	
(i) current	4
(ii) past and no evidence of current disease for 5 years	3
ENDOMETRIAL CANCER	1
OVARIAN CANCER	1

(continued)

* For more detailed clarifications, consult the WHO website.

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
UTERINE FIBROIDS	
a) Without distortion of the uterine cavity	1
b) With distortion of the uterine cavity	1
PELVIC INFLAMMATORY DISEASE (PID)	
a) Past PID (assuming no current risk factors for STIs)	
(i) with subsequent pregnancy	1
(ii) without subsequent pregnancy	1
b) PID-current or within the last 3 months	1
STIs	
a) Current purulent cervicitis or chlamydial infection or gonorrhea	1
b) Other STIs (excluding HIV and hepatitis)	1
c) Vaginitis without purulent cervicitis	1
d) Increased risk of STIs (e.g., multiple partners or partner who has multiple partners)	1
HIV/AIDS	
HIGH RISK OF HIV	1
HIV-INFECTED	1
AIDS	1*
OTHER INFECTIONS	
SCHISTOSOMIASIS	
a) Uncomplicated	1
b) Fibrosis of liver	1
TUBERCULOSIS	
a) Non-pelvic	1*
b) Known pelvic	1*
MALARIA	1

(continued)

* For more detailed clarifications, consult the WHO website.

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
ENDOCRINE CONDITIONS	
DIABETES	
a) History of gestational disease	1
b) Non-vascular disease	
(i) non-insulin dependent	2
(ii) insulin dependent	2
c) Nephropathy/retinopathy/neuropathy	3/4*
d) Other vascular disease or diabetes of >20 years' duration	3/4*
THYROID	
a) Simple goiter	1
b) Hyperthyroid	1
c) Hypothyroid	1
GASTROINTESTINAL CONDITIONS	
GALL-BLADDER DISEASE	
a) Symptomatic	
(i) treated by cholecystectomy	2
(ii) medically treated	3
(iii) current	3
b) Asymptomatic	2
HISTORY OF CHOLESTASIS	
a) Pregnancy-related	2
b) Past COC-related	3
VIRAL HEPATITIS	
a) Active	4
b) Carrier	1
CIRRHOSIS	
a) Mild (compensated)	3
b) Severe (decompensated)	4

(continued)

* For more detailed clarifications, consult the WHO website.

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
LIVER TUMORS	
a) Benign (adenoma)	4
b) Malignant (hepatoma)	4
ANAEMIAS	
THALASSAEMIA	1
SICKLE CELL DISEASE	2
IRON DEFICIENCY ANEMIA	1
DRUG INTERACTIONS	
COMMONLY USED DRUGS WHICH AFFECT LIVER ENZYMES	
a) Certain antibiotics (rifampicin)	3*
b) Certain anticonvulsants (phenytoin, carbamezapine, barbiturates, primidone, topiramate, oxcarbazepine)	3*
OTHER ANTIBIOTICS (excluding rifampicin)	1
a) Griseofulvin	2
b) Other antibiotics	1
ANTIRETROVIRAL THERAPY	2*

* For more detailed clarifications, consult the WHO website.

Source: WHO (2004),[131] with permission.
For references and update, please consult
http://www.who.int/reproductive-health/publications/MEC_3

FOLLOW-UP

Because side effects can appear in the first few months of OC use, a follow-up visit at 3 or 6 months is quite commonly recommended. A woman who has used the pill for 3 to 6 months, has no problems, and wants to continue the pill, may be given 7 to 13 packets (a 6-month to 1-year supply). One author of this chapter strongly recommends providing only 3 cycles of pills at the first visit with a 9-month refill, followed by a 12-month supply every subsequent year. Recent suggestions that it may be appropriate to provide OCs over-the-counter also suggest that new OC users may not need such frequent reassessment.[134,135] An alternative approach is to prescribe or give a woman a full year's supply of pills the very first visit and then encourage a revisit or two in the first year for a blood pressure

and headache check. After a woman has used OCs for 1 year, you could consider prescribing a full year's supply of pills (or even 18 cycles) in an effort to increase OC continuation rates.

Women who are planning major surgery requiring prolonged immobilization should discontinue use of estrogen-containing OCs 1 month prior to surgery. Similarly, women being treated with anticoagulants should stop their OCs 1 month prior to finishing their anticoagulant.

CHOICES FOR PILL INITIATION

Quick start. For the Quick Start method, the patient takes the *first* pill in the pill pack on the day of her office visit, as long as she is not pregnant and not in need of emergency contraception. If she needs emergency contraception, she should take both tablets of Plan-B or its equivalent at once on the visit day, and start her pills no later than the next day. Tell her to use a back-up method with her pills for at least 7 days. Her next menses will be delayed until she completes the active pills in her pack and starts the placebo pills. If she has concern about an undetectable early pregnancy, she can start her pills and be instructed to return for a urine pregnancy test in 2 to 3 weeks, or do one at home. Alternatively, she can use a first-day start. The hormones in the pills will not adversely affect an early pregnancy and the prompt repeat pregnancy testing will detect the pregnancy early enough to begin the pregnancy care she chooses.

The Quick Start approach was more successful getting women started on the pill than are the two methods discussed below; more women were using the pill in the third cycles, especially if they had menstrually-related problems.[136] However, it is an off-label practice. The reason Quick Start is preferred is because other approaches leave a time gap between the time the patient is prescribed her pills and the time she is intended to start taking them. As many as 25% of young women starting by one of the conventional start methods (see below) failed to begin taking the pills as instructed because they had conceived in the interim, forgot the pill-taking instructions, failed to fill the prescription, or were worried about taking the pill after their visit.[137,138] Quick Start does not increase irregular spotting or bleeding.[139]

First-day start. The first-day start was introduced to gain early control of ovarian follicles during the first cycle. In this approach, a woman takes her first pill on the first day of her next period. It is important to have the woman determine that her period is normal—that it occurs at the predicted time and is preceded by symptoms that are usual for her. If there is any question that the menses is not normal, have her rule out pregnancy before she starts her pills.

Sunday start. The Sunday start was the most common method for starting pills for decades. Women were told to start their first active pill on the first Sunday of their menses. For example, if a woman were to start bleeding on Friday, she should take her first pill two days later on Sunday. If her period were to start on Sunday, she should start on that day. Make

sure the patient understands that she should not wait to start the first pill on the Sunday after her menses ends. Today, the Sunday start is not generally recommended because it is often difficult for women to get refills when they need them on weekends. In addition, many women are working outside the home and prefer not to menstruate during their work week. A Sunday start often requires that a back-up method be used for 7 days.

SWITCHING FROM OTHER METHODS

Women who switch from other methods can start OCs immediately, using the guidelines for the pill Quick Start initiation. For example, women who have implants or IUDs removed can start their OCs that same day and be told to use a back-up contraceptive method for the next week. Women who have had recent unprotected intercourse can be given Plan B emergency contraception (EC) immediately and start their OCs no later than the next day coupled with a back-up method for at least 7 days. A urine pregnancy test in 2 to 3 weeks may be offered to detect any EC failures. Women using injectable methods generally start their OCs at the end of the effective period of the injection. However, if a woman is amenorrheic as a result of the injection and is late for reinjection, she can start the OCs the same day with a 7-day course of a back-up method. For any woman with a recent history of unprotected intercourse, provide EC, OCs, and back-up methods followed by a repeat pregnancy test in 2 to 3 weeks.

CHOOSING A PATTERN OF PILL USE

1. **Monthly cycling 21/7.** Conventional pill packaging contains 3 weeks of active pills followed by 7 placebo pills to provide a predictable, coordinated withdrawal bleed that women will interpret to be a normal menses. Pioneers in the development of the birth control pill touted this feature as a distinct benefit for women,[140] which it was at the time.
2. **Shortened pill-free interval.** It is possible that the 7-day pill-free interval allows too much time for follicular development and increases to the failure rate with low-dose OCs. Shortening the pill-free interval with 20 mcg EE pills from 7 to 5 days suppressed ovarian activity more effectively.[141] One way to implement this approach is to have the patient use the "first-day start" for every cycle, in which she begins a new pill pack each month on the first day of her withdrawal bleeding. If she has no menses by the 5th placebo pill day, she should start her new pack that day. A pregnancy test is not necessary, but may provide comfort to the woman. In a trial comparing a 23-day regimen to the traditional 21-day regimen of 20 mcg EE pills, the withdrawal bleeding was shorter in the group using more active pills.[142] Mircette has 21 active pills, 2 placebos, and 5 pills with 10 mcg EE.
3. **Extended use.** Recent studies have found that many of the "pill side effects" (such as headache, cramping, breast tenderness, bloating

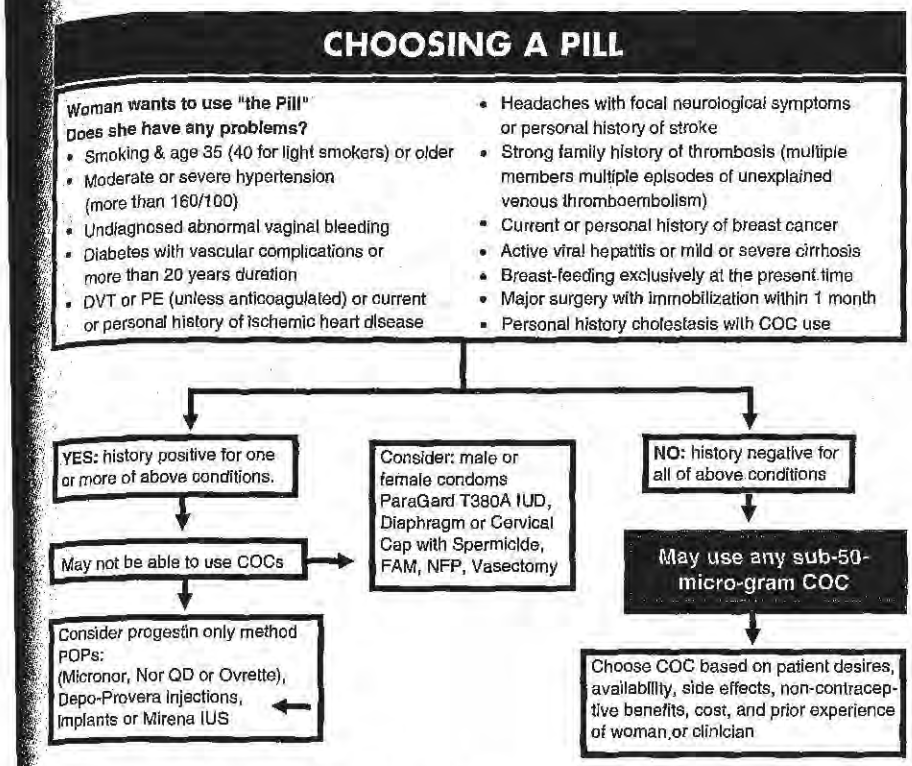
and/or swelling) occur during the week women take their placebo pills.[143] Because recent surveys have shown that many women would prefer to bleed less frequently than once a month,[144] it is time to re-evaluate the need for monthly withdrawal bleeding.[145] The purpose of menstruation in spontaneously cycling women is to resolve the prior unsuccessful cycle (no pregnancy) and to prepare for the next cycle (which may result in pregnancy). With OC use, however, conception is not desired; there is no biological need to provoke artificial withdrawal bleeding on a monthly basis. Unless the patient wants to use bleeding as a reassurance that she is not pregnant, monthly cycling is *not* necessary and may be replaced by extended OC use.[146] In clinical studies, women with prolonged flow had fewer menstrually related problems, and the majority of those women continued to use the extended cycle.[147] The regimen using extra packs of pills is cost-effective for women with menorrhagia.[148] Other women for whom extended use would be particularly attractive are those with dysmenorrhea or menstrual migraines, and those on active military duty or who have similarly demanding jobs.

Options for extended use include the following:

- *Brief manipulation of a cycle for convenience* such as for a honeymoon, trip, athletic event, camping experience, business meetings, exams or presentations.
- *Bicycling*, which is the back-to-back of 2 packs of active pills by taking the first pack of 21 active pills, throwing away the 7 placebo pills in that first pack and immediately starting the second pack of 21 active pills followed by the 7 placebo pills at the end of the second package. Recent studies of extended cycles ("bicycling") found that the longer cycles had significant reduction in the days of bleeding and in annual expenditures for female hygiene.
- *Tricycling*, meaning taking the 21 active pills from 3 packages followed by the 7 placebo pills from the third package.
- *Taking Seasonale*, which contains 84 active pills followed by 7 placebo pills. A woman using this regimen has four periods a year, hence the name, Seasonale.
- *No-cycling*, meaning taking active pills indefinitely (for many months or years) with no placebo pills as long as the woman has no troublesome spotting. Seasonale or any strong progestin monophasic pills may be used in this off-label manner.

CHOOSING A FORMULATION

Clinicians in the United States have numerous OCs from which to choose. (See the color insert for photographs and formulations of pills available in the United States). Select an OC based on the hormonal dose and on the woman's clinical picture. Figure 19-2 gives an algorithm to help clinicians.



- The World Health Organization and the Food and Drug Administration both recommend using the **lowest dose pill** that is effective. All combined pills with less than 50 µg of estrogen are effective and safe.
- There are no studies demonstrating a decreased risk of deep vein thrombosis (DVT) in women on 20 mcg pills. Data on higher dose pills (50 mcg EE vs. 30 mcg) have demonstrated that the less the etrogen dose, the lower the risk for DVT.
- All COCs lower free testosterone. In the US, only Ortho Tri-Cyclen and Estrostep have FDA labeling indicating it as a treatment of moderate acne vulgaris, based on results of randomized, placebo controlled trials. Other formulations are under study. Class labeling in Canada for all combined pills states that use of pills may improve acne. In Canada, only Tri-Cyclen has "treatment of moderate acne vulgaris" as an indication for use.
- To minimize discontinuation due to spotting and breakthrough bleeding, warn women in advance, reassure that spotting and breakthrough bleeding become better over time.
- To attain the most favorable lipid profile, consider norgestimate, desogestrel pill or low dose norethindrone acetate, or norethindrone (Ovcon-35) or ethnodiol diacetate (Demulen 1/35 or Zovia 35). No clinical benefits have been demonstrated to be attributable to difference in lipids caused by these pills. Estrogen has a beneficial effect on the walls of blood vessels. All currently available COCs raise triglycerides.

Source: Modified from Hatcher RA, et al. (2003),[149] with permission.

Figure 19-2 Choosing a pill

SPECIAL POPULATIONS

ADOLESCENT WOMEN

Menstruating teenage women who are sexually active and those who are contemplating becoming sexually active are usually healthy; therefore, for young women, the medical and social risks of pregnancy far outweigh the small health risks associated with OC use. Explore the teen's decision to become (or stay) sexually active. Is she comfortable with that decision or would she prefer to delay sexual intercourse? (See Chapter 13, Abstinence and the Range of Sexual Experience.) Many teens can benefit from taking OCs to treat primary dysmenorrhea, anovulatory cycling, or acne. A pelvic examination is not needed prior to OC initiation for an asymptomatic woman (see the section on Pill Initiation). Reassure anxious parents that OC use for noncontraceptive indications has not been shown to encourage young women to become sexually active. A teenager who has had irregular periods or late onset of menses will have regular menses while taking OCs; however, when she stops taking her OCs, her periods may again become irregular. Estrogen in the current low-dose OCs do not limit height due to premature closure of the epiphyses in young, menarchal women. Teens may be more likely to abandon OCs because of minor side effects such as nausea or spotting, so take all minor side effects in teenagers seriously.

Provide concrete counseling to adolescents, who may find it more challenging to use OCs correctly and consistently than do older women. Instruct each teen who wants to use OCs about condom use, both for reducing the risk of acquiring STIs and for back-up in case she discontinues taking the pill. Provide emergency contraception and instructions on how to use it if she needs it. Studies have shown that women of all ages are more able to successfully use the once-a-week or once-a-month methods than they are able to remember to take a pill once a day. However, in the patch study, 18- and 19-year-olds showed the greatest improvement in successful utilization rates. For this reason, offer the vaginal ring and patch to teens considering OCs.

PERIMENOPAUSAL WOMEN

Healthy, nonsmoking women in their 40s are candidates for combined hormonal contraception. OCs can help regulate menstrual bleeding and reduce the risks of irregular bleeding and endometrial hyperplasia associated with anovulatory cycling during the perimenopausal years. Women in their 40s are at highest risk for menorrhagia due to leiomyoma and adenomyosis; OCs can provide medical alternatives to hysterectomy. OCs also help reduce the risk of ovarian and endometrial cancers. Another significant advantage OCs offer many women who are experiencing hormonal fluctuations is reduction of vasomotor symptoms, especially if OCs are used on an extended cycle basis. (See the Menopause Chapter.)

No special testing is required prior to prescribing OCs for women in their 40s, except for blood pressure measurement. Screening measures such as clinical breast exams, mammograms, serum lipids, and pelvic exam with Pap smears are important elements of well-woman care, but need not be performed in apparently healthy women of any age prior to OC initiation.

OC users in their late 40s or early 50s may not experience traditional symptoms of menopause while taking OCs. They will not experience menstrual irregularities or hot flashes, especially if the OCs are used on an extended basis. In this context, it may be difficult to detect when menopause occurs. Do not rely on blood tests to diagnose menopause in perimenopausal women. (See Chapter 5 on Menopause.)

SMOKERS

Heavy smoking by women older than 35 precludes the use of estrogen-containing hormonal methods. *Any* smoking by women older than 40 precludes use of estrogen-contining contraceptive on an ongoing basis. Light smoking by women age 35 to 40 merits caution (WHO category 3). For example, smoking increases an OC user's risk of heart attack nearly 13- to 14-fold.[150] Indeed, women who smoke as few as 1 to 4 cigarettes a day have a 2.5 fold increased risk of coronary heart disease.[151] The older the smoker, the more cigarettes she smokes, and the more concomitant cardiovascular problems she faces, the less likely she is to be a candidate for OCs, especially if she can use more effective methods such as progestin-only injections or IUDs. In otherwise healthy young women, the absolute risk of cardiovascular disease is low, so that estrogen-containing contraceptives in women who smoke are still safer than the risks of pregnancy. The first priority in caring for a woman who smokes is to encourage and aid her to stop smoking, or to significantly reduce the number of cigarettes she smokes each day. Three to 12 months after stopping smoking, past smokers have the same OC-related cardiovascular risks as nonsmokers.

In selecting a pill for smokers, the clinician is conflicted. On the one hand, the ideal pill would have the lowest estrogen content (to reduce arterial thrombosis) and the lowest androgenicity (to minimize any adverse impacts on lipids). Smokers tend to metabolize estrogen more rapidly and to increase SHBG levels more than nonsmokers do, so that the 20-mcg EE dose pill may not provide as much contraceptive efficacy for a smoker. However, there are no clinical trials to provide guidance. It may be prudent to start smokers and nicotine patch/gum/etc. users on 20 mcg EE formulation with a strong (low androgenic) progestin, advise them to use a back-up method during the first 2 to 3 months, and monitor breakthrough bleeding as a marker of adequate serum levels. If she has persistent breakthrough bleeding on a 20-mcg EE pill, use of a 25 to 30 mcg EE formulation or delivery system may be advisable. Shortening the pill-free interval may be helpful.

POSTPARTUM WOMEN

Pregnancy is a hypercoagulable state. Estrogen increases the risk of venous thrombosis and embolism (VTE). As a result, it is generally recommended that postpartum women delay use of estrogen-containing contraception until 3 to 4 weeks postpartum, when those pregnancy-induced changes in the coagulation system have waned.

BREASTFEEDING WOMEN

Although many progestin-only methods may be used immediately postpartum, estrogen may decrease the quantity and quality of breast milk (see Chapter 23 on Postpartum Contraception and Lactation). Therefore, the American Academy of Pediatrics advises against use of estrogen as long as the woman is exclusively breast-feeding. Estrogen can be used as soon as supplemental sources of nutrition are introduced into the infant's diet (if the mother is at least 3 to 4 weeks postpartum).

WOMEN WITH MEDICAL PROBLEMS

Diabetes. As the WHO guidelines state, only women with uncomplicated diabetes can be considered for OC use. Women with advanced diabetes complicated by nephropathy (proteinuria), retinopathy, neuropathy, or diabetes of more than 20-years duration are not candidates for estrogen-containing methods (WHO:4). If uncomplicated diabetes is combined with hypertension, smoking, or other major risk factors for cardiovascular disease, estrogen-containing contraceptives may not be used.

For diabetic women who are candidates for OCs, consider each of the components of the pill. Progesterone is a competitive inhibitor of insulin at the insulin receptor; therefore, a pill with low progesterone activity is important. Estrogen can decrease insulin release by the islet cells of the pancreas, so a relatively low-dose estrogen formulation may be favored. Androgens can have an adverse impact on lipids and increase the woman's risk for cardiovascular disease. However, any low-dose pill with similar properties is quite reasonable.

Sickle cell anemia. Women with sickle cell disease are predisposed to occlusion of the microvasculature. However, OC users and non-users appear to have no differences with regard to coagulation studies, blood viscosity measurements, or incidence or severity of painful sickle cell crises. In addition, women with sickle cell anemia can ill afford to lose menstrual blood. Sickle cell disease (WHO:1) and thallassemia (WHO:2) are not reasons to avoid OCs.[130]

Gallbladder disease. WHO recommends that women with symptoms of gallbladder disease and those who are being treated medically for gallbladder disease not use estrogen-containing contraception if more appropriate methods are acceptable (WHO:3). Similarly, women who have experienced cholestatic jaundice in pregnancy may use OCs with caution (WHO:2), although those who experienced jaundice with past OC use fall into category 3.

Cervical dysplasia. Women who have cervical dysplasia or who have a history of previously treated cervical dysplasia may still use combined hormonal contraception (WHO:2).

Special issues for drospirenone-containing OCs. Do not prescribe Yasmin or such formulations to patients with conditions that predispose to hyperkalemia (i.e., renal insufficiency, hepatic dysfunction, and adrenal insufficiency).

MANAGING SIDE EFFECTS

A double-blind trial showed no difference in the incidence of any of the traditionally "hormonally-related" side effects during the 6-month comparison of OC users and placebo pills users. Similar percentages of women in each group developed headaches, nausea, vomiting, mastalgia, weight gain, etc.[152] This finding differs from the impression given by the pill package labeling, because the side effect numbers in labeling come from clinical trials and reflect the events that women had *while* they use pills that could possibly be related to pill use, not events that occur *because* of the pill. Similarly, when women with "pill side effects" such as nausea, headache, irritability, fatigue, weight gain, breast tenderness, and breakthrough bleeding were treated in another study with either Vitamin B_6 or sugar pill, both groups improved in all symptoms.[153]

However, 59% to 81% of women who discontinued OC use in one study reported that they stopped due to side effects. Therefore, management of side effects on OCs is crucial to successful use of hormonal contraceptives. Counsel all potential hormonal contraceptive users that side effects are possible (Table 19-5), but not necessarily to be expected. Advise women that side effects are usually transient and often respond to changes in pill formulation.

Absence of withdrawal bleeding

Advise women that the amount of withdrawal bleeding may be significantly lower with hormonal methods. Even scant bleeding or spotting on the placebo pills counts as withdrawal bleeding. The incidence of complete lack of withdrawal bleeding varies with different formulations and increases with duration of use. Some women deliberately extend the numbers of active pills they use (bicycling, tricycling, or extended use) to achieve amenorrhea. For women using cyclic regimens of hormonal contraceptives who fail to have withdrawal bleeding, obvious causes of amenorrhea (such as pregnancy) must be excluded. Other specific conditions, such as cervical stenosis, need to be evaluated, particularly if the patient has recently had cervical surgery (e.g., D&C, cone biopsy, LEEP,etc). When women use hormonal contraceptives, it is far less likely that other common causes of amenorrhea are present. For example, thyroid problems, prolactinoma, and hypothalamic amenorrhea due to stress or excessive exercise or anovulatory states such as PCOS or obesity are important considerations when a woman not using hormonal contraceptives develops amenorrhea. However, combined

hormonal contraceptives restore predictable menstrual cycling in women with these problems.

Women who enjoy the lack of withdrawal bleeding but just want to reassure themselves periodically that they are not pregnant may use home pregnancy tests or may want to monitor their basal body temperature (BBT) during 3 sequential days of placebo pills. If that BBT is <98°F, the likelihood of pregnancy is very low. If women desire to have cyclic withdrawal bleeding, switching to a more estrogenic formulation or to a triphasic formulation may decrease the likelihood of amenorrhea.

Table 19-5 Estrogenic, progestogenic, and combined effects of oral contraceptive pills

Estrogenic effects	Estrogen + progestin effects	Progestin effects
• Nausea • Increased breast size (ductal and fatty tissue) • Leukorrhea • Cervical eversion or ectopy • Hypertension • Rise in cholesterol concentration in gallbladder bile • Telangiectasia • Hepatocellular adenomas • Cerebrovascular accidents (rare) • Thromboembolic complications including DVT or pulmonary emboli (rare) • Decreased libido and/or enjoyment of intercourse • Pruritus (Most pills with less than 50 mcg of ethinyl estradiol are less likely to produce troublesome estrogen-mediated side effects or complications.	Both the estrogenic and the progestational components of oral contraceptives may contribute to the development of the following adverse effects: • Breast tenderness • Headaches • Hypertension • Myocardial infarction (rare) • Cyclic weight gain due to fluid retention • Growth of leiomyomata • Stimulation of breast neoplasia (exceedingly rare)	All low-dose combined pills suppress a woman's production of testosterone, which has a beneficial effect on acne, oily skin and hirsutism. The progestin component may have androgenic as well as progestational effects: • Increased appetite and weight gain • Depression, fatigue, tiredness • Acne, oily skin • Increased LDL cholesterol levels • Decreased HDL cholesterol levels • Decreased carbohydrate tolerance; increased insulin resistance • Bloating • Constipation

Acne, oily skin, hirsutism

Two formulations have FDA approval for the treatment of acne (Ortho TriCyclen and Estrostep). Progestin inhibits LH release, which decreases ovarian androgen production. Estrogen increases hepatic production of sex

hormone-binding globulin, which binds testosterone and other androgens in the woman's circulation. Occasionally (<10%) women will report worsening or new onset of acne, oily skin, or hair growth. Consider other causes of androgen exposure (other medications, ovarian tumors, etc.). If it appears her OC may be contributing to her problem, switch to a less androgenic formulation (e.g., Yasmin, Ortho Tri-Cyclen, Desogen, Ovcon-35).

Gastrointestinal complaints

Working at the level of the central nervous system, estrogen can cause nausea or vomiting. Sex steroid hormones do not directly affect the gastric lining, although new research has demonstrated a hormonal impact on the intrinsic firing rate of the gastric pacemaker cells. Progesterone slows peristalsis and can induce constipation and sensations of bloating and distention. Most affected women acclimate to the hormones, and nausea resolves within 1 to 3 months of use. If a woman complains of nausea, she can try taking her pills with food or at night. Avoid double dosing. Counsel the patient to "catch up" any pills she forgets by taking pills at 12-hour intervals, rather than 2 pills at one time, which increases the likelihood of nausea. In addition, advise more fluids and fresh fruits and vegetables. Women with recent onset of severe gastrointestinal symptoms should be evaluated promptly to rule out problems, such as cholecystitis, appendicitis and diverticulitis.

If vomiting or diarrhea is related to taking the pill, try the following approaches:

- Decrease hormone dose. A 20 mcg OC dramatically decreases nausea for many women, although it may also lead to more spotting and breakthrough bleeding.
- Bloating and constipation may be helped with a reduction in the progestin component in the pill. Bloating associated with menses can be diminished by extended cycle or continuous active pill use.
- Try progestin-only formulations to control nausea and other symptoms.
- Consult the Instructions for Using Oral Contraceptives for guidance on how to manage missed pills due to vomiting or poor absorption due to diarrhea.

Headaches

Headaches occur commonly. Controlled trials found that women using placebo pills experienced as many headaches as did OC users.[152] Nonetheless, headaches in an OC user deserve evaluation, because they are the major warning sign that precedes stroke. (See Figure 19-3.) If a woman begins having headaches or her headaches worsen after she starts OCs, consider all differential diagnoses. Measure the patient's blood pressure to rule out hypertension.

- Determine the type of headache. Ask about the severity of the headache, aura, duration, character (throbbing or constant),

cyclicity, and location (including asymmetry). Ask about associated symptoms, such as photophobia, nausea, vomiting, dizziness, scotomata, blurred vision, watering of the eyes, loss of vision or speech, weakness or numbness. Can the patient function when the headaches are most severe? What medication provides relief?

- Rule out other causes, such as transient ischemic attacks, migraine headaches, vascular headaches, or cerebrovascular accident; hypertension; cyclic fluid retention induced by OCs; sinusitis, viremia, sepsis, or allergy; temporomandibular joint (TMJ) disorders or dental problems; drug use, alcohol or caffeine withdrawal, or central nervous system tumor.

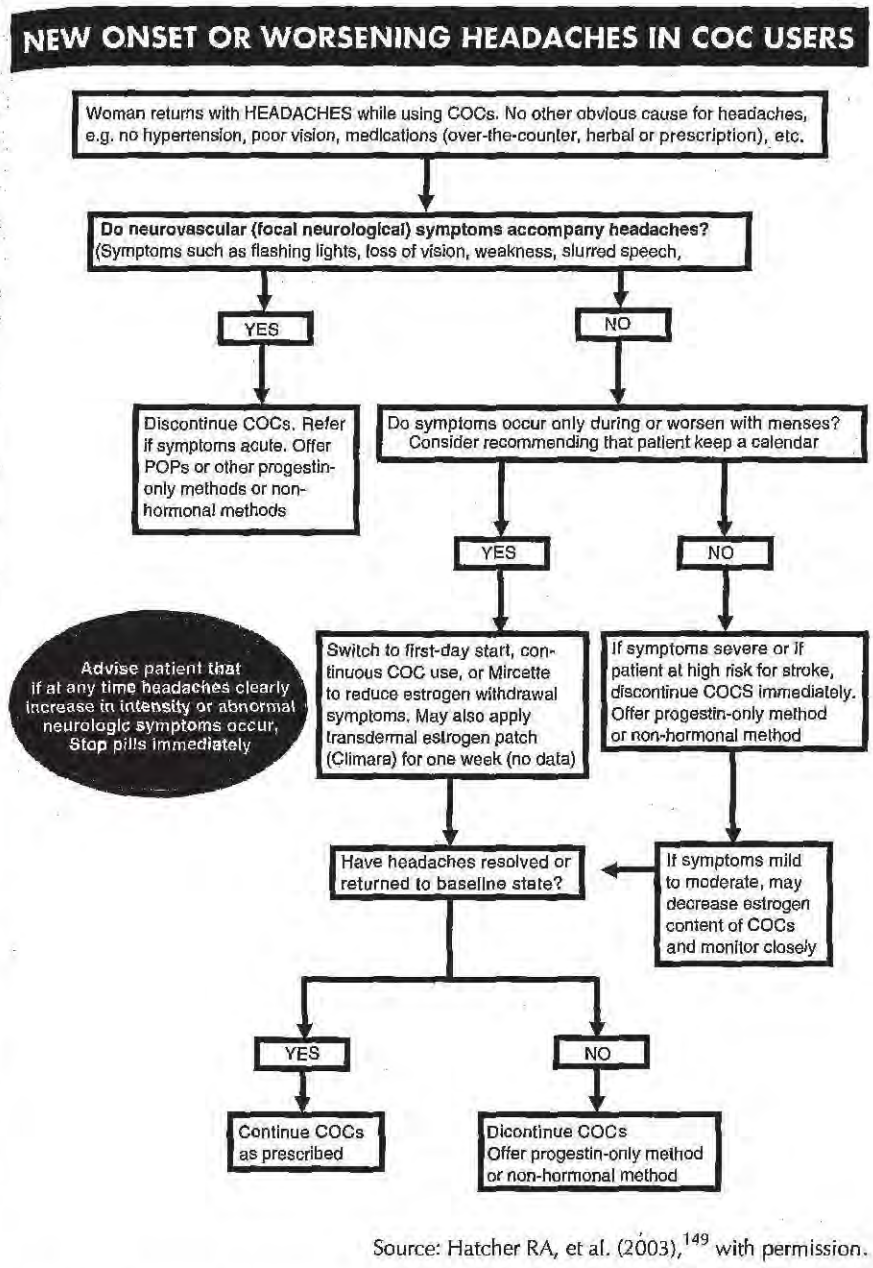
Tension headache. The most common headache is the tension headache, which usually starts as a neck pain late in the day and radiates through the occipital area over the scalp to involve the forehead. There are no associated neurologic sensations, but women with tension headaches may experience nausea or vomiting from the intensity of the pain. These headaches usually respond to over-the-counter analgesics and/or rest. Rarely is it necessary to change pill formulations.

Migraine headache. The headache that causes most medical concern is the migraine headache, which tends to occur in the temporal region and is more frequently unilateral. Although the word "migraine" has become almost synonymous with severe headaches, it is important to identify the true migraines. If a woman develops new-onset migraine or a worsening in the severity or frequency of her headache, promptly reassess if she is still a candidate for using estrogen-containing contraceptives. If she has any associated neurological auras (flashing lights, tingling sensation, paraesthesias, etc), stop the OCs and provide contraception without estrogen. On the other hand, if her symptoms develop or worsen on the days she takes placebo pills (when the estrogen levels drop), it maybe possible to offer her extended-use, low-dose OCs to reduce her menstrual migraines.

Stroke. Strokes are often preceded for weeks or months by either visual symptoms or headaches or both. If a patient has experienced transient, total, or partial loss of vision; elevated blood pressure; or other neurologic symptoms, discontinue estrogen-containing hormonal contraceptives immediately and refer her to a neurologist. If visual impairment accompanies migraine headaches that have become worse, discontinue OCs immediately.

If the headaches are not serious and are related to OC use, consider the following approaches:

- Discontinue the OCs.
- Lower the dose of estrogen.
- Lower the dose of progestin.
- Tricycle. Eliminate the pill-free interval for 2 to 3 consecutive cycles of pills. This recommendation is helpful only if a woman's headaches occur during the pill-free interval.



Source: Hatcher RA, et al. (2003),[149] with permission.

Figure 19-3 New onset or worsening headaches in OC users

Lens effects

Women who wear contact lenses may note some visual changes or change in lens tolerance with OC use. Normal saline eye drops often provide adequate treatment, but consultation with an ophthalmologist may be helpful.

Libido decrease

Though infrequent, decreased libido is occasionally a problem and may be the reason a woman seeks a different pill or a different contraceptive. When a patient notes a decrease in libido, also ask about depression as both symptoms may occur in the same patient. In some women, the pill alters vaginal secretions and decreases levels of free testosterone, both of which may decrease libido.[154] An estrogen deficiency may decrease vaginal lubrication and make sexual intercourse less comfortable and occasionally painful. Consider using the vaginal ring to increase lubrication. Even if the initiation of OCs is accompanied by a clear loss of interest in sex or an inability to have orgasms, evaluate other potential causes of the decreased libido or anorgasmia, including depression. Many women, however, may find more enjoyment from sex because the risk of pregnancy is reduced.

Hyperlipidemia

Routine screening for lipids is not necessary before prescribing OCs unless a patient has pre-existing hyperlipidemia or a very strong family history of premature cardiovascular disease. Estrogen is known to increase HDL-C, triglycerides, and total cholesterol levels and to decrease LDL-C. The androgen-derived progestins may be neutral or may reverse some of estrogen's effects on HDL-C and triglycerides and increase LDL-C. The net effect depends upon the dose, potency, and estrogen/androgen balance of each formulation. If LDL levels rise or HDL levels drop significantly with OC use, change to a more estrogenic, less androgenic formulation.

Hypertriglyceridemia is an independent risk factor for early cardiovascular disease in women. Although most modern formulations increase triglycerides by about 30%, these estrogen-induced triglycerides are differently sized fragments than are endogenously produced triglycerides, and they do not increase a woman's risk for atherosclerosis. However, excessively high serum triglycerides (>500 mg/dl) can cause pancreatitis. Therefore, women with triglycerides of >350 mg/dl should use estrogen-containing hormonal contraceptives only with caution. Lower dose pills (20–25 mcg EE) would clearly be preferred to higher dose ones; progestin-only formulations may be necessary.

Mastalgia

Both estrogen and progestin affect the breast. The average woman experiences up to a 20% increase in breast volume in the luteal phase due to venous and lymphatic engorgement. Estrogen causes hypertrophy of the adipose cells in the breast and can cause increase in breast size. In addition,

both hormones stimulate the terminal ductal lobular tuft growth especially in nulliparous women. Nearly 30% of women experience mastalgia or breast tenderness after they start taking OCs. A proper fitting bra is the first recommendation. Reduction of the doses of both steroids may be necessary if symptoms do not resolve rapidly enough to satisfy the patient. Lower dose pills (20 mcg) produced less mastalgia than higher dose (35 mcg) pills in one comparative trial.[155] If the symptoms develop just before menses, extended cycle length can help.

Melasma and chloasma

Estrogen stimulates the production of melanocytes and can cause darkening of pigmented areas (linea nigra). Darkening of patches on the face, often called the "mask of pregnancy," chloasma, or melasma can also develop. Women with darker skin pigment are more susceptible. The melasma fades slowly and incompletely after discontinuation of estrogen. Progestin-only methods may be preferable for at-risk women. Recommend consistent use of sunscreen and hats.

Mood swings, depression

Multiple studies have demonstrated no increase in the risk of clinical depression in women using OCs. Both estrogen and progestin in high-dose pills interact with tryptophans and serotonin; however, low-dose pills have not been implicated in any of these complaints.[55,155] Women on OCs remain solidly within normal ranges for all vitamins and do not require vitamin B supplementation.[156] Some women do report an increase in depressive symptoms, moodiness, and other emotional states when on OCs. This may represent an idiosyncratic response to hormones, which may warrant a decrease in hormone doses or pill cessation. However, it is important to identify when in a woman's cycle these symptoms develop. If the symptoms appear just before the menses, then extended or continuous use of active pills may dampen the hormonal swings.[147] If the patient desires withdrawal bleeding, restart her active pills each month on the first day of her menses. If there is any concern about an underlying depressive or anxiety disorder, these conditions deserve an explicit evaluation and treatment; cessation of hormonal contraceptives is not adequate therapy. Suicidal women need emergency treatment by specialists. Less acutely ill women may be managed locally with close follow-up.

Pregnancy

There is no evidence that OC users have higher rates of spontaneous abortion, preterm delivery, birth defects,[157–161] or compromise of fertility of offspring.[162] The risk of significant congenital anomalies is no higher than in the general population; no extra testing during prenatal care is needed because of early pregnancy exposure to steroidal hormones. Women should consider all their pregnancy options (keeping the baby, adoption, foster care, and abortion) based on their own personal situations; combined hormonal use should not influence that decision process.

Women who want to become pregnant should seek preconceptional care. They should start folic acid supplementation at least 1 to 3 months before they stop taking their pills. A routine dose of 0.4 mg folic acid supplement as found in prenatal vitamins is usually adequate. However, adolescent women who have had poor diets and prolonged OC use may benefit from 1 mg doses of folic acid preconceptionally and in the first trimester of pregnancy.

Once a woman discontinues the OCs, patches, or rings, her fertility returns rather rapidly to baseline rates. On average, there is a 2-week delay in the resumption of ovulation, but the normal time to ovulation ranges from 0 to 26 weeks. Barrier methods used to be suggested until a woman had her first spontaneous withdrawal bleed after stopping the pills. This was recommended to permit dating the pregnancy from the last menses. However, if a woman conceives the first month after stopping the pills, a dating ultrasound can be used to confirm the accuracy of her expected due date.

Vaginal discharge

Some women notice an increase in vaginal secretions with estrogen-containing contraceptives. These secretions generally are not an indication of infection. Women who use low OCs are not at any increased risk for developing uncomplicated candidal infections or bacterial vaginosis (BV). Reassurance is generally the only intervention needed once infection has been ruled out. Point out to the woman that these secretions are healthy and serve as lubricant during coitus.

Vaginal spotting and bleeding

Breakthrough spotting and bleeding are common (30% to 50%) in the first few months of OC use and generally resolve by the third to fourth month of use. Progestins administered early in the cycle reduce estrogen's proliferative influence and induce atrophy (thinning) of the uterine lining. When women first start to use OCs, their endometria must adjust to the exogenous hormones, so irregular spotting and bleeding is understandable. However, by the third pack of pills, 70% to 90% of women (depending upon the formulation) have no further breakthrough bleeding or spotting.

Before changing OC type, rule out more likely and more serious causes: pregnancy, infection (such as vaginitis and cervicitis), medications that block hormone aborption (olestin) or increase their metabolism by the liver (anticonvulsants, cigarette smoking, St. John's Wort, rifampin, griseofulvin), and gastrointestinal problems such as vomiting and diarrhea that may prevent adequate hormone absorption to sustain the uterine lining. *One of the most common causes of pill-associated spotting and bleeding is missed pills.*

For women with persistent irregular bleeding after 2 to 3 months of use, consider changing to other formulations, although no research indicates that any specific OC is best at eliminating spotting or bleeding.

- Women who report spotting or bleeding before they complete their active pills probably need more endometrial support. Increase the progestin content of their pills, either by changing to a different monophasic formulation or by switching to a triphasic formulation that increases progestin levels in the last active pills.
- Women with continued spotting after the withdrawal bleed need more estrogen support. Increase the estrogen in each tablet or decrease the progestin in the early pills (especially with a triphasic formulation). The cause of mid-cycle spotting/bleeding is not clear. One approach to this relatively uncommon bleeding pattern is to increase both estrogen/progestin mid-cycle with agents such as Triphasil and Tri-Levlen.

Seasonale. Some women experience spotting and breakthrough bleeding while using an extended-use pill such as Seasonale. Here are two suggestions to reduce these problems:

- Inform users that, as with all other pills, they will have more spotting initially when they begin taking pills. This spotting will decrease rapidly over time.
- One approach for Seasonale users is to take one pill every day for the first 21 days whether or not spotting occurs. Thereafter, on the first day of significant spotting, they can stop taking pills for 2-3 days to allow a withdrawal bleed to start, and then they should restart the active pills, taking at least 1 full pack each time before they stop again. As they take pills in this pattern, the length of time between spotting will increase and they will be able to eventually take pills for the full 84 days.

Weight change

A placebo-controlled, randomized clinical trial has demonstrated that there is no difference in weight gain due to low-dose OC use.[163] Similarly, a prospective trial of women using triphasic OCs with daily weight measurements for 4 months showed no change in mean weight at the end of the trial compared to baseline, although some weight fluctuations were noted during the cycle.[164] Oral contraceptive use by adolescent women has been shown not to be associated with either weight gain or increased body fat in a 9-year study.[165] In clinical trials, women who use OCs do not typically gain any more weight than women living in the United States typically gain in the same time interval.

However, some women may respond robustly to any of the pill's hormones. Increased measurements in the breasts, hips, and thighs reflect estrogen's impact on adipose cells (hypertrophy). Decreasing estrogen in the pill can reduce this impact. Weight gain similar to premenstrual fluid retention is due to increased aldosterone release and results from estrogen activity augmented by progesterone. In this situation, switch to a pill with both lower estrogen and progestin levels. Drospirenone-containing OCs, which have an antimineralocorticoid activity (mild diuretic effect), may

also be an appropriate choice in this condition. Steadily increasing weight may be attributed to the nitrogen retention and increase in muscle mass stimulated by androgens. Although it is unlikely that the pill would be responsible for this type of weight gain, switching to a low androgenic pill (Ortho Tri-Cyclen, Ovcon-35, Modicon, Yasmin, etc.) may address that patient's concerns. Every woman should be encouraged to adopt a healthy diet and to exercise routinely to achieve and maintain a healthy weight.

PILLS AND DRUG INTERACTIONS

Some drugs may negatively influence the effectiveness of combined hormonal contraceptives:

Anti-tuberculosis. Rifampicin (Rifampin) and rifabutin increase hepatic clearance of EE and progestins.[166] Although rifampicin did not permit break-through ovulation in one small study,[167] product labeling and several published reports recommend women using these agents avoid taking OCs.

Antifungal (systemic). Griseofulvin increases microsomal enzyme activity and theoretically may decrease OC efficacy.

Anticonvulsants. Many of the anticonvulsants, such as barbituates, carbamazepine (Tegretol), oxcarbazepine, (Trileptal), phenobarbital, phenytoin (Dilantin), primidone (Mysoline), topiramate (Topamax) and felbamate (Felbatol) induce various cytochrome p450 activities and reduce circulating levels of contraceptive hormones. In some women, low doses can induce profound changes in circulating estrogen levels; in others, high doses of anticonvulsants produce minimal effect. Do not offer low-dose (<35 mg EE) formulations to a woman using these anticonvulsants unless she uses a back-up contraceptive method. If she has no breakthrough bleeding while using a 35-mcg EE pill with a back-up barrier method for 3 months, she may rely on the pills exclusively. However, many women using these anticonvulsants do require 50 mcg EE (not mestranol) pills to control breakthrough bleeding and possibly prevent escape ovulation. These drugs also affect the circulating levels of estrogen and progestin from the patches and vaginal rings. No data are available yet about efficacy of these methods in women using anticonvulsants. Therefore, exercise caution and recommend barriers. Progestin-only injections and IUDs are generally better choices. It should be noted that neither valproic acid nor gabapentin affects serum levels of estrogen or progestin.

Anti-HIV protease inhibitors. Several of the anti-HIV protease inhibitors can change (either increase or decrease) serum levels of estrogen and progestins. Consult the labeling for specific anti-HIV protease inhibitors to see if OC use requires additional back-up methods or if different methods may need to be considered.

Broad-spectrum antibiotics. Broad-spectrum antibiotics such as amoxicillin and tetracycline, which alter the intestinal flora thought to be

instrumental in promoting absorption of the sex steroids, do *not* reduce the efficacy of OCs. Women using the antibiotics do have statistically significant but *not* clinically significant lower serum levels of estrogen and progestins. However, virtually every woman taking these antibiotics has remained well within the therapeutic range for the sex steroids.[168–170] As a result, back-up methods should not be necessary unless the patient has problems taking her pills, e.g., if her underlying medical condition interferes with pill taking or absorption. Long-term use of broad-spectrum antibiotics (such as erythromycin or tetracycline for acne) is compatible with OC use; back-up methods are not routinely needed for pregnancy prevention.[171]

Over-the-counter drugs. St. John's Wort is taken by many women to treat mild depression. Since this botanical agent does not require a prescription, women sometimes neglect to tell their health care providers that they are using it. St. John's Wort greatly increases hepatic metabolism of exogenous estrogen and progestin. Although little published data are available about the impact of this agent on pregnancy rates with OC use, some experts have recommended increasing the dose of emergency contraceptives by 50% in women using this over-the-counter antidepressant. The FDA has alerted providers that St. John's Wort may decrease the therapeutic effect of OCs.[172]

Another unanswered concern is that women who use Orlistat to block fat absorption may also reduce intestinal absorption of OC hormones. This concern is magnified if the woman experiences diarrhea from Orlistat use.

On a lighter note, the German National Chemists Association has advised women who use OCs to avoid eating too much licorice. Eating more than 10 to 50 gm a day of black licorice may trigger edema or elevate blood pressure, and OCs may do likewise.

OC effects on drug metabolism

The estrogen in combined hormonal contraceptives may alter hepatic clearance of other medications. Serum levels of fluoroquinolones, such as moxifloxacin and trovafloxacin, are significantly lower in OC users.[173] Similarly, estrogen promotes more marked metabolic clearance of some anticonvulsants, which would reduce circulating levels. Women starting these methods should have their anticonvulsant levels checked 1 month after OC initiation to insure that their medications are still in the therapeutic range. Conversely, estrogen-containing hormonal contraceptives may increase the effect of theophylline (used to treat asthma), the antipsychotic drugs diazepam (Valium) and chlordiazepoxide (Librium), and cyclic antidepressants. Doses of these drugs may need to be lowered with combined hormonal contraceptive use.

Drospirenone acts as an antimineralocorticoid and can interact with other potassium-sparing drugs to cause hyperkalemia. Women using ACE

inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDS on a daily basis to treat chronic conditions or diseases should have their serum potassium checked during the first cycle of drospirenone use.

INSTRUCTIONS FOR USING COMBINED PILLS

Pills work primarily by stopping ovulation (release of an egg), and they thicken a woman's mucus in her cervix to keep sperm out of the upper genital track. Pills have less than a 1% rate of failure if taken every day on schedule. In addition to preventing pregnancy, pills lower your risk of ovarian cancer, cancer of the lining of the uterus (endometrium), benign breast masses, and some kinds of ovarian cysts. Pills decrease menstrual blood loss, cramps, and pain. Pills tend to make acne and oily skin better. Pills also decrease your chance of having a dangerous ectopic pregnancy—a pregnancy outside of the uterus.

Remember: pills do not protect you from AIDS (acquired immunodeficiency syndrome) or other sexually transmitted infections. Use a latex or polyurethane male condom or a female condom every time you have sexual intercourse that could expose you or your partner to infection.

Be sure you know your clinician's telephone number in case of questions or problems.

Getting started

Your clinician will suggest one of three ways to begin taking pills:

- *Quick Start.* Take your first pill while you are in your clinician's office. This is the preferred method. Use a back-up contraceptive method for 7 days. You will not get your period until you finish taking the active pills.
- *First-day start.* Take your first pill on the first day of your next period.
- *Sunday start.* Take your first pill on the first Sunday, during your period. Use a backup method for 7 days.

Daily pill routine

1. Take 1 pill a day until you finish the pack. Then:
   - If you are using a 28-day pack, begin a new pack immediately. Skip no days between packages.
   - If you are using a 21-day pack, stop taking pills for 1 week and then start your new pack.
   - An alternative is to begin each new pack the day withdrawal bleeding begins.
2. Associate taking your pill with something else that you do at about the same time every day, like going to bed, eating a meal, or brushing your teeth.

3. Mark your calendar to remind yourself of the days you will begin a new pack of pills. Some women mark their calendar each day as they take their pills.
4. Check your pack of pills each morning to make sure you took your pill the day before.
5. Use a back-up contraceptive method if any of the following occur to make your pills less effective: you missed taking pills, were late starting your new pill pack, had severe vomiting or diarrhea, or are taking medications that lower the ability of the body to absorb contraceptive hormones (see the instructions on these specific problems). If you think you may have had sexual intercourse that was not adequately protected, consider emergency contraception. Call 1-888-NOT-2-LATE for more information.
6. Use condoms if you suspect, even a little, that you or your partner may be exposed to a sexually transmitted infection.
7. If you see a clinician for any reason or are hospitalized, be sure to mention that you are taking birth control pills.
8. You do *not* need to take a "rest" from taking pills. If you stop taking your pills, you risk becoming pregnant.

Missed pills

OC pills should be taken every day at about the same time. Missing a pill means taking it after an interval of more than 24 hours or not at all (completely missing a pill). The impact of a missed pill depends upon when in the pill packet you miss a pill (which week), how many pills you may have missed earlier in the pack, and whether you need to use emergency contraception. If you had only one episode of missed pills in packet, follow these directions:

# Pills Missed	Week Pills Missed	OC Recommendation	Finish this pack	Emergency contraception	7-day Back-up
1	1	Take 2 pills ASAP	Yes	Yes*	Yes
1	2-3	Take 2 pills ASAP	Yes	No	No
1	4	Skip placebo pills	Yes	No	No
2-4	1	Take 2 pills ASAP	Yes	Yes*	Yes
2-4	2	Take 2 pills ASAP	Yes	No	No
2-4	3	Start new pack	N/A	No	No
2-4	4	Skip placebo	Yes	No	No
5	Any	Take 2 pills – start new pack	N/A	Yes*	Yes

* Start emergency contraception as soon as possible. No need to double up on pills. Take the the next pill on the next day.

While these instructions are very complete, they are also very complicated. The odds are that if you miss a pill late in the pack, you probably missed a pill or took it late sometime earlier in the pill pack. For this reason, it has been suggested that if you miss active pills, think about whether you had intercourse in the last 120 hours:

- If you had no intercourse in the last 5 days, take 2 active OCs all at once, use a back-up method for 7 days, and finish the pill pack by taking 1 pill daily. You can skip the placebo pills in this pack and start a new pack immediately if you missed more than 4 pills.
- If you had intercourse in the last 5 days, use emergency contraception today (call your clinician to get some if you do not have any on hand). Restart daily OCs the next day to finish the pack. Use a back-up method for 7 days. You can skip the placebo pills of this pack and start a new pack immediately if you missed more than 4 pills.

Vomiting or diarrhea

Repeated vomiting or severe diarrhea can decrease the absorption of the hormones in pills. The longer you have vomiting or diarrhea, the greater the concern and the more important it would be to avoid intercourse, use condoms as a back-up contraceptive, and/or use emergency contraceptive pills.

Pills and your periods

1. *Short and scanty.* A drop of blood, or a brown stain on your panty liner, pad or on your underwear during the week you are taking no hormonal pills is counted as a period when you are on the pills.
2. *Spotting.* You may have very light bleeding between periods for the first few months you are on pills. If you have bleeding between periods, try to take your pills at the same time every day. Spotting is generally not a sign of any serious problem. If after the first few months you suddenly begin to have bleeding between periods (especially after intercourse) and have not missed pills or taken pills late, have your clinician check you for an infection or other problems. Spotting between periods may also signal decreased pill effectiveness. *Start each new package of pills on time.* Some clinicians recommend a back-up contraceptive when you have spotting, especially if you are taking a medication that may make the pill less effective.
3. *Missed period.* If you have not missed any pills and you miss one period without any other signs of pregnancy, pregnancy is very unlikely, but you may wish to get a pregnancy test if you are worried. Many women miss one period now and then. Call your clinician if you are worried. You are fairly safe and can start a new pack of pills on your regular day.

Here Is a Simple Way to Confirm That You Are Not Pregnant

If your period does not start during the last few days on 'reminder' pills or during the first 3 days of the pill-free interval, take your temperature with a special kind of thermometer. The basal body temperature (BBT) thermometer measures your lowest temperature, generally in the morning before you get out of bed. If your BBT is 98° F for 3 days in a row during the pill-free week, you are probably not pregnant.

Pills and pregnancy

1. If you decide you want to become pregnant, stop taking pills. Use prenatal vitamins for 1 to 3 months before you try to get pregnant. It is safe to become pregnant immediately after you stop the pill. The pill does not decrease your fertility; however, after you stop taking pills, you may have a 1- to 2-month delay before your periods become regular. You may wish to use another contraceptive method until you have at least 1 normal menstrual period off the pill. That way, when you become pregnant, your date of delivery can be calculated more easily.
2. If you become pregnant while taking pills, do not worry about the pills' impact on your pregnancy. It does not seem to increase the risk of having a baby with birth defects or of having a spontaneous abortion.

ACHES—PILL WARNING SIGNALS

Call your clinician if you have any of the Pill Warning Signs (next page) or if you develop depression, yellow jaundice, a breast lump, a bad fainting attack or collapse, a seizure (epilepsy), difficulty speaking, a blood pressure above 160/95 mm Hg, a severe allergic skin rash, or if you are immobilized (in a wheelchair or bedridden) after an accident or major surgery. If major surgery is planned, switch from an estrogen containing contraceptive method 4 weeks before the operation. The risk of a blood clot in a vein is greatest if any of the following conditions are present: if you are overweight, immobile, have severe varicose veins, or if several members of your family have had a blood clot in a vein before age 45. Usually these warning signs have an explanation other than pills; get checked to be sure. *Do not ignore these problems or wait to see if they disappear.*

Pills and future fertility

1. Pills are a good option for women who want to become pregnant in the future.
2. By reducing the risk of causes of infertility such as pelvic infections, uterine fibroids, ectopic pregnancies, ovarian cysts, ovarian cancer, endometrial cancer, and endometriosis, OCs may improve your future ability to become pregnant.

PILL WARNING SIGNALS

Pills have been studied extensively and are very safe. However, very rarely pills lead to serious problems. Here are the warning signals to watch out for while using pills. These warning signals spell out the word **ACHES**. If you have one of these symptoms, it may or may not be related to pill use. You need to check with your clinician as soon as possible. The problems that could possibly be related to using pills are as follows:

ABDOMINAL PAIN

- Blood clot in the pelvis or liver
- Benign liver tumor or gall bladder disease

CHEST PAIN

- Blood clot in the lungs
- Heart attack
- Angina (heart pain)
- Breast lump

HEADACHES

- Stroke
- Migraine headache with neurological problems (blurred vision, spots, zigzag lines, weakness, difficulty speaking)
- Other headaches caused by pills
- High blood pressure

EYE PROBLEMS

- Stroke
- Blurred vision, double vision, or loss of vision
- Migraine headache with neurological problems (blurred vision, spots, zigzag lines)
- Blood clots in the eyes
- Change in shape of cornea (contacts don't fit)

SEVERE LEG PAIN

- Inflammation and blood clots of a vein in the leg

You should also return to the office if you develop severe mood swings or depression become jaundiced (yellow-color skin), miss 2 periods or have signs of pregnancy.

Source: Hatcher RA, et al. (2003),[149] with permission.

3. If your periods are irregular prior to taking pills, they may again become irregular after you stop taking pills.
4. Return of fertility is not improved by taking a break from pills.
5. You may experience some delay (an average of 2 to 3 months) in becoming pregnant compared with the amount of time it would have taken if you had not taken the pills. Do *not* count on this; if you do not want to become pregnant now, start using another contraceptive method right after you stop taking pills.
6. Between 1% and 2% of women will not menstruate for 6 months or more after stopping pills. However, it is not certain that OCs are responsible for this lack of periods.

Pills and smoking

If you smoke, stop. This is the single most important thing you can do for your health. If you cannot stop, try to cut back on the number of cigarettes you smoke. It is all the more important that you watch for the pill warning signals. If you smoke, you should probably *stop* taking pills at age 35, and definitely by age 40.

Pills and mood changes

If you notice mood changes—depression, irritability, or a change in sex drive—see your clinician. Switching pill brands may help if your mood changes are related to the pill. Depression, premenstrual symptoms (PMS), and sexual pleasure can improve on pills, but in some women they become worse.

Pills and Drug Interactions

A few drugs you may need to take for medical conditions may decrease the effectiveness of your pills. Be sure to tell all your clinicians that you are using OCs. If you are using drugs such as rifampin, griseofulvin, Dilantin (phenytoin), phenobarbital, topirimate, Tegretol (carbamazepine), or St. John's Wort, tell your clinician, because you may need to use stronger pills or a back-up method of contraception. Women using antiretroviral drugs may need lower or higher dose OCs.

DO BIRTH CONTROL PILLS CAUSE BREAST CANCER?

After more than 50 studies, most experts believe that *pills have little, if any, effect on the risk of developing breast cancer.* The Woman's Care Study found no increased risk for breast cancer among women currently using pills and a decreased risk of breast cancer for those women who had previously used pills. Use of pills by women with a family history of breast cancer was not associated with an increased risk for breast cancer, nor was the initiation of pill use at a young age.[174]

A recent summary of studies suggested that current users of pills are slightly more likely to be *diagnosed* with breast cancer.[175] Two factors may explain the increased risk of breast cancer being diagnosed in women currently taking pills: 1) a *detection bias,* meaning that pill users are simply more likely to have existing breast cancer identified because they have more breast exams or more mammography, or 2) *promotion* of an existing lesion that is nearly cancer into one that is cancer, usually an early cancer. Most authorities think the first explanation is most likely because the duration of pill use has no effect on risk and the excess risk seen in current users is restricted to breast cancers that are localized. Breast cancers diagnosed in women currently on pills or women who have taken pills in the past are more likely to be localized.[175] *By the age of 55,* the risk of having had breast cancer diagnosed is the *same* for women who have used pills and those who have not.

The conclusion of several studies of the risk for breast cancer in women on pills is that women with a strong family history of breast cancer do not further increase their risk for breast cancer risk by taking pills.[174–179]

While there are still unanswered questions about pills and breast cancer, today, four decades after their arrival on the contraceptive scene, the overall conclusion is that pills have little or no effect on breast cancer. *"Many years after stopping oral contraceptive use, the main effect may be protection against metastatic disease."* [175,180]

Transdermal Contraceptive Patch

The Ortho Evra transdermal contraceptive patch is a lightweight, wafer-thin, flexible, beige-colored, 20 cm^2 matrix patch. The patch consists of three layers: an outer protective layer of polyester; a medicated, adhesive layer; and a clear, polyester release liner, which protects the adhesive layer and is removed prior to application. Once the hormones are in circulation, they act the same way as orally administered hormones do to prevent pregnancy.

Each patch lasts 7 days. Women replace the patch each week for 3 weeks each cycle, then have a 7 day patch-free week, during which time they will start their withdrawal bleeding.

Advantages and Indications

The transdermal patch system is safe, effective, and rapidly reversible and can be used by healthy, nonsmoking women throughout the

reproductive years. Because the hormonal mechanisms of action are similar, it is expected that the patch may provide many of the same advantages and non-contraceptive health benefits that OCs do, although data about long-term health benefits may not be documented for decades.

The patch offers the clear advantage of once-a-week dosing, which makes it easier to use successfully. In addition, the user can easily verify the presence of the patch, which can reassure her of continued protection. This reduces the anxiety many women report with OCs—questioning if they remembered to take today's pill and worrying that they might forget to take it. Given that by the third cycle of OCs, studies show that 54% of women missed more than 2 pills,[181] this concern seems justified. In a comparison of the clinical 3 trials, perfect use with the patch ranged from 92.9% to 93.6% whereas OCs were taken correctly by only 77.2% to 88.77% of women.

DISADVANTAGES AND CAUTIONS

Although the patch avoids the challenges of daily administration, it still needs to be changed every week. It is difficult to conceal, so privacy is sub-optimal. Costs, storage and access issues are still present. The patch, as with all hormonal contraceptive methods, provides no protection against sexually transmitted infections. At-risk women should be counseled about safer sex practice and offered male condoms to reduce their vulnerability.

In addition to the health complications associated with combined hormonal contraceptives (myocardial infarction, stroke, VTE, hypertension, diabetes, gallbladder disease, cholestatic jaundice, hepatic neoplasms, etc.), the transdermal delivery system is associated with an increased risk of local skin irritation, redness or rash. The residual adhesive clinging to the skin after the patch is removed may need to be lifted off with baby oil.

Side effects

In the comparative clinical trials done in the United States, side effects reported by patch users were similar to those reported by pill users except that 20% of the patch users had unique complaints related to reactions at the application site. In addition, women using the patch were more likely than OC users to experience breast tenderness, vaginal spotting, and dysmenorrhea in the first 2 cycles. Within 3 months of use, the occurrence of these hormone-related side effects was similar between patch and pill users. The numbers of women who withdrew from the trial due to serious adverse effects were relatively small. However, overall more patch users than OC users withdrew from the study due to adverse effects (8.6% vs. 1.8%) or for specific complaints such as skin reactions (2.6% vs. 0%), nausea (1.5% vs. 0.3%), and dysmenorrhea (1.5% vs. 0.3%). Hyperpigmentation may develop under the patch application site. It is reversible but may take some time.

PRECAUTIONS

None of the women with medical contraindications to pill use is a candidate for the patch, unless the problem with pills relates to intestinal absorption of hormones. Additionally, women with conditions that affect the skin beneath the patch should not use the patch. The patch should not be placed over skin that is red, irritated, or cut. Women with psoriasis, eczema or sunburn may not be able to use the patch. Women should periodically confirm that the patch is firmly adherent and avoid using any creams, lotion, or oils near the patch since those agents may cause the patch to detach. The effectiveness of the patch is reduced in women who weigh more than 198 pounds.

PROVIDING THE TRANSDERMAL PATCH

Talk to the patient about how and where to store her patches. Remind her that when she removes a patch, she should fold it closed to reduce release of the hormones. She should not flush the used patch into the water system, but should dispose of it in the garbage as solid waste.

The patient can start her patch on the Sunday following the first day of her menses or on the first day of her flow. If she starts on Sunday, she should use a back-up method for 7 days; if she starts on the first day of her flow, she needs no back-up method. The calendar reminders that accompany the patches can accommodate either approach. The Quick Start for the patch may be reported soon.

Switching from other methods. Contraceptive sex hormone levels reach reliably therapeutic levels about 48 hours after patch placement; therefore, women switching from OCs should apply their first patch as soon as their pill withdrawal period starts, but no later than 4 to 5 days after their last active pill. If they use the Sunday start method, they will need 7 days of back-up contraception. They should *not* wait until they complete their last pack of pills to start the patch. Women switching from injectable contraceptives (DMPA) should apply their patches when they are due for their next injection.

MANAGING PROBLEMS AND FOLLOW UP

Dislodged or detached patches. During clinical trials involving over 70,000 patches, fewer than 3% required replacement for partial detachment and fewer than 2% were replaced because they became fully detached. Patches adhered well in humid conditions (saunas), in exercise conditions, and during swimming. In freezing weather, the patch should be worn beneath clothing.

- If the patch is partially detached, it should be firmly pressed in place for 10 seconds. Reconfirm that the edges are sticking well. If it sticks well, the woman can continue to use it for the full 7 days. If it does not stick well, tell her to remove it and apply a replacement patch.

- If the patch is completely detached, she should try to reapply the same patch if it is clean and usable. If it cannot be used, tell her to apply a new patch immediately.

If the patch has been partially or completely detached for more than 24 hours or if the woman does not know how long it has been loose, instruct her to use a back-up method for 7 days. Consider the need for emergency contraception.

Missed patches and late patches. Management of missed patches depends upon which patch is forgotten and how long it is missed:

When patched missed	Management
1st week patch.	• If a patch is forgotten or late the first week, give emergency contraception if the woman has had unprotected intercourse. • Tell her to place the patch immediately. • She should use a back-up method for 7 days. • The woman will change her patch each week on the day of the week she started this new patch from now on.
2nd—3rd week patch	• *1-2 days late*: the woman must remove the old patch and place a new one immediately. No back-up method or emergency contraception is needed. • *More than 2 days late*: Have her remove the old patch and place a new one on immediately. Provide emergency contraception if she has had unprotected intercourse (especially if she is 4 days or more late applying her patch). She should use back-up method for 7 days. Tell her to change the patch each week on the day of the week that she placed this new patch.
4th week patch	• Tell her to remove the patch. • She should place a new one on the usual day. • No back-up method or emergency contraception is needed.

USING THE TRANSDERMAL SYSTEM

One patch is used for 7 days. Apply a new patch once a week on the same day for 3 weeks in a row. During the 4th week, do not wear a patch. At the end of the week, start another cycle of patches.

Applying the patch

1. Each patch is packaged in an individual foil packet. To place the patch, open the pouch by tearing along the top edge and one side edge. Peel the foil pouch apart and open it. Lift the patch and its clear plastic cover out of the foil pouch together by using a fingernail to peel the unit off the foil pouch.
2. Fold the patch open. Hold onto one half and peel the plastic off the other half. Apply the sticky side of the opened patch to the skin. Press it in place. The patch can be placed on the buttock, abdomen, upper torso (excluding the breasts), or on the outside

of the upper arm. Avoid placing patches in areas of friction such as under bra straps or thongs. The patch should be applied only to clean, dry skin. Do not put it over skin that is irritated, sunburned, red or infected. Make sure there are no creams, oils, sunscreen, or sweat on the skin or the patch will not adhere.

3. Fold the patch in half, remove the clear plastic cover, open it and apply the rest of the sticky side of the patch to the skin. Press firmly on the patch for 10 seconds. Run your finger around the edges of the patch to make sure that all parts of the patch are sticking properly.

Wearing the patch

1. Keep the patch in the same place for 7 days; then remove it. Check the patch every day to make sure it is fully adherent.
2. Apply a new patch in a different spot on your body. Wear it for 7 days. Repeat the procedure for a third week.
3. During the fourth week, do not wear a patch. You will begin your menstrual period.
4. After a week without wearing a patch, apply a new "first-week" patch on the same day of the week you applied your other patches.
5. Store the patches in their protective pouches at room temperature.

Removing the patch

1. To remove the patch, grasp it by an edge and pull it off. Fold it closed on itself on the adhesive side to seal in the medication.
2. Discard the patch in the solid waste garbage; do not flush it into the waste water system.
3. If any stickiness or adhesive remains on your skin, remove it by using baby oil; do not use harsh chemicals such as nail polish remover, alcohol, etc.

Vaginal Contraceptive Ring

The vaginal contraceptive ring (NuvaRing) is a flexible, soft, transparent ring made of the plastic ethylene vinyl acetate. The ring has an outer diameter (side to side) of 54 mm and a cross-sectional diameter of 4 mm. The ring releases ethinyl estradiol and etonorgestrel in steady, low doses so that serum levels are lower than the patch or pills.

The woman places one ring high in the vaginal once every 28 days. The ring is kept in place for 21 days and removed for a 7-day ring-free period to permit withdrawal bleeding. Hormonal levels needed to suppress ovulation are achieved within the first day of vaginal ring use, so there is no delay in onset of contraceptive protection, as seen with the transdermal patch. The ring has a steady release rate, so serum hormone levels do not fluctuate during the day the way they do with OCs.

COLOR PHOTOS

of Combined and Progestin-Only Oral Contraceptives

The eight color pages of pills are organized as follows:

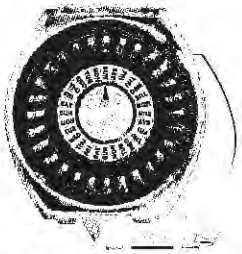
Color photos of pills from lowest to highest estrogen dose

- Progestin-only pills with **no estrogen**: Micronor, NOR-QD, and Ovrette
- Lowest estrogen pills with **20 micrograms** of the estrogen, ethinyl estradiol: Alesse, Levlite, LoEstrin 1/20, and Mircette
- All of the **30- and 35-microgram** pills (all ethinyl estradiol)
- All of the **phasic** pills
- Highest estrogen pills, with **50 micrograms** of estrogen (ethinyl estradiol OR mestranol). Mestranol is converted in the body to ethinyl estradiol; 50 mcg of mestranol is equivalent to 35 mcg of ethinyl estradiol

There are prominent horizontal or vertical parallel lines ("equal signs") between pills which are pharmacologically exactly the same. The color and packaging of pills dispensed in clinics may differ from pills in pharmacies.

Pills you can prescribe as emergency contraceptive pills

PROGESTIN-ONLY PILLS



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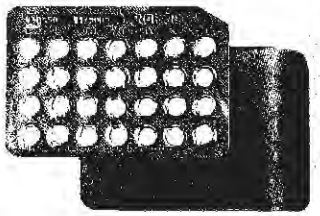
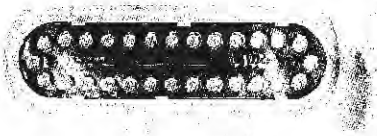


MICRONOR® TABLETS
28-DAY REGIMEN
(0.35 mg norethindrone) (lime green)
Ortho-McNeil

NOR-QD® TABLETS
(0.35 mg norethindrone) (yellow)
Watson



OVRETTE® TABLETS
(0.075 mg norgestrel) (yellow)
Wyeth

COMBINED PILLS - 20 microgram PILLS

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AVIANE
(0.1 mg levonorgestrel/ 20 mcg ethinyl estradiol)
(active pills orange)
Barr Laboratories

LEVLITE™ - 28 TABLETS
(0.1 mg levonorgestrel/20 mcg ethinyl estradiol)
(active pills pink)
Berlex

ALESSE - 28 TABLETS
(0.1 mg levonorgestrel/20 mcg ethinyl estradiol)
(active pills pink)
Wyeth

LOESTRIN® FE 1/20
(1 mg norethindrone acetate/20 mcg ethinyl estradiol/75 mg ferrous fumarate [7d])
(active pills white)
Pfizer

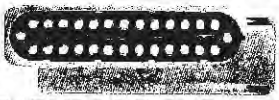
MIRCETTE - 28 TABLETS
(0.15 mg desogestrel/ 20 mcg ethinyl estradiol X 21 (white)/ placebo X 2 (green)/10 mcg ethinyl estradiol X 5 (yellow)
Organon

(B)

COMBINED PILLS - 30 microgram PILLS

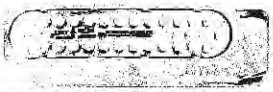
LEVLEN® 28 TABLETS
(0.15 mg levonorgestrel/30 mcg ethinyl estradiol)
(active pills light orange)
Berlex

=



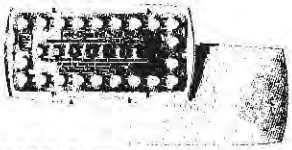
LO/OVRAL®-28 TABLETS
(0.3 mg norgestrel/30 mcg ethinyl estradiol)
(active pills white)
Wyeth

||



NORDETTE®-28 TABLETS
(0.15 mg levonorgestrel/30 mcg ethinyl estradiol)
(active pills light orange)
Monarch

||

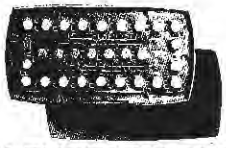


LOW-OGESTREL - 28
(0.3 mg norgestrel/30 mcg ethinyl estradiol)
(active pills white)
Watson

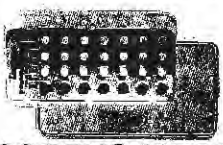
||

SEASONALE
(0.15 mg levonorgestrel/30 mcg ethinyl estradiol)
84 active pills followed by 7 placebo pills
Barr Laboratories

=



LEVORA TABLETS
(0.15 mg levonorgestrel/30 mcg ethinyl estradiol)
(active pills white)
Watson



DESOGEN® 28 TABLETS
(0.15 mg desogestrel/30 mcg ethinyl estradiol)
(active pills white)
Organon

LOESTRIN® 21 1.5/30
(1.5 mg norethindrone acetate/ 30 mcg ethinyl estradiol)
(active pills green)
Pfizer

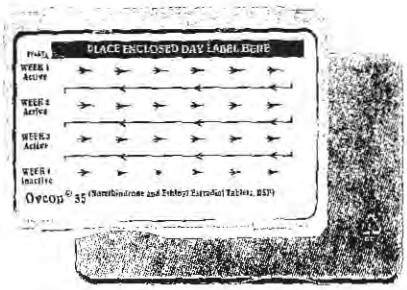
||

ORTHO-CEPT® TABLETS
28-DAY REGIMEN
(0.15 mg desogestrel/30 mcg ethinyl estradiol)
(active pills orange)
Ortho-McNeil

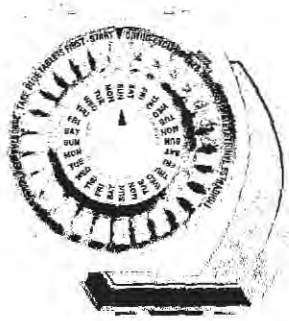
YASMIN 28 TABLETS
(3.0 mg drospirenone/30 mcg ethinyl estradiol)
(active pills yellow)
Berlex

(C)

COMBINED PILLS – 35 microgram PILLS

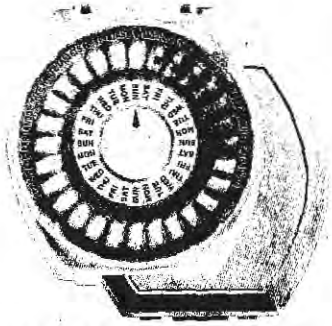


OVCON® 35 28-DAY
(0.4 mg norethindrone/35 mcg ethinyl estradiol)
(active pills peach)
Warner-Chilcott
Now there is a chewable Ovcon-35 pill! ←



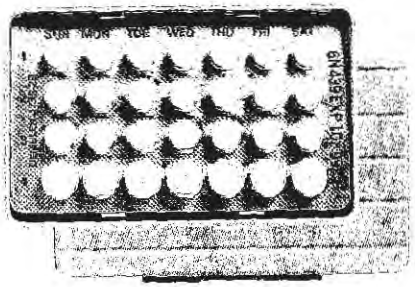
ORTHO-CYCLEN® 28 TABLETS
(0.25 mg norgestimate/35 mcg ethinyl estradiol)
(active pills blue)
Ortho-McNeil

=



BREVICON® 28-DAY TABLETS
(0.5 mg norethindrone/35 mcg ethinyl estradiol)
(active pills blue)
Watson

MODICON® TABLETS 28-DAY REGIMEN
(0.5 mg norethindrone/35 mcg ethinyl estradiol)
(active pills white)
Ortho-McNeil



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DEMULEN® 1/35-28
(1 mg ethynodiol diacetate/35 mcg ethinyl estradiol)
(active pills white)
Pharmacia
A Division of Pfizer

ZOVIA® 1/35E–28
(1 mg ethynodiol diacetate/35 mcg ethinyl estradiol)
(active pills light pink)
Watson

(D)

COMBINED PILLS - 35 microgram PILLS (continued)

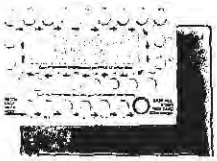
=

NORETHIN 1/35E–28
(1 mg norethindrone/35 mcg ethinyl estradiol)
(active pills white)
Shire

=

ORTHO-NOVUM® 1/35 28 TABLETS
(1 mg norethindrone/35 mcg ethinyl estradiol)
(active pills peach)
Ortho-McNeil

=



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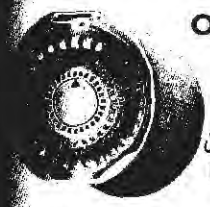
NORINYL® 1+35 28-DAY TABLETS
(1 mg norethindrone/35 mcg ethinyl estradiol)
(active pills yellow-green)
Watson

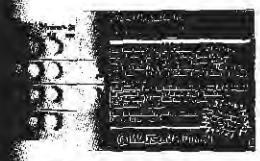
NECON 1/35-28
(1 mg norethindrone/35 mcg ethinyl estradiol)
(active pills dark yellow)
Watson

COMBINED PILLS - PHASIC PILLS



ORTHO TRI-CYCLEN® LO - 28 TABLETS
(norgestimate/ethinyl estradiol)
0.18 mg/25 mcg (7d) (white),
0.215 mg/25 mcg (7d) (light blue),
0.25 mg/25 mcg (7d) (dark blue)
remaining 7 placebo pills are green
Ortho-McNeil

CYCLESSA
(desogestrel/ethinyl estradiol–triphasic regimen)
0.1 mg/25 mcg (7d) (light yellow)
0.125 mg/25 mcg (7d) (orange)
0.150 mg/25 mcg (7d) (red)
Organon



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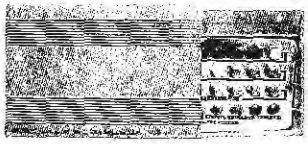


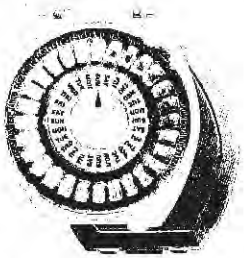
TRIVORA®
(levonorgestrel/ethinyl estradiol–triphasic regimen)
0.050 mg/30 mcg (6d), 0.075 mg/40 mcg (5d), 0.125 mg/30 mcg (10d) (pink)
Watson

TRIPHASIL®-28 TABLETS
(levonorgestrel/ethinyl estradiol–triphasic regimen)
0.050 mg/30 mcg (6d) (brown),
0.075 mg/40 mcg (5d) (white),
0.125 mg/30 mcg (10d)
(light yellow)
Wyeth

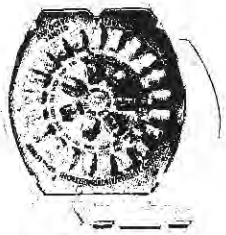
TRI-LEVLEN® 28 TABLETS
(levonorgestrel/ethinyl estradiol–triphasic regimen)
0.050 mg/30 mcg (6d) (brown),
0.075 mg/40 mcg (5d) (white),
0.125 mg/30 mcg (10d)
(light yellow)
Berlex

(E)

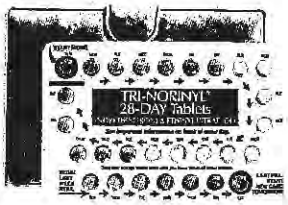
COMBINED PILLS - PHASIC PILLS (continued)



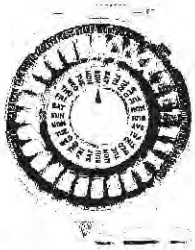
ORTHO-NOVUM® 10/11
28 TABLETS
(norethindrone/ethinyl estradiol)
0.5 mg/35 mcg (10d) (white),
1 mg/35 mcg (11d) (peach)
Ortho-McNeil



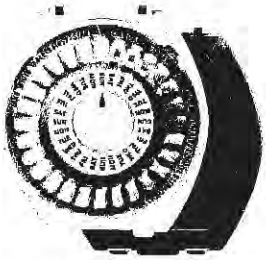
JENEST 28 TABLETS
(norethindrone/ethinyl estradiol)
0.5 mg/35 mcg (7d) (white),
1 mg/35 mcg (14d) (peach)
Organon



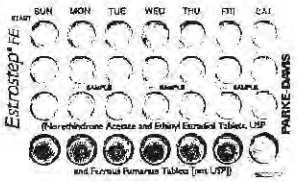
TRI-NORINYL®
28-DAY TABLETS
(norethindrone/ethinyl estradiol)
0.5 mg/35 mcg (7d) (blue),
1 mg/35 mcg (9d) (yellow-green),
0.5 mg/35 mcg (5d) (blue)
Watson



ORTHO-NOVUM® 7/7/7
28 TABLETS
(norethindrone/ethinyl estradiol)
0.5 mg/35 mcg (7d) (white),
0.75 mg/35 mcg (7d) (light peach),
1 mg/35 mcg (7d) (peach)
Ortho-McNeil



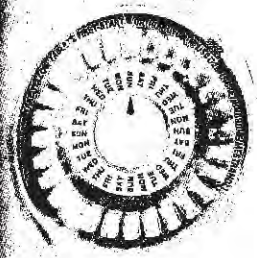
ORTHO TRI-CYCLEN®
28 TABLETS
(norgestimate/ethinyl estradiol)
0.18 mg/35 mcg (7d) (white),
0.215 mg/35 mcg (7d) (light blue),
0.25 mg/35 mcg (7d) (blue)
Ortho-McNeil



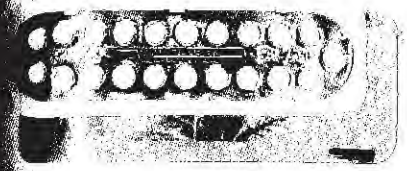
ESTROSTEP® FE
28 TABLETS
(norethindrone acetate/ethinyl estradiol)
1 mg/20 mcg (5d) (white triangular),
1 mg/30 mcg (7d) (white square),
1 mg/35 mcg (9d), 75 mg ferrous
fumarate (7d) (white round)
Pfizer

COMBINED PILLS - 50 microgram PILLS

Pills with 50 micrograms of mestranol are not as strong as pills with 50 micrograms of ethinyl estradiol



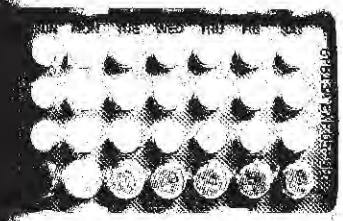
ORTHO-NOVUM® 1/50
28 TABLETS
(1 mg norethindrone/50 mcg mestranol)
(active pills yellow)
Ortho-McNeil



OVRAL - 21 TABLETS
(0.5 mg norgestrel/50 mcg ethinyl estradiol)
(active pills white)
Wyeth

=

OGESTREL
Watson



DEMULEN® 1/50-28
(1 mg ethynodiol diacetate/50 mcg ethinyl estradiol)
(active pills white)
Pharmacia
A Division of Pfizer

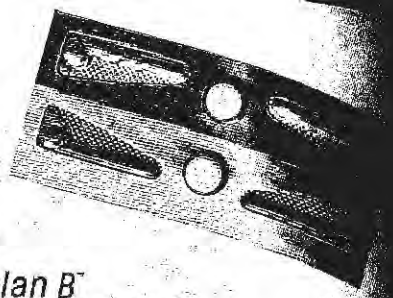
OVCON® 50 28-DAY
(1 mg norethindrone/50 mcg ethinyl estradiol)
(active pills yellow)
Warner-Chilcott

(G)

PILLS AS EMERGENCY CONTRACEPTIVES

2 Different Approaches: Progestin-Only Pills OR Combined Pills

PROGESTIN-ONLY PILLS



Plan B

1 + 1 pill 12 hours apart OR
2 Plan B pills ASAP
after unprotected sex

20 + 20 pills 12 hours apart

Ovrette *(yellow pills)*

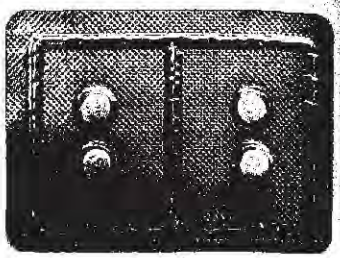
(Plan B and Ovrette are NOT carried in all pharmacies. Check in advance. Ask your pharmacy to carry Plan B

plan B (LEVONORGESTREL)

PLAN B

Antinausea meds not necessary

COMBINED ORAL CONTRACEPTIVES



2 + 2 pills 12 hours apart

Preven* *(blue pills)* OR
Ogestrel *(white pills)*
Ovral *(white pills)*

(Preven Ogestrel and Ovral are NOT carried in all pharmacies. Check in advance.)*

PREVEN*

4 + 4 pills 12 hours apart

Low-Ogestrel *(white pills)*
Lo-Ovral *(white pills)*,
Levora *(white pills)* OR
Levlen *(light orange pills)* OR
Nordette *(light orange pills)* OR
Triphasil *(yellow pills)*,
Tri-Levlen *(yellow pills)* OR
Trivora *(pink pills)*

5 + 5 pills 12 hours apart

Alesse *(pink pills)* OR
Levlite *(pink pills)* OR
Aviane *(orange pills)*

Have your patient take antinausea medication an hour before the first dose if using any of the combined oral contraceptives as emergency contraception. This is not necessary if using Plan B.

* NOTE: Preven Discontinued in 2004

(H)

ADVANTAGES

The once-a-month self-administered use permits convenience, privacy, and ease of use. It is relatively easy for a woman to confirm that the device is in place. The NuvaRing releases low, steady amounts of ethinyl estradiol and etonorgestrel. Cycle control is another advantage; in every cycle, fewer than 10% of women experienced any untimely spotting or bleeding. In a comparative trial of vaginal ring versus a 30 mcgEE/0.15 levonorgestrel OC, the NuvaRing provided significantly better cycle control.[182] Overall satisfaction with the method was relatively high (85%); 96% to 98% of users reported that the ring was easy to insert and remove; and 83% said they rarely or never felt the ring during intercourse. Nine out of 10 study participants said they would recommend the vaginal ring to a friend.[183]

DISADVANTAGES AND CAUTIONS

Some women may be hesitant to touch their genitalia to place and remove the rings. Although the rings may be stored at room temperature for up to 4 months, it is generally preferred that rings be kept refrigerated to prolong their active life. This may pose challenges for women who need private methods.

Health complications. In addition to the health complications associated with combined hormonal contraceptives (myocardial infarction, stroke, VTE, hypertension, diabetes, cholestatic jaundice, hepatic neoplasms, etc.), the vaginal delivery system may be associated with localized conditions such as vaginal discomfort and vaginal discharge.

Side effects. Overall, relatively few users reported hormone-related side effects: headaches (5.8%), nausea (3.2%), and breast tenderness (2.0%). Local side effects specific to the ring were also reported at the following rates: vaginitis (5.6%), leukorrhea (4.6%), other device-related problems (4.4%), and vaginal discomfort (2.4%).

In the combined (North American and European) clinical trial, 15.1% of women withdrew because of adverse events such as the sensation of a foreign body, coital problems and expulsion; headaches (1.3%); emotional lability (1.2%); and weight increase (1%). Fewer than 1% of women stopped because of bleeding irregularity, vaginitis, or leukorrhea.

Precautions

Women who have medical contraindications to OC use (except for those contraindications related to intestinal absorption problems) are not candidates for the vaginal ring, nor are women who have significant pelvic relaxation, are unable to touch their genitalia, or who have vaginal obstruction. The NuvaRing may not be suitable for women with conditions that make the vagina more susceptible to infection or ulceration. The NuvaRing should not be used in conjunction with a diaphragm, since it may prevent correct placement of that barrier.

PROVIDING THE VAGINAL RING

The NuvaRing should be inserted no later than cycle day 5, even if the patient has not finished her menstrual bleeding. If a woman has not used a hormonal method of contraception the cycle before she starts NuvaRing, she should use a back-up method of contraception (male or female condom or spermicide) for the first 7 days of continuous ring use.

Switching from other methods. If a woman switches from OCs, she should place the NuvaRing on the day she would start a new pack of pills. If she is switching from progestin-only pills, she should place the first ring on the same day she takes the last pill. Similarly, she should place the first ring on the day the implants or IUDs are removed. If she is switching from a copper IUD, she may also need emergency contraception if she has had recent intercourse, and she may need to use a back-up method for 7 days if she is not having her menses. If she is switching from injections, she should start the ring the day she is due for her next injection. The ring may be started within 5 days of completion of a first-trimester elective abortion or pregnancy loss. Postpartum women who are not breastfeeding or women who have second trimester losses may start begin the patch 4 weeks after delivery.

MANAGING PROBLEMS AND FOLLOW UP

If the NuvaRing is removed or expelled during the 21 days it should be in place, it should be rinsed with cool to lukewarm (not hot) water and reinserted as soon as possible, but at the latest within 3 hours from the time it was lost. If the NuvaRing is lost, a new vaginal ring should be inserted for a new 21-day period.

If a NuvaRing is out of the vagina for more than 3 hours, a back-up method must be used for the next 7 days. If the NuvaRing is inserted late and the woman has had unprotected intercourse prior to placement, administer emergency contraception.

USING THE VAGINAL RING

1. Insert one ring into your vagina. Use any position you find most comfortable: standing with one leg up, squatting, or lying down. Compress the rim of the ring and place the leading edge into the opening of the vagina.
2. Place the ring high in the vault of your vagina, against the wall. The exact position of the NuvaRing is not critical for its function.
3. Leave the ring in place for 3 weeks. Do not remove the ring for intercourse.
4. After 3 weeks, remove the vaginal ring for 7 days. During this break, you will experience withdrawal bleeding. Remove the

NuvaRing by hooking your index finger under the forward rim or by grasping the rim between your index and middle finger and pulling it out. Place the used ring in the sachet (foil pouch) and discard it in a waste receptacle out of the reach of children and pets (do not flush it down the toilet).

5. After the 7-day break, insert a new vaginal ring to begin the cycle again. Insert the new NuvaRing on the same day of the week you inserted the previous ring, even if you have not finished your period.
6. If the NuvaRing is out of your vagina for more than 3 hours during the 21-day period, re-insert it and use back-up contraception for the next 7 days. If you have had unprotected intercourse, use emergency contraception.

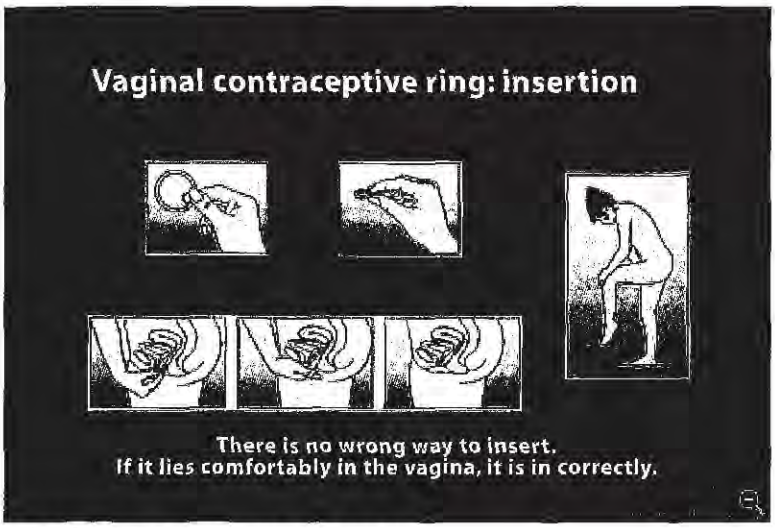


Figure 19-4 Vaginal contraceptive ring: insertion

Source: Ballagh SA (2002),[184] with permission courtesy of Organon USA.

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