An update on oral contraceptive options

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Abstract

The oral contraceptive marketplace has undergone evolutionary changes over the years. Early oral contraceptive formulations contained higher doses of estrogen and progestin, which were associated with several safety concerns. Consequently, scientists returned to the laboratories to develop lower-dose formulations that would minimize risk without compromising efficacy. To date, numerous formulations have entered the marketplace that allow for tailored dosing to meet a woman's clinical and individual needs. In order to provide additional treatment options and create more convenient oral contraceptive regimens, monophasic, multiphasic, extended-cycle, progestin-only, and chewable regimens have emerged. This article will review the main health risks and benefits of oral contraceptives, the concept of extended-cycle regimens, and the financial implications associated with oral contraceptive use. (*Formulary.* 2004;39:104–121.)

One of the nation's most significant medical and social advances occurred in 1960 when FDA approved Enovid-10, the first monophasic oral contraceptive (OC) for women as a means of preventing pregnancy.[1,2] Use of "the Pill" as a contraceptive method was not without controversy. Some religious groups said this practice was an "artificial" means of birth control and consequently attempted to outlaw its use.[1] Dr John Rock, one of the inventors of the Pill, argued that OCs were a "natural" method of birth control since they contained hormones also present in the human body.[1]

Upon FDA approval, women quickly accepted the Pill, with an estimated 1.2 million women using this method within 2 years.[3] The first Pill contained anywhere from 100–175 mcg of estrogen and up to 10 mg of progestin per tablet per day.[3] Use continued to skyrocket until safety concerns (eg, instances of blood clots, heart attacks, and stroke) associated with the high estrogen content surfaced in the mid-1960s. Many of these safety concerns were addressed with the development of lower-dose estrogen formulations. In addition, these safety issues also encouraged the development of the "mini-pill," the first progestin-only OC. OCs remain the most common form of nonsurgical contraception in the United States today, with more than 10 million of the 60 million females of childbearing age using this method.[4,5]

Combination OCs, which contain both estrogen and progestin, prevent pregnancy by blocking follicle-stimulating hormone (FSH) and luteinizing hormone (LH) surges, thereby inhibiting ovulation and altering cervical mucus and the endometrium.[5] Progestin-only pills (POPs), or "mini-pills," exert their contraceptive effect mainly by thickening the cervical mucus to slow sperm motility and interfering with or preventing sperm penetration.[5,6] Progestins may also work to inhibit ovulation and create a thin, atrophic endometrium.[5] Each hormonal component is described in more detail later in this article.

It has been well-accepted for some time that the average length of the menstrual cycle in a woman of child-bearing age is 28 days. Hence, Dr John Rock and colleague Dr Gregory Pincus, in an attempt to mimic spontaneous menstrual cycles and make the Pill appear as natural as possible, determined the regimen would be comprised of 3 weeks of active medication followed by 1 week of inactive placebo tablets.[1,7] In essence, a cycle of any length could be produced based on their findings that the Pill could prevent menstrual bleeding for as long as it was taken. The inventors felt that a regimen allowing for a withdrawal bleed would offer women a certain level of comfort by reassuring them that they are not pregnant.[1] It wasn't until some years later that scientists began to further question the need for a 28-day Pill cycle.

Early studies of primitive cultures suggest that the average number of menstrual cycles a woman experienced in her lifetime were 3–4 times less than that of a Western civilization female.[1,7] This was largely due to the increased number of pregnancies per woman in these cultures compared with that of an American woman. Interestingly, the disproportionately lower number of menstrual cycles experienced by women living in early primitive societies was thought to be protective against health risks such as breast and gynecologic cancers during these times.[7] Consequently, investigators pursued the concept of longer menstrual cycles. Furthermore, in response to the number of side effects and safety

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concerns that surfaced with combination OC use, including myocardial infarction, ischemic stroke, and pulmonary embolism, scientists began to investigate the possibility of decreasing the doses of each hormonal component without compromising the contraceptive efficacy.[4] Thus, lower-dose monophasic or multiphasic OCs with varying amounts of estrogen and/or progestin within the active tablets were created.[5]

In addition, extensive research conducted over the years has led to the emergence of a variety of hormonal contraceptive therapies. The numerous hormonal contraceptive options now available in the United States include oral, injectable, transdermal, and intravaginal products. This article will provide an update on oral contraceptives, the most popular option.

COMPONENTS

All currently available OCs are composed of a combination of an estrogen and a progestin or contain only a progestin. Compared to older formulations, present-day OCs contain approximately one-fifth and one-tenth of the doses of estrogen and progestin, respectively.[4] Monophasic OCs keep the doses of estrogen and progestin constant during the 3 weeks of active tablets of the woman's cycle. Biphasic OCs vary the dose of estrogen and/or progestin over 2 phases of the active tablet cycle. Triphasic OCs may vary the dose of estrogen, progestin, or both during 3 phases of active tablets.

Estrogen. Mestranol and ethinyl estradiol (EE) are the 2 commonly used synthetic estrogens in OC formulations in the United States. The main difference between the 2 estrogen compounds lies in their chemical structures. The presence of a methyl group attached to the C-3 site of the mestranol structure differentiates it from EE.[5] Mestranol is approximately 50% less potent than EE and requires metabolism to become pharmacologically active.[5,6] Common doses of EE in OCs range from 20–50 mcg, while mestranol is only found commercially in a dose of 50 mcg in 1 OC combination (including 1 brand and 2 generic versions).[8]

Progestin. Several types of progestins have been utilized in OC products. They are often referred to by generation: first, second, third, and now fourth. Categorization by generation has not always been consistent as some studies correlate the generation with entrance of the product onto the market, while other trials base the generation on progestin structure (estrane vs gonane).[4,5] The progestins found in OCs differ based on their estrogenic, antiestrogenic, progestational, and androgenic properties (Table 1).[2,5,9-11] The estrogenic or antiestrogenic activity of the progestin is usually secondary to the degree of its metabolism to estrogenic substances.[5] The structural similarity of the progestins to testosterone largely determines their androgenic activity. It is this androgenic activity that is often associated with the side effects of acne, hirsutism, and weight gain.[5] The newest progestin, drospirenone, is a spironolactone analog with antimineralocorticoid and antiandrogenic properties.[9] A 3 mg/d dose displays antimineralocorticoid activity similar to 25 mg of spironolactone, which may be a good choice in women who experience significant sodium and water retention during their cycle.[9,12]

To date, numerous oral contraceptive formulations have entered the marketplace that allow for tailored dosing to meet a woman's clinical and individual needs. In order to provide additional treatment options and create more convenient oral contraceptive regimens, monophasic, multiphasic, extended-cycle, progestin-only, and chewable regimens have emerged.

EFFICACY

All oral contraceptives have demonstrated greater than 99% effectiveness in preventing pregnancy when taken exactly as prescribed.[6] Actual efficacy tends to be lower, approximately 95%, with "typical use," which takes into account inappropriate use or patient noncompliance.[5,6] Overall efficacy is related to several factors such as the dose of each hormonal component, patient tolerability, concomitant medication use, and patient compliance. Approximately 50% of the users of reversible contraceptive methods discontinue use within 1 year.[13] These statistics highlight the need for tailoring therapies to optimize efficacy while minimizing adverse events. Patient education may also improve adherence to contraceptive therapy.

Direct head-to-head comparative studies to establish superiority among all the different combination OC formulations have not been conducted. In addition, significant differences in pregnancy rates have not been found, regardless of what the estrogen dose is when used in a range of 20–50 mcg/d.[9] Furthermore, direct

■ Table 1

Activity of progestin agents found in oral contraceptive agents

Generation*	Progestin	Estrogenic	Progestational	Androgenic	Type of progestin
First	Ethynodiol diacetate	>>>	>>	>	Estrane
	Norethindrone	>	>	>	Estrane
	Norethindrone acetate	>	>	>	Estrane
	Norethynodrel†	>>>	>	0	Estrane
	Norgestrel	0	>>>	>>>	Gonane
Second	Levonorgestrel	0	>>>>	>>>>	Gonane
Third	Norgestimate	0	>>>	>>	Gonane
	Desogestrel	>/0	>>>>	>> />	Gonane
Fourth	Drospirenone	0	>/0	0	Spironolactone analog

>>>>=highest; >>>=high; >>=intermediate; >=low; >/0=low to none; 0=none

*Classification based on entrance into the market. †Not currently contained in any OC combination marketed in the United States.

Formulary/Source: Refs 2,5,9–11

comparisons of the various progestins contained in combination OCs have not been adequately studied to determine differences in efficacy.

Progestin-only pills have been associated with lower efficacy than combination OCs. A plausible explanation for this lies in the fact that the progestin dose in these formulations is lower than that found in combination OCs, suggesting a weaker effect on ovulation inhibition and cervical mucus.[6] The effect on cervical mucus decreases rapidly 22 hours after dosing; therefore, patients must be diligent about administering POPs at the same time each day.[6] A dose that is late by 3 or more hours is considered to be a missed dose.[6] There is no placebo interval with POPs as is common with combination OCs.

■ Table 2

Common adverse effects attributed to specific hormonal components

Estrogenic*	Progestational*	Androgenic*
N/V	Mastalgia	Acne, oily skin
Bloating, fluid retention (edema)	H/A	Hirsutism
Breast fullness/edema	Hypertension	Weight gain (noncyclical)
Irritability		Fatigue
Weight gain (cyclical)		Mood swings/depression
H/A (tension, migraine)		Rash
Bleeding irregularities, BTB		Alterations in lipids (LDL, HDL)
Chloasma		Alterations in glucose
Hypertension		
Telangiectasis		

N/V=nausea and vomiting; H/A= headache; BTB=breakthrough bleeding; LDL=low-density lipoprotein; HDL=high-density lipoprotein

*Progestin component can contribute to androgenic, estrogenic, and progestational effects, while estrogen component contributes to estrogenic effects.

Formulary/Source: Refs 2,5,6,9,10,14,16

ADVERSE EVENTS

The emergence of adverse events is the most common reason for patient discontinuation of OCs. Transient headache, nausea, weight gain, mood alterations, mastalgia, and bleeding abnormalities are the most frequently reported adverse events.[9,10] The extent to which these side effects occur is often dependent upon the ability of the estrogen and progestin to bind to their respective receptors.[14] The severity and type of the side effect may differ slightly between individual OCs due to variations in the amount and kind of estrogen and progestin contained within each product. The product labeling for Yasmin (Berlex) alerts the clinician to the possibility of hyperkalemia due to the antimineralocorticoid properties of the progestin, drospirenone.[12] Consequently, this product should not be given to patients with conditions that may predispose them to elevated potassium levels (ie, renal impairment, hepatic dysfunction, adrenal insufficiency) or in combination with medications that increase potassium levels (eg, ACE inhibitors, potassium supplements, potassium-sparing diuretics, etc).[12] Due to their lack of an estrogen component, mini-pills are preferred in women who are lactating or who have a contraindication to estrogen use.[6] In addition, POP package labeling does not contain warnings associated with the estrogen component in combination OCs, such as thromboembolic disorders (eg, myocardial infarction and cerebrovascular disease) and gallbladder disease. POP package labeling warns against a higher incidence of ectopic pregnancy when compared to other contraceptive methods.[15]

Table 3
Dose-related adverse effects

Component	Excess	Deficiency
Estrogen	N/V	Amenorrhea
	Bloating	BTB/spotting (early cycle, days 1–9)
	Mastalgia, breast fullness	Vaginal dryness
	Leukorrhea	Nervousness
	Decreased libido	
	Chloasma	
	Weight gain (cyclical)	
	Headaches	
	Hypertension	
	Heavy menstrual flow	
Progestin	Acne, oily skin	BTB/spotting (late cycle, days 10–21)
	Fatigue	Amenorrhea
	Depression	Heavy menstrual flow
	Hirsutism	
	Rash	
	Increased appetite/weight gain	
	Hypertension	

N/V=nausea and vomiting; H/A= headache; BTB=breakthrough bleeding; LDL=low-density lipoprotein; HDL=high-density lipoprotein

Formulary/Source: Refs 2,5,6,9,10,14,16

Many of the short-lived side effects associated with OCs tend to dissipate by the third or fourth cycle.[9] It is important that the clinician communicate this to the patient in order to prevent premature discontinuation or noncompliance. Specific side effects can usually be attributed to either the estrogen or progestin component of the OC. Table 2 distinguishes the most common side effects associated with each component.[2,5,6,9,10,14,16] Once the responsible constituent has been identified, it can then be determined if an excess or deficiency of the hormone is contributing to the adverse event (Table 3).[2,5,6,9,10,14,16] Breakthrough bleeding (BTB) is an extremely common reason for patient noncompliance. BTB typically occurs at a higher rate with POPs, often leading to discontinuation rates ranging from 3%–4%.[5,14] If BTB occurs consistently either early or late in the cycle, the clinician should consider switching to an OC with a higher estrogen or progestin content, respectively.

Many OC-related side effects are considered minor and may be alleviated by switching to a different OC. However, serious adverse events have also been reported and should lead to immediate discontinuation, especially in high-risk females (eg, patients who smoke, are hypertensive, and/or have a family history of clotting disorders). It is crucial for clinicians to counsel patients on the warning signs of potentially serious adverse events. The mnemonic device "ACHES" (A [abdominal pain], C [chest pain], H [headache], E [eye or vision problems], S [severe leg pain]) is an aid for clinicians and patients to help identify signs of serious adverse events such as MI, stroke, deep vein thrombosis, or pulmonary embolism.[6] Table 4 lists warning signs of potentially serious adverse events.[6,9] Health concerns that have been linked to OCs are described in more detail in the information that follows.

POTENTIAL HEALTH CONCERNS

Breast cancer. The risk of developing breast cancer is one of the most common major health concerns among women considering a hormonal contraceptive method. Many clinicians feel that OCs have little effect, if any, on the risk of developing breast cancer.[6] The Cancer and Steroid Hormone (CASH) study, a landmark study published in 1986, provided women with some reassurance, as it failed to demonstrate a strong association between OC use and breast cancer.[17,18] Conversely, a pooled analysis of 54 epidemiological studies found a small increase in relative risk (1.24; 95% CI, 1.15–1.33) of having breast cancer diagnosed among current users, but no increased risk 10 or more years after discontinuation.[19]

In the Women's Contraceptive and Reproductive Experiences (Women's CARE) study by Marchbanks et al,[11] the risk of breast cancer in former and current users of OCs was examined in women aged 35–64 years. Results were similar to that of the CASH study. Patterns of OC use such as any current or past use; duration; age at first use; interval since last use; and dose of estrogen did not appear to be associated with an increased risk of breast cancer.[11] Relative risk was 1.0 (95% CI , 0.8–1.3) for current users and 0.9 for former users (95% CI, 0.8–1.0) compared to controls.[11] In addition, the type of progestin did not appear to impact the risk of developing breast cancer. The study had several limitations such as failure to validate OC usage information, patients of only white and black ethnicity, lack of consideration of diet and environmental exposures, analysis of only specific age groups (aged 35–64 y only), and variability in results by study site, which may have influenced the interpretation of the results. [11]

Combined OC use has also been linked to a greater increase in baseline risk of breast cancer among women with a positive family history of the disease.[9] Despite the availability of more recent reassuring evidence to refute the association of OCs and breast cancer, regular screening continues to be an important factor for early detection. Even after

■ Table 4
Warning signs signaling a serious adverse event

Symptoms	Potential complication
Abdominal pain (severe in nature)	MI, gallbladder disease, hepatic disease
Chest pain (severe) with cough, shortness of breath, or sharp pain on inspiration	PE, MI, ischemic heart disease
Headache (severe) with dizziness, weakness, numbness	CVA (TIA, stroke), HTN
Eye or vision problems (loss, blurring), speech difficulties	
Severe leg pain (especially calf or thigh)	DVT
Breast mass, pain, and/or swelling	Breast cancer
Hyperglycemia (thirst, increased urination)	Exacerbation of diabetes mellitus
Increase in LFT levels, jaundice, severe abdominal pain	Hepatic adenoma, gallbladder disease

DVT=deep vein thrombosis; PE=pulmonary embolism; MI=myocardial infarction; CVA=cerebrovascular accident/event; TIA=transient ischemic attack; HTN=hypertension; LFT=liver function test

Formulary/Source: Refs 6,9

4 decades of widespread OC use, this remains an area of ambiguity.

Myocardial infarction and ischemic stroke. An abundance of literature has evaluated the possibility of an association between MI and combination OC use, mainly with older high-dose formulations (estrogen dose ≥50 mcg). The relative risk of MI among current users of all combination OCs (1.4; 95% CI, 0.78–2.52) was not found to be statistically significant compared to nonusers in the Myocardial Infarction and Oral Contraceptives (MICA) study.[20] The risk of MI in combination OC users is highest among smokers and those taking a formulation containing at least 50 mcg of estrogen.[21] Cigarette smoking is the most prominent risk factor for MI in combination OC users.[9] The increase in MI risk has not been clearly demonstrated in healthy nonsmokers. True risk cannot be adequately determined in smokers receiving a low-dose formulation (estrogen dose <50 mcg) due to the limited available data.

The effect of the quantity of cigarettes smoked per day on the incidence of MI in OC users also has been studied. Women using combination OCs who smoked at least 25 cigarettes per day had more than a 4-fold increase in relative risk when compared to female smokers who never used a combination OC.[21] Similar results were reported in a study by Goldbaum et al,[22] which found that OC users who smoked 25 or more cigarettes per day had an MI risk of almost 40 times that of nonsmokers.

Overall incidence of stroke in women of child-bearing age is stated to be approximately 11 per 100,000 women over 1 year.[21,23] Similar to MI, studies examining the link between ischemic stroke and combination OC use have also produced conflicting results. In a meta-analysis of 16 studies, 11 of the 16 studies found that current users of combination OCs had a significantly increased relative risk of ischemic stroke (2.75; 95% CI, 2.24–3.38) compared to nonusers.[24] Lower estrogen doses demonstrated a smaller increased risk of ischemic stroke, especially when controlled for factors such as hypertension and smoking, ultimately translating into a rate of approximately 4 ischemic strokes per 100,000 OC users.[24] A study by Petitti et al[23] also supported the finding that low-dose estrogen OCs do not significantly increase the risk of stroke. Similar to findings in the MI trials, these researchers determined that the combination of smoking and OC use creates a synergistic effect that elevates the risk of stroke.[23]

Clinicians should be aware that although the risk of stroke and MI in women using OCs is considered to be low, it is not obsolete.[16,21] In summary, among otherwise healthy women who do not smoke, use of a low-dose combination OC has not been associated with an increased risk for MI or stroke.[9,25] This risk may increase significantly in women who smoke or have additional risk factors such as hypertension, diabetes, and/or being aged 35 years or older.

Venous thromboembolism. Oral contraceptive use is contraindicated in any woman with a history of thromboembolic disorders.[7,9] Dose of the estrogen component, age, family history, factor V Leiden mutation, and obesity are examples of important factors that may determine the risk of venous thromboembolism (VTE).[9] Early users of combination OCs with EE doses of 50 mcg or higher had a 4-fold increase risk of venous thrombosis.[26] The estimated incidence of VTE with OC use has been reported to be between 8 and 11 per 100,000 OC users.[16,21] Of note, these rates may be significantly higher in pregnancy. In the mid-1990s, the progestin component in OCs emerged as a potentially significant contributing risk factor.[26]

Third-generation progestins, such as desogestrel (and gestodene, not available in the United States), have been associated with a higher risk of VTE compared to the second-generation progestin levonorgestrel.[26] Product labeling for OCs containing desogestrel warn of the higher risk of VTE associated with their

use in comparison to other OCs.[26] A transnational case-control study of both hospital- and community-based patients found a 4-fold increase in VTE among current users compared to nonusers of OCs.[27] Furthermore, when a specific type of progestin was analyzed, the risk of VTE was 1.5 times higher among third-generation progestins versus second-generation progestins.[27] A meta-analysis of 27 studies by Kemmeren et al[28] further corroborated earlier results, reporting a 1.7-fold increased risk of VTE among users of third-generation compared to second-generation progestins.[28] This risk appeared to be greater in first-time users of OCs.[28]

The association between third-generation progestins and VTE has been debated extensively because of suggestions that confounding, bias, or both inherent in the trial designs influenced the findings. Some argue that physicians prescribed a third-generation OC for women who were at higher risk for thromboembolism, under the assumption that these newer agents were safer. In contrast, a 1999 review by the Medicines Commission, a UK regulatory body similar to FDA, determined that neither bias nor confounding could account for the excess risk with third-generation OCs.[29] Identifying women whose risks associated with OC use far outweigh the benefits and selecting a formulation that minimizes any risks are among the greatest challenges clinicians face when prescribing any hormonal contraceptive product. Complicating matters, screenings for thrombophilia due to factor V Leiden or other prothrombotic-gene mutations to identify potentially high-risk patients are not routinely performed before initiation of an OC agent. Factor V Leiden is a prothrombotic disorder defined by a genetic mutation in the coagulation factor V, which is associated with resistance to protein C, an innate anticoagulant.[26] The literature suggests that OCs may exert a prothrombotic effect by increasing levels of circulating clotting factors (eg, prothrombin, factor VII) and causing an acquired resistance to activated protein C.[26] The limited availability and high costs associated with these screening tests are the main reasons for their low utility.[26]

Cervical cancer. Several studies have been conducted to determine the impact of OC use on cervical cancer risk. Pooled data from 8 case control studies found an increase in cervical cancer risk in women using OCs for 5–9 years as well as in those who used OCs for 10 or more years, with odds ratios of 2.82 (95% CI, 1.46–5.42) and 4.03 (95% CI, 2.09–8.02), respectively.[30] This study included women who were positive for human papillomavirus (HPV). Smith et al[31] conducted a review of 28 studies to examine the relationship between duration of OC and cervical cancer in women with HPV infection. Although the researchers reported an increased relative risk of cervical cancer proportional to duration of OC use, it is implied that this risk may decrease upon discontinuation of the OC.[31] HPV infection is a known risk factor for cervical cancer; nevertheless, the possibility of an increased risk with OC use cannot be ruled out.[31]

POTENTIAL HEALTH BENEFITS

Over the years, a flourishing body of literature has accumulated to support the health benefits of OC use. In addition to providing a highly effective and convenient method of contraception, OCs have been associated with several beneficial gynecologic effects such as a reduction in menstrual-related disorders, decreased pelvic inflammatory disease (PID) cases, and a reduction in risk of ovarian and endometrial cancers.[4,9] OCs have also demonstrated nongynecologic benefits on acne, bone mineral density, and possibly anemia.[9,16,32]

Menstrual disorders. OCs are extremely effective agents for maintaining cycle control and alleviating cyclical symptoms. A trial by Sulak et al[33] found that the most troublesome symptoms related to a woman's menstrual cycle, such as headache, breast tenderness, pelvic pain, cramps, and nausea and vomiting, recur or worsen during the hormone-free interval. In addition, this and other studies have demonstrated that the number of days with moderate to heavy menstrual flow is lower in women who use OCs when compared to new users or nonusers.[16,33] OC use has also been associated with a 60% reduction in menstrual flow, suggesting a benefit in women with menorrhagia that may predispose them to develop anemia.[16,33]

Initial research and development of the OC based the cycle on 28 days to closely mimic that of the natural cycle; however, it has since been discovered that the period of withdrawal bleed is not required for contraceptive action.[34] Subsequently, interest in reducing the number of menstrual cycles a woman experiences per year has peaked among researchers. Continuous administration of active tablets for a period of 2 or 3 consecutive months has been referred to as "bicycling" or "tricycling," respectively.[6,9] This concept of an extended-cycle regimen will be discussed in further detail.

Extending the menstrual cycle. Interest in lengthening the menstrual cycle is not a new concept. Extended cycling refers to a prescribed regimen of continuous active OC tablets for periods longer than the traditional 21 days followed by 7 days of placebo.[35] For years, clinicians have used combination OCs "off-label" in women to extend their menstrual cycles, often times to avoid severe menstrual symptoms, to reduce pain associated with endometriosis, and to avoid menstruation during vacations or other important social events. Limited data exist regarding extended cycling in adolescents aged 15–19 years; most of the available data only reflect use in adults.[35]

Results of earlier trials highlight 2 important findings: 1) most symptoms occur during the hormone-free interval, and 2) ovarian suppression is greater with shortened hormone-free intervals.[33] Sulak et al[36] conducted a study to examine the acceptance rates of extending the standard 21-day/7-day regimen.[33,36] Among the 267 patients who received an extended-cycle dosing regimen, approximately 64% were still using this regimen at follow-up.[36] It is important to note that a monophasic regimen containing 30–35 mcg of EE was used in

this trial. Consequently, the results cannot be generalized to multiphasic regimens. Low-dose (EE=20–35 mcg) monophasic regimens containing a progestin with a long half-life (ie, levonorgestrel, norgestimate) are preferred for extended cycling.[35] Changes in hormone levels found in multiphasic preparations may increase the incidence of breakthrough bleeding, making them less attractive for this regimen.

A small study (N=32) examined the acceptability and bleeding patterns among women receiving either a standard 28-day or a continuous regimen containing a lower dose of EE (20 mcg) combined with levonorgestrel 100 mcg.[37] No significant difference in the number of days with spotting or bleeding was found between groups; however, bleeding requiring sanitary protection was significantly higher in the standard regimen group.[37] The authors acknowledged that the sample size of those women completing the study was too small to detect a significant difference in the overall number of days of bleeding and spotting.[37] In addition, a high acceptability rate among women was reported regardless of the regimen utilized.

Seasonale (Barr) is an FDA-approved, 91-day extended-cycle regimen containing 30 mcg of ethinyl estradiol in combination with 150 mcg of levonorgestrel.[38] Although the individual components of this OC are not unique, it is the first combination OC packaged as a regimen containing 84 days of consecutive active tablets followed by 7 days of placebo.[38] The safety and efficacy of the Seasonale 91-day cycle were evaluated in a yearlong trial using an active control group receiving the comparable 28-day regimen (21 days of EE 30 mcg/levonorgestrel 150 mcg, 7 days of placebo) (Nordette, Wyeth-Ayerst).[39] Similar numbers of women became pregnant in the continuous and conventional regimens, 0.9% and 1.3%, respectively.[39] Despite the higher frequency of reports of unscheduled bleeding with the extended-cycle regimen early-on in the study, the incidence was similar for the 2 groups by the end of the study.[39] Safety profiles were comparable between the 2 groups and similar to other combination OCs.

Mircette (Organon), a combined OC comprised of only 2 hormone-free days followed by 10 mcg of EE for the remaining 5 days of the last week, is the only other approved combination OC that offers a variation on the traditional 21-day/7-day regimen.[33,36] In light of the evidence supporting extended cycling, this remains a highly debated topic. Some clinicians feel that monthly bleeding is beneficial to help "flush out" the endometrium, while others argue that the 28-day cycle causes women to experience potentially avoidable cycle-related symptoms.[40,41]

Pelvic inflammatory disease (PID). The effect of OCs on PID has been debated frequently in the literature. Oral contraceptives are said to offer protection against PID through various mechanisms. Thickening of the cervical mucus, reduction in menstrual blood loss, and weakened uterine contractions created by OCs are thought to create a hostile environment that discourages bacterial access to the upper genital tract.[9,16] When PID develops in OC users it often tends to be of lower severity.[16] While most studies indicate a decreased risk of PID with OC use, others suggest that an increase in unrecognized cases offsets the apparent protective benefit.[16] Furthermore, it has been suggested that distinguishing between gonococcal or nongonococcal PID infection is important.[42] Some clinicians warn against promoting OC use as protection against gonococcal PID since OC use has been associated with enhancing *Chlamydia trachomatis* infection, a major cause of nongonococcal PID.[42]

Ovarian and endometrial cancer. Among the most important benefits that have been linked to OC use is the decrease in the risk of developing ovarian and endometrial cancers. An abundance of literature suggests a 20%–80% decrease in the risk of ovarian cancer in users of OCs compared to nonusers.[14] Although many of the clinical trials used a dose of estrogen equal to or greater than 50 mcg, more recent literature suggests that lower-dose formulations offer a similar protective benefit.[43] The beneficial effects have consistently been higher with longer durations of use and may even persist for 15 years after discontinuation.[9,14,16] Modan et al[44] set out to examine the relevance of parity and OC use in a population-based case-control study of Jewish women with a *BRCA1* or *BRCA2* mutation, known risk factors for developing ovarian cancer. Interestingly, multiparity was associated with a reduced risk of ovarian cancer in both carriers and noncarriers of the mutation, while OC use reduced risk to a smaller extent and only in noncarriers of the mutation.[44] These data suggest that while OC use is beneficial in reducing the risk of ovarian cancer among many women, this benefit may not apply to females who are carriers of the *BRCA1* or *BRCA2* mutation.

Similarly, a 40% reduction in endometrial cancer risk has been reported in women using an OC for at least 2 years and 60% when used for 4 or more years.[16] The US Centers for Disease Control and Prevention (CDC) analyzed data from the CASH study and reported a 50% decreased risk of endometrial cancer in women who used OCs for at least 12 months at some point in their lives.[45] This protective benefit was sustained for 10 years after cessation of OC use.[45] Although OCs are not routinely prescribed as chemoprevention, evidence suggests that their use may offer significant benefit in women with risk factors for these cancers. Examples of risk factors for ovarian cancer include family history and nulliparity. Infertility, polycystic ovarian syndrome, and obesity are risk factors for endometrial cancer.[9]

Acne. It appears counterintuitive that combination OCs would improve acne since most progestins are derived from testosterone; however, research indicates that combination OCs suppress acne by several mechanisms. These include, but are not limited to, a reduction in free circulating testosterone secondary to elevated sex-hormone-binding globulin and a reduction in endogenous testosterone via negative feedback on the anterior pituitary gland.[9,16,32] A randomized, placebo-controlled clinical trial

found that patients who received the combination OC Ortho Tri-Cyclen (Ortho-McNeil), containing 35 mcg of EE in combination with a triphasic dose of norgestimate (0.18 mg, Week 1; 0.215 mg, Week 2; and 0.25 mg, Week 3), displayed a significant reduction in the severity and number of acne lesions compared to the placebo group.[46] Thorneycroft et al[47] compared the effects of 2 combination OCs, containing 20 mcg of EE in combination with either levonorgestrel or norethindrone acetate, on androgenic markers. Another randomized trial found similar results when comparing a second-generation progestin (levonorgestrel) with a third-generation progestin (desogestrel).[48] Both studies found similar improvements in acne and demonstrated comparable reductions in bioavailable testosterone levels, regardless of progestin.[47,48] Hence, the effects on acne appear to be independent of specific progestin found in the combination OC. Even though a combination OC containing a progestin with a low androgen-to-progestin ratio may be most desirable, all low-dose combined OCs contribute to reductions in testosterone to improve acne.[49]

Bone mineralization. A reduction in estrogen levels is an important determining factor for the development of osteoporosis in women. It is logical that combination OCs may prove beneficial in preventing osteoporosis by providing a consistent dose of a potent estrogen, yet available literature provides conflicting results. A meta-analysis of 13 clinical trials found that although none of the studies demonstrated a decrease in bone mineral density (BMD), only 9 of the studies supported a beneficial effect of combination OCs on BMD.[49] The remaining 4 studies showed no such benefit. The protective benefit is thought to be dependent on duration of combination OC use and estrogen dose.[9] In fact, a 25% reduction in hip fracture was reported by Michaelsson et al[50] in a case-control study of postmenopausal women who had a history of combination OC use. This reduction in risk of hip fracture jumped to 44% in those women who reported using a combination OC containing 50 mcg or more of estrogen.[50] Results of the various trials imply that maximal benefits of combination OC use on bone health have been seen with higher estrogen doses (≥50 mcg of EE), prolonged use (typically 5 or more years), and use in the late reproductive years (aged 40 y or older).

In addition, several other potential benefits are associated with OC use, including reduction in the risk of benign breast disease, prevention of ectopic pregnancy and functional ovarian cysts, and improvement in endometriosis, to name a few.[16] Many clinicians and patients perceive these benefits to outweigh the potential risks associated with OC use. Despite the benefits reviewed here, it is prudent that the clinician consider each individual patient's medical background before initiating therapy to avoid a potentially serious adverse event.

MARKETPLACE CHANGES

All OCs are indicated to prevent pregnancy. In addition, Ortho-McNeil's Ortho Tri-Cyclen and Estrostep (Galen) are also indicated to treat moderate acne vulgaris in females aged 15 years or older.[6,9,10,51] Combination OCs are commercially available with static doses of estrogen and progestin throughout the cycle (monophasic), with varying doses of estrogen and/or progestin throughout the cycle (multiphasic), with an extended-cycle regimen, and now in a chewable formulation. The type and amount of progestin and estrogen vary among the different products, allowing for enhanced individualized dosing. In the past few years numerous brand-name OCs have lost patent protection and have become available in generic formulations. FDA also recently approved 2 new OCs: Ovcon-35 Chewable (Galen), the first chewable combination OC, and Barr's Seasonale, the first combination OC with an extended-cycle dosing regimen.[38,52]

Table 5 provides a list of OCs currently marketed in the United States and a representative sampling of the corresponding generic versions, where applicable.[8,10,53–57] Selection of an OC relies on a culmination of patient factors including convenience, medical history, concomitant medication use, age, and cost.

OC ALTERNATIVES

The hormonal contraceptive marketplace has undergone an evolutionary change, providing women with a variety of choices in addition to OCs to best suit their clinical and individual needs. Non-OC developments in the hormonal contraceptive category include several unique delivery methods such as an intravaginal ring (Nuvaring, Organon), a transdermal patch (Ortho Evra, Ortho-McNeil), a monthly combined estrogen and progestin injectable (Lunelle, Pfizer), a long-acting progestin depot injection (Depo-Provera, Pfizer), and a progestin-releasing intrauterine device (Mirena, Berlex). Lunelle is not currently available due to a voluntary recall of the prefilled syringes by the manufacturer in October 2002.[58] Subdermal agents were once attractive options for women because they provided contraceptive protection for a number of years. The subdermal contraceptive Norplant (Wyeth-Ayerst), containing levonorgestrel-filled silastic capsules, is no longer available in the United States.[58] A new subdermal agent composed of the progestin etonogestrel (Implanon, Organon), which may offer 3 years of contraceptive protection, is currently under investigation.[58]

Cost issues and benefit coverage. Hormonal contraceptives display variable pricing depending on the dosage formulation and generic availability. When comparing the cost of contraceptive agents, it is important to realize that several of the dosage forms provide contraceptive protection that extends beyond 1 month. For example, the long-acting progesterone depot injectable Depo-Provera provides up to 90 days of protection against pregnancy with 1 injection, compared with OCs that provide month-to-month protection when taken on a daily basis. The costs provided in Table 6 do not reflect any indirect costs associated with use of contraceptive agents, such as any necessary lab monitoring or procedures required for administration.[6,10,55]

Table 5
Components of various oral contraceptives

Brand name	Estrogen	Progestin	Generic*
MONOPHASIC			
Ortho-Novum 1/50 (Ortho-McNeil)	M=50 mcg	NE=1 mg	Norinyl 1+50 (Watson) Necon 1/50 (Watson)
Ovcon-50 (Galen)	EE=50 mcg	NE=1 mg	N/A
Demulen 1/50 (Searle)		ED=1 mg	Zovia 1/50E (Watson)
Ovral (Wyeth-Ayerst)		NGL=0.5 mg	Ogestrel 0.5/50 (Watson)
Ortho-Novum 1/35 (Ortho-McNeil)	EE=35 mcg	NE=1 mg	Norinyl 1+35 (Watson) Necon 1/35 (Watson) Nortrel 1/35 (Barr)
Modicon (Ortho-McNeil) Brevicon (Watson)		NE=0.5 mg	Necon 0.5/35 (Watson) Nortrel 0.5/35 (Barr)
Ovcon-35 (Galen) Ovcon-35 Chewable (Galen)		NE=0.4 mg	N/A
Ortho-Cyclen (Ortho-McNeil)		NGM=0.25 mg	Mononessa (Watson) Sprintec (Barr)
Demulen 1/35 (Searle)		ED=1 mg	Zovia 1/35E (Watson)
Yasmin (Berlex)	EE=30 mcg	DP=3 mg	N/A
Loestrin-21 1.5/30 (Galen)		NEA=1.5 mg	Junel 1.5/30 (Barr) Microgestin 1.5/30 (Watson)
Loestrin Fe 1.5/30 (Galen)†			Junel FE 1.5/30 (Barr) Microgestin Fe 1.5/30 (Watson)
Lo/Ovral (Wyeth-Ayerst)		NGL=0.3 mg	Low-Ogestrel (Watson) Cryselle (Barr)
Desogen (Organon) Ortho-Cept (Ortho-McNeil)		D=0.15 mg	Apri (Barr)
Nordette (Wyeth-Ayerst) Levlen (Berlex) Seasonale (Barr)‡		LNG=0.15 mg	Portia (Barr) Levora (Watson) N/A for extended-cycle regimen
Alesse (Wyeth-Ayerst) Levlite (Berlex)	EE=20 mcg	LNG=0.1 mg	Aviane (Barr) Lessina (Barr)
Loestrin-21 1/20 (Galen)		NEA=1 mg	Junel 1/20 (Barr) Microgestin 1/20 (Watson)
Loestrin Fe 1/20 (Galen)†			Microgestin Fe 1/20 (Watson) Junel FE 1/20 (Barr)
BIPHASIC			
Ortho-Novum 10/11 (Ortho-McNeil)	EE=35 mcg	NE=0.5 mg (Phase 1: 10 tablets) NE=1 mg (Phase 2: 11 tablets)	Necon 10/11 (Watson)
Mircette (Organon)	EE=20 mcg (days 1-21)/10 mcg (days 24–28)	D=0.15 mg	Kariva (Barr)
TRIPHASIC			
Tri-Norinyl (Watson)	EE=35 mcg	NE=0.5/1/0.5 mg	N/A
Ortho-Novum 7/7/7 (Ortho-McNeil)		NE=0.5/0.75/1 mg	Necon 7/7/7 (Watson) Nortrel 7/7/7 (Barr)
Tri-Levlen (Berlex) Triphasil (Wyeth Ayerst)	EE=30/40/30 mcg	LNG=0.05/0.075/0.125 mg	Trivora (Watson) Enpresse (Barr)
Ortho Tri-Cyclen (Ortho-McNeil)	EE=35 mcg	NGM=0.18/0.215/0.25 mg	Tri-Sprintec (Barr) Tri-Nessa (Watson)
Ortho Tri-Cyclen Lo (Ortho-McNeil)	EE=25 mcg	NGM=0.18/0.215/0.25 mg	N/A
Estrostep 21 (Galen)	EE=20/30/35 mcg	NEA=1 mg	N/A
Estrostep Fe (Galen)†			N/A
Cyclessa (Organon)	EE=25 mcg	D=0.1/0.125/0.15 mg	N/A
PROGESTIN-ONLY PILLS			
Ortho Micronor (Ortho-McNeil) Nor-QD (Watson)	N/A	NE=0.35 mg	Errin (Barr) Camila (Barr) Nora-BE (Watson)
Ovrette	N/A	NGL=0.075 mg	N/A

M=mestranol; EE=ethinyl estradiol; NE=norethindrone; NEA=norethindrone acetate; NGL=norgestrel; NGM=norgestimate; LNG=levonorgestrel; D=desogestrel; ED=ethynodiol diacetate; DP=drospirenone

*Representative sampling, not meant to be all-inclusive. †Last 7 tablets contain 75 mg ferrous fumarate. ‡Extended-cycle regimen containing 84 tablets of active hormones, followed by 7 inert tablets.

Formulary/Source: Refs 8,10,53–57

Several OCs are available in less costly generic formulations, which may be attractive to patients without prescription coverage or for those insured with large differentials in co-payment tiers or cost-sharing percentages. Tri-Sprintec (Barr) and Tri-Nessa (Watson), generic versions of Ortho Tri-Cyclen, the popular triphasic combination OC, also recently entered the market.[56,57] Clinical and financial issues must be weighed when prescribing an extended-cycle regimen for a patient. Prior to the availability of Seasonale, several standard combination OCs have been utilized "off-label" in extended-cycle regimens.

Pharmacoeconomic data indicate that the noncontraceptive benefits of OCs lead to lower health-care expenditures per patient, outweighing the pharmacy-related costs.[59] Historically, major obstacles to universal contraceptive access have included inadequate coverage and the high cost of therapy. A report by the Alan Guttmacher Institute indicates that employers who provide contraceptive coverage could potentially save 15%–17% in medical expenditures, as opposed to not offering such benefits.[60] Based on the potential savings, many federal and state groups are endorsing the development of public policies that would require expanded coverage for contraceptives. The Equity in Prescription Insurance and Contraceptive Coverage Act (EPICC) was passed in 1997, strongly recommending that employer-based health plans provide coverage of contraceptives similar to that of other FDA-approved prescription medications.[60] Approximately 20 states have since enacted such laws.[60] Many different benefit designs exist among health insurance plans, some of which may shift most, if not all, of the cost to the member. A key point to remember when estimating the out-of-pocket cost to the patient for OC therapy is that most are available in cost-saving generic formulations.

CONCLUSION

Evolutionary changes have provided women and clinicians with a variety of contraceptive options. Numerous dosage formulations are now available, and OCs remain the most popular form of nonsurgical contraception. Individual OCs display similar efficacy and safety profiles when used as directed. Patient tolerability to OCs will vary based on the amount and type of estrogen and progestin component within each agent. It is incumbent on the clinician to review the patient's medical history and assess her expectations in order to select the most appropriate contraceptive method. Although prevention of pregnancy is the most common reason for the use of OCs, they have also been linked to numerous noncontraceptive benefits with sustained use. Approximately half of OC users discontinue use within the first year, often due to adverse effects. Thus it is imperative to counsel the patient on the expected side effects associated with OC use as well as warning signs of potentially serious adverse events. Whether it is clinically necessary to experience withdrawal bleeding each month remains an area of debate. Extended-cycle regimens may become more popular among women since they offer the convenience of fewer menstrual cycles. The level of OC insurance coverage varies widely and often depends upon the payor's benefit design. Several OCs are

■ Table 6

Average cost of various hormonal contraceptive methods

Hormonal contraceptive method	Average cost/Rx*	Average monthly cost	Frequency of administration
Nuvaring (Organon) Intravaginal Ring	$40	$40	After insertion remains in place for 3 weeks each month.
Ortho Evra (Ortho-McNeil) Transdermal	$39	$39	Patch applied weekly for 3 consecutive weeks each month.
Depo-Provera (Pfizer) Progestin-Only Injectable†	$58	$20	IM injection once every 3 months (90 days).
Combination OC (21- to 28-day packs) (Brand and generic)	$8–54	$8–54	Require daily administration, with the exception of the inactive tablets of each cycle.
POPs	$40–48	$40–48	Require daily administration.
Seasonale (Barr) Extended Cycle COC‡	$120	$40	Requires continuous daily administration for 84 consecutive days followed by 7 days of inactive tablets.
Mirena (Berlex) Intrauterine Device§	$454	N/A‖	After insertion, provides up to 5 years of contraceptive protection.

COC=combination oral contraceptive; POPs=progestin-only pills; IM=intramuscular

*Cost is based on average wholesale price (AWP) and does not reflect any contractual discounts. Also, cost is for the medication or device itself; does not factor in medical expenses that may be required for certain methods such as procedural costs (insertion of IUD, administration of injection, monitoring, etc). †One injection provides 90 days of contraceptive protection. ‡Packaged as a 3-month cycle (91 tablets). §Dollar amount provided does not factor in procedural costs related to the insertion. ‖Precise cost not available (monthly cost difficult to estimate based on length of contraceptive protection provided).

Formulary/Source: Refs 6,10,55

available in generic formulations, which may offer attractive cost-saving options for patients and health plans. Ultimately, the pharmacy-related costs of OC therapy may be offset by a decrease in overall health expenses related to the use of OCs.

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