THE JOURNAL OF FAMILY PRACTICE

ONLINE EXCLUSIVE

Oral contraceptives: Does formulation matter?

OCs come in a variety of formulations, but verifiable differences are hard to find. Here's help selecting the one that's best for your patient.

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The authors reported no potential conflict of interest relevant to this article.

PRACTICE RECOMMENDATIONS

› *Consider prescribing monophasic pills as the first choice for women starting oral contraceptives (OCs), given the lack of advantage in using multiphasic formulations and the larger number of studies showing the safety and efficacy of monophasic pills.* (B)

› *Avoid prescribing OCs with estrogen—even with ultra-low estrogen—for women at high risk for venous thromboembolism, given that there are no studies that show differences in low (25-35 mcg) ethinyl estradiol vs ultra-low (10 mcg) formulas.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

For a healthy woman interested in contraception, there are multiple oral contraceptive (OC) formulations on the market from which to choose. But are there any significant differences in their effectiveness or safety profiles that make one formulation superior?

Comparative trials of OCs have attempted to answer these questions by evaluating formulations that contain the synthetic components: ethinyl estradiol, norethindrone, levonorgestrel, desogestrel, norgestimate, gestodene, and drospirenone.

Unfortunately, many studies that have evaluated OCs have had methodological weaknesses, making their clinical significance confusing. Few randomized controlled trials (RCTs) have been double blinded or adequately powered to find infrequent outcomes like pregnancy or adverse events. Trials are rarely reproduced by other researchers, and many have been funded by pharmaceutical companies with conflicts of interest. Despite these shortcomings, it is possible to glean valuable data from existing studies.

With that in mind, our purpose here is to consider whether there are significant differences in effectiveness, cycle control (bleeding), side effects, or satisfaction that may help physicians and patients select the appropriate formulation.

Comparing OC effectiveness

OC effectiveness is determined by the inherent properties to prevent ovulation, conception, and/or implantation when the formulation is used correctly,[1,2] and during typical inconsistent use in the population (ie, adherence).[3] Effectiveness is also measured by whether the method is discontinued and there is a gap in contraception, allowing pregnancy to occur.

There is no evidence that any combined or progesterone-only hormonal formulation is inherently better at preventing ovulation, conception, or implantation. (For more on com-

Extended-cycle OCs have a greater risk of breakthrough bleeding, which can decrease adherence and increase discontinuation, thus increasing the risk of pregnancy.

bined OCs, see "A closer look at combined OCs" on page E3.) Theoretically, progestins with longer half-lives may be more effective at preventing ovulation if a pill is not taken the same time each day, and extended cycle pills provide more continuous suppression of ovulation. But, no studies have found any formulation to be more effective than another.

A 2004 Cochrane review[4] compared progestins in OCs by examining 22 different trials with various study protocols. The review found a lower rate of discontinuation in patients taking OCs with second-generation progestins compared with first-generation progestins (relative risk [RR]=0.79; 95% confidence interval [CI], 0.61-0.91), and an even lower rate of discontinuation with third-generation OCs. Additionally, cycle control was better in second-generation progestin OCs compared with first-generation progestin OCs. Rates of effectiveness, cycle control, and side effects were similar between drospirenone (DRSP) and desogestrel. The reviewers concluded that second- and third-generation progestins are preferred over first-generation progestins in combined OCs,[4] although the evidence is not strong.

What about generics? To be considered an FDA-approved bioequivalent generictoabrandnameformulation,pharmacokinetic studies must demonstrate that a product provides equivalent serum levels. There are no studies evaluating differences in effectiveness of generic vs brand name OCs. Generic OCs typically cost about 50% less than brand name OCs.[5] The Society of Obstetricians and Gynaecologists of Canada supports generic formulations "providing increased choice and less expensive options."[6]

What are the differences among the options?

While OCs, in general, are thought to cause side effects, when compared with a placebo, no significant findings have been noted in the frequency of headache, nausea, vomiting, breast pain, or weight gain.[7,8] This being the case, it is unlikely that there are differences among formulations.

Ultra-low estrogen. Estrogen in OCs has been reduced to 10 to 35 mcg to minimize side effects and adverse events yet remain at a level sufficient to provide menstrual cycle control with minimal breakthrough bleeding. Advantages of ultra-low estrogen (10 mcg) products include reduction of estrogenic side effects,[9] but disadvantages include breakthrough bleeding, which can negatively affect adherence.[10] In a double-blind RCT of 649 women comparing OCs with gestodene 75 mcg and either 20 or 30 mcg ethinyl estradiol (EE), more intermenstrual breakthrough bleeding occurred with the 20 mcg group ($P<.05$). This difference was not enough to cause an increased discontinuation rate in the 20-mcg EE group.[11]

Progestin-only pills (POPs) are recommended for women who cannot or should not take estrogen in OCs, and women who are breastfeeding. The advantages of POPs include a simplified and fixed regimen. Disadvantages include irregular bleeding and menstrual cycle length. A 2010 Cochrane review examined various POP formulations in 6 different trials and concluded that there is insufficient research to compare POPs in terms of efficacy, acceptability, and continuation rates.[12]

Monophasic vs multiphasic OCs. Biphasic and triphasic OCs were introduced in an effort to decrease the amount of hormone and the side effects. Their phasic nature also attempts to mimic the pattern of rising and falling estrogen and progesterone levels seen during a normal menstrual cycle. Cochrane reviews in 2009[13] and 2011[14] compared the cycle control and side effects of biphasic vs monophasic, and triphasic vs monophasic formulations of OCs, respectively. The 2009 review comparing biphasic and monophasic OCPs was limited to one study of 533 women using biphasic pills and 481 women using monophasic pills. No differences were found in intermenstrual bleeding, amenorrhea, or discontinuation due to intermenstrual bleeding.

The 2011 review comparing triphasic and monophasic OCs included 21 studies, and found no significant difference in discontinuation due to medical reasons, cycle disturbance, intermenstrual bleeding, or adverse events. Both of the Cochrane reviews concluded that monophasic pills should be the first choice for women starting OCs given

the lack of advantage in using multiphasic formulations, and the larger number of studies showing the safety and efficacy of monophasic pills.

The 2009 Cochrane review compared biphasic and triphasic OCPs in terms of cycle control and side effects.[13] The first trial examined in this review included 458 women and compared 2 biphasic pills and one triphasic pill, all containing levonorgestrel (LNG) and EE. It found no important differences among the 3 formulations, but found that 252 of the initial 458 women (55%) discontinued the study for various reasons.

The second trial included 469 women (169 [36%] of whom withdrew from the study), and compared a biphasic pill containing norethindrone with 2 triphasic pills, one containing LNG and the other containing norethindrone. This study showed no differences between the biphasic and triphasic pills containing norethindrone, but inferior cycle control in the biphasic pill containing norethindrone compared with the triphasic containing LNG. The review concluded that the choice of progestin type (LNG preferred over norethindrone) might be more important than the choice of phasic regimen.[13]

Monthly vs extended-cycle OCs. When OCs were first introduced, researchers believed that women would prefer a 21-day formulation followed by a 7-day pill-free time that mimicked an average woman's menstrual cycle because the withdrawal bleeding would be an indicator that she was not pregnant. Extending the time between menses has since garnered increased interest. Extended-cycle preparations are available for durations ranging from 84 to 365 days.[15]

A study of 99 women evaluated the impact of omitting the first 3 combined OC pills (second and third generation) on ovulation during a 28-day cycle. While none of the women experienced ovulation, follicle-stimulating hormone (FSH) reached a maximal serum concentration in most women during the first 7 pill-free days, indicating complete pituitary recovery. Additionally, the researchers detected increases in serum estradiol, indicating that follicular growth up to preovulatory size is common in women missing the first one to 3 pills of their contraceptive cycle.[16] Nonadherence often occurs during transitions between successive packs of OCs.[17] It has been reported that 47% of women using OCs miss one pill, and 22% miss 2 pills per cycle.[18] Ovulation and pregnancy are more likely to occur if pills are missed in the first week after menses.

Extended-cycle OCs prevent hormonal fluctuations and provide continuous suppression of FSH and luteinizing hormone (LH), decreasing the likelihood of ovulation and, therefore, pregnancy. Because the extended-cycle regimen decreases the number of transitions between packs of OCs, one might expect a reduction in the risk associated with nonadherence at the beginning of a cycle. However, extended-cycle OCs have a greater risk of breakthrough bleeding, which can decrease adherence and increase discontinuation of the method, thereby increasing the risk of pregnancy.

A multicenter RCT of 682 women examined the efficacy and safety of the extended-cycle OC Seasonale (30 mcg EE/150 mcg LNG) compared with a traditional cycle OC Nordette-28 (30 mcg EE/150 mcg LNG). Women received either 4, 91-day extended cycles (n=456) or 13, 28-day regular cycle (n=226) regimens over the course of one year. On average, 38% of women in the extended- cycle group reported unscheduled (breakthrough) bleeding, while 18% of women in the conventional cycle group reported unscheduled bleeding. Breakthrough bleeding decreased with each successive cycle of the extended reg-

A closer look at combined OCs

Combined oral contraceptives (OCs) have only one estrogen, ethinyl estradiol (EE), in various doses, formulated with a progestin. Progestins can be grouped chronologically. First-generation progestins, commonly referred to as "estranes," include norethindrone, norethindrone acetate, and ethynodiol diacetate. Second-generation progestins, called "gonanes," are more potent and allow the use of lower doses. They include norgestrel and levonorgestrel (LNG).

Third-generation progestins, also called "gonanes," have reduced androgenic and metabolic effects and include norgestimate, desogestrel, and gestodene (not available in the United States). Finally, there is a newer miscellaneous category: drospirenone, an antimineralocorticoid with progestogen and antiandrogenic activity.

TABLE

Oral contraceptives: A review of the options

	Generic name	Brand name	Estrogen dose (mg)	Progestin dose (mg)	Mono- vs multiphasic	Monthly vs extended cycle
Progestin only	Norethindrone acetate	Aygestin	-	5	Monophasic	Monthly
	Norethindrone only	Camila, Errin, Jolivette, Nora-BE, Nor-QD, Ortho Micronor	-	0.35	Monophasic	Monthly
First-generation progestin	Ethinyl estradiol and ethynodiol diacetate	Demulen*	Days 1-21: 0.05 Days 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Monophasic	Monthly
		Kelnor, Zovia	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Monophasic	Monthly
	Ethinyl estradiol and norethindrone	Gildess Fe 1/20† Junel 1/20, Junel 1/20 Fe,† Loestrin 21 1/20, Loestrin 1/20 Fe,† Microgestin 1/20, Microgestin 1/20 Fe†	Days 1-21: 0.02 Days 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Monophasic	Monthly
		Gildess 1.5/30 Fe,† Junel 1.5/30, Junel 1.5/30 Fe,† Loestrin 21 1.5/30, Loestrin 1.5/30 Fe,† Microgestin 1.5/30, Microgestin 1.5/30 Fe†	Days 1-21: 0.03 Days 22-28: inert pills	Days 1-21: 1.5 Days 22-28: inert pills	Monophasic	Monthly
		Balziva, Femcon Fe,† Ovcon 35, Zenchent, Zeosa†	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-21: 0.4 Days 22-28: inert pills	Monophasic	Monthly
		Brevicon, Modicon, Nelova, Necon 0.5/35,* Nortrel 0.5/35	Days 1-21: 0.035 Day 22-28: inert pills	Days 1-21: 0.5 Day 22-28: inert pills	Monophasic	Monthly
		Cyclafem 1/35, Genora 1/35, Necon 1/35, Norethin 1/35, Norinyl, Nortrel 1/35, Ortho-Novum 1/35	Days 1-21: 0.035 Day 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Monophasic	Monthly

TABLE

Oral contraceptives: A review of the options *(continued)*

	Generic name	Brand name	Estrogen dose (mg)	Progestin dose (mg)	Mono- vs multiphasic	Monthly vs extended cycle
First-generation progestin *(continued)*	Ethinyl estradiol and norethindrone *(continued)*	Ovcon 50	Days 1-21: 0.05 Days 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Monophasic	Monthly
		Loestrin 24 Fe†	Days 1-24: 0.02 Days 25-28: inert pills	Days 1-24: 1 Days 25-28: inert pills	Monophasic	Monthly
		Necon 10/11*	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-10: 0.5 Days 11-21: 1	Biphasic	Monthly
		Aranelle, Leena, Tri-Norinyl	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-7: 0.5 Days 8-16: 1 Days 17-21: 0.5 Days 22-28: inert pills	Triphasic	Monthly
		Estrostep Fe,† Tri-Legest Fe,† Tilia Fe†	Days 1-5: 0.02 Days 6-12: 0.03 Days 13-21: 0.035 Days 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Triphasic	Monthly
		Cyclafem 7/7/7, Necon 7/7/7, Nortrel 7/7/7, Ortho-Novum 7/7/7	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-7: 0.5 Days 8-14: 0.75 Days 15-21: 1	Triphasic	Monthly
Second generation progestin	Ethinyl estradiol and levonorgestrel	Alesse,* Aviane, Lessina,* Levlite, Lutera, Sronyx	Days 1-21: 0.02 Days 22-28: inert pills	Days 1-21: 0.1 Days 22-28: inert pills	Monophasic	Monthly

CONTINUED

TABLE

Oral contraceptives: A review of the options *(continued)*

	Generic name	Brand name	Estrogen dose (mg)	Progestin dose (mg)	Mono- vs multiphasic	Monthly vs extended cycle
Second-generation progestin *(continued)*	Ethinyl estradiol and levonorgestrel *(continued)*	Altavera, Levlen,* Levora,* Microgynon, Nordette,* Ovranette, Portia*	Days 1-21: 0.03 Days 22-28: inert pills	Days 1-21: 0.15 Days 22-28: inert pills	Monophasic	Monthly
		Enpresse, Levonest,* Triphasil,* Tri-Levlen,* Trivora	Days 1-6: 0.03 Days 7-11: 0.04 Days 12-21: 0.03 Days 22-28: inert pills	Days 1-6: 0.05 Days 7-11: 0.075 Days 12-21: 0.125 Days 22-28: inert pills	Triphasic	Monthly
		Lybrel	Days 1-28: 0.02	Days 1-28: 0.09	Monophasic	365-day cycle
		LoSeasonique	Days 1-84: 0.02 Days 85-91: 0.01	Days 1-84: 0.1	Monophasic	91-day cycle
		Introvale, Jolessa, Quasense, Seasonale	Days 1-84: 0.03 Day 85-91: inert pills	Days 1-84: 0.15 Day 85-91: inert pills	Monophasic	91-day cycle
		Seasonique	Days 1-84: 0.03 Days 85-91: 0.01	Days 1-84: 0.15	Monophasic	91-day cycle
	Ethinyl estradiol and norgestrel	Cryselle-28, Lo/Ovral-28, Low-Ogestrel*	Days 1-21: 0.03 Days 22-28: inert pills	Days 1-21: 0.3 Days 22-28: inert pills	Monophasic	Monthly
		Ovral-28, Ogestrel	Days 1-21: 0.05 Days 22-28: inert pills	Days 1-21: 0.5 Days 22-28: inert pills	Monophasic	Monthly
Third -generation progestin	Ethinyl estradiol and desogestrel	Desogen, Emoquette, Ortho-Cept, Reclipsen, Solia	Days 1-21: 0.03 Days 22-28: inert pills	Days 1-21: 0.15 Days 22-28: inert pills	Monophasic	Monthly
		Azurette, Kariva, Mircette	Days 1-21: 0.02 Day 22-23: inert pills Day 24-28: 0.01	Days 1-21: 0.15	Biphasic	Monthly

TABLE

Oral contraceptives: A review of the options *(continued)*

	Generic name	Brand name	Estrogen dose (mg	Progestin dose (mg)	Mono- vs multiphasic	Monthly vs extended cycle
Third -generation progestin *(continued)*	Ethinyl estradiol and desogestrel *(continued)*	Caziant, Cesia, Cyclessa, Velivet	Days 1-21: 0.025 Days 22-28: inert pills	Days 1-7: 0.1 Days 8-14: 0.125 Days 15-21: 0.15 Days 22-28: inert pills	Triphasic	Monthly
	Ethinyl estradiol and norgestimate	MonoNessa, Ortho-Cyclen, Previfem, Sprintec	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-21: 0.25 Days 22-28: inert pills	Monophasic	Monthly
		Ortho Tri-Cyclen Lo, Tri-Lo-Sprintec, TriNessa Lo	Days 1-21: 0.025 Day 22-28: inert pills	Days 1-7: 0.18 Days 8-14: 0.215 Days 15-21: 0.25 Days 22-28: inert pills	Triphasic	Monthly
		Ortho Tri-Cyclen, TriNessa, Tri-Previfem, Tri-Sprintec	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-7: 0.18 Days 8-14: 0.215 Days 15-21: 0.25 Days 22-28: inert pills	Triphasic	Monthly
Miscellaneous progestin	Ethinyl estradiol and drospirenone	Beyaz,‡ Gianvi, Yaz	Days 1-24: 0.02 Days 25-28: inert pills	Days 1-24: 3 Days 25-28: inert pills	Monophasic	Monthly
		Ocella, Safyral,‡ Yasmin, Zarah	Days 1-21: 0.03 Days 22-28: inert pills	Days 1-21: 3 Days 22-28: inert pills	Monophasic	Monthly
	Estradiol valerate and dienogest	Natazia	Days 1-2: 3 Days 3-7: 2 Days 8-24: 2 Days 25-26: 1 Days 27-28: inert pills	Days 1-2: 0 Days 3-7:2 Days 8-24: 3 Days 25-26: 0 Days 27-28: inert pills	Multiphasic	Monthly

*21-day formulation without inert pills also available.

†Also contains 75 mg ferrous fumarate in pills Days 22-28 or Days 24-28.

‡Beyaz and Safyral also contain 0.451 mg levomefolate calcium in Days 1-28.

Adapted from: Oral contraceptives. *Monthly Prescribing Reference.* October 9, 2012. Available at: http://www.empr.com/oral-contraceptives/article/123837/#. Accessed September 23, 2013.

imen, from a median of 12 days with the first cycle, to a median of 4 days during the fourth and final cycle. This study also reported no significant differences in side effects between the extended- and traditional- cycle regimens, including changes in lipids, body weight, blood pressure, or endometrial hyperplasia.[19]

Another RCT examined the difference in bleeding patterns, side effects, and acceptability between a standard 28-day cycle OC and an extended-regimen 168-day cycle OC in 32 women. Both OCs contained 20 mcg EE and 100 mcg LNG, and the study was conducted over 6 months. Women in the extended-cycle regimen reported significantly fewer days of bloating (0.7 vs 11.1 days; P=.04), and menstrual pain (1.9 vs 13.3 days; P<.01). There was no significant difference in reported headache, breast tenderness, nausea, depression, or premenstrual symptoms. Women in the extended cycle group also reported significantly fewer bleeding days that required sanitary pads (18.4 vs 33.8 days; P<.01). However, there was no statistically significant difference in the total number of days in which any degree of bleeding occurred (34.9 days in the monthly cycle group, 25.9 days in the extended cycle group; P=.33).[20]

In a study of 126-day extended-cycle OCs with 30 mcg EE and 3 mg drospirenone, the bleeding profile improved over time, and endometrial biopsies revealed no hyperplasia.[21] Another benefit of the extended cycle is personal preference, ie, controlling the timing of one's menses,[22] for example, in athletes during training and competition.

Continuous use of OCs prevents the cyclic fluctuations of serum levels of EE and progestogen and, hence, the cyclic variations of related serum-based metabolic parameters. Extended-cycle OCs can make it easier to titrate other medications affected by hormonal fluctuations. Another study of extended-cycle DRSP OCs compared with monthly OCs over 6 months showed no difference in lipid, carbohydrate, and coagulation markers.[23]

Six RCTs were included in a Cochrane review of monthly vs extended-cycle combined pills. It found no significant differences in efficacy, adherence, discontinuation rates, and patient satisfaction. Significant differences noted included improvement of menstrual-associated symptoms of "headaches, genital irritation, tiredness, bloating and menstrual pain" with the extended-cycle regimen.[24]

OCs effect on weight, BP, and premenstrual symptoms

Weight gain. A 2008 Cochrane review examined 3 placebo-controlled RCTs and concluded that the available evidence was insufficient to determine the effect of combined hormonal contraceptives on weight, and that larger doses of estrogen were not shown to cause larger weight gain.[25]

One RCT examined the effects of OCs on variations in total body water, fat mass, and fat-free mass throughout the menstrual cycle to determine if different doses of estrogen (15 vs 30 mcg EE) or different types of progestins (gestodene 60 mcg vs DRSP 3 mg) affect weight gain. This study only included 80 women randomized to the 2 treatment groups, plus a control group using male condoms. No differences were found in total body water or fat mass. There was, however, a significant increase in fat-free mass in women in the EE/gestodene group compared with the controls, indicating a possible effect of the androgenic properties of gestodene compared with DRSP (which has antiandrogenic properties) in increasing muscle mass.[26]

In a 6-month study of DRSP compared with LNG, mean body weight fell by 0.8 to 1.7 kg in women treated with DRSP compared with a 0.7 kg weight gain in the LNG group (P<.05).[27] A multicenter RCT comparing OCs with EE 30 mcg/DRSP 3 mg vs EE 30 mcg/desogestrel 150 mcg concluded that EE/DRSP has a more favorable effect on body weight than EE/desogestrel. This finding may have resulted from the antimineralocorticoid and mild diuretic effects of DRSP.[28]

Hypertension. In a review of progestin-only OCs in normotensive women, the authors could find no evidence to show a statistically significant increase in blood pressure.[29]

In a study of 120 women randomized to drospirenone/EE or LNG/EE, the drospirenone group had a mean decrease in systolic blood pressure from 107 to 103 mm Hg, and a significantly lower mean blood pressure compared with the LNG group.[30] Another study of 80 women over 6 months random-

ized into 3 groups, each having 3 mg DRSP with either 30, 20, or 15 mcg EE, found that systolic blood pressure decreased by 1 to 4 mm Hg compared with an elevation in blood pressure of 4 mm Hg in the LNG/EE group.[27]

In women with well-controlled blood pressure who are younger than 35 years old, nonsmokers, and otherwise healthy, the American College of Obstetricians and Gynecologists (ACOG) recommends a trial of OCs with blood pressure monitoring.[31]

Acne. One Cochrane review looked at studies that compared combined OCs with placebo, and found that OCs improved the condition. However, there was insufficient evidence regarding the difference in effectiveness of various formulations of OCs in treating acne.[32] There was no difference between first-and second-generation progestins,[33] between second- and third-generations,[34] or third-generation progestins vs DRSP.[35]

Premenstrual symptoms. A 2005 open-label RCT compared the effects of DRSP/20 mcg EE with the second-generation progestin LNG/30 mcg EE on premenstrual symptoms after 6 menstrual cycles. In the premenstrual phase, the DRSP/EE group showed less negative mood and weight gain.[36]

A 2012 Cochrane review examined the effects of OCs containing DRSP on premenstrual dysphoric disorder (PMDD) vs placebo and other OC formulations. The review included 5 trials and found that DRSP is associated with significantly greater improvements than placebo in symptoms of PMDD, but was inconclusive on whether DRSP formulations have greater effects on PMDD than other OC formulations.[37]

Dysmenorrhea. A 2009 Cochrane review compared 10 studies examining the role of different formulations of combined OCs in management of dysmenorrhea and concluded there is no difference in improvement among different OC preparations.[38]

OCs and coronary heart disease

Estrogen has several favorable effects on circulating lipoproteins, including increasing high-density lipoprotein (HDL), and increasing low-density lipoprotein (LDL) receptor activity, thereby enhancing removal of LDL.

Women using a 20 mcg EE/100-mcg LNG OC experienced reductions in HDL and small increases in LDL and triglycerides compared with a 30 mcg EE/150-mcg LNG OC.[39] A study of gestodene 75 mcg with either 20 or 30 mcg EE for 13 cycles found a greater increase in triglyceride levels in the formulation with a higher dose of estrogen ($P = .029$).[40]

Barkfeldt and colleagues[41] conducted a double-blind RCT that evaluated the effects of lipid metabolism on 98 women who received 2 different types of progestin-only pills, desogestrel 75 mcg/d vs LNG 30 mcg/d. There were minimal changes in the lipid profile except for decreasing trends in levels of HDL, its subfractions, and apolipoprotein-I and -II. No differences were observed between the 2 formulations, including LDL and apolipoprotein-B, despite the higher progestin dose found in desogestrel.[41]

Third-generation progestins with "lesser androgenicity" may allow more "expression" of the effects of estrogen on lipids. A prospective study of 66 women over 9 months comparing either desogestrel (50/100/150 mcg) and EE (35/30/30 mcg) with LNG (50/100/150 mcg) and EE (30/40/30 mcg) showed that the desogestrel formulation increased HDL, whereas LNG decreased HDL.[42] Another study compared monophasic desogestrel/EE with triphasic LNG/EE in 37 healthy young women. While both preparations led to an increase in total cholesterol, the desogestrel formulation led to a reduction in the LDL.[43] A 1995 study of DRSP compared with LNG for 6 months showed that HDL increased in the DRSP group ($P<.05$) but triglyceride levels showed a greater increase in the DRSP group ($P<.05$).[27]

The use of OCs in the absence of risk factors does not appear to promote coronary artery disease (CAD), and there is no reason to withhold OCs from dyslipidemic women. In women with LDL of more than 160 mg/dL or multiple cardiac risk factors, ACOG recommends a nonhormonal method of contraception, such as an intrauterine device (IUD).[31]

OCs and glucose metabolism, thromboembolism

Glucose metabolism. Oelkers and colleagues[27] studied glucose levels in 80 healthy

While OCs are thought to cause side effects, when compared with a placebo, there have been no significant findings regarding the frequency of headache, nausea, vomiting, breast pain, or weight gain.

ACOG recommends a nonestrogen hormonal alternative, such as progestin-only pills or an IUD, for obese women.

women assigned to 4 equal groups who received 3 mg DRSP combined with 30-, 20-, and 15-mcg doses of EE or LNG/30-mcg EE. Each woman underwent oral glucose tolerance testing pretreatment and at the end of the 6-month OC cycle. On treatment, fasting glucose was unchanged for all groups, but the area under the curve for the glucose tolerance increased for all formulations. Although not statistically significant among groups, the DRSP/30-mcg EE group had a 19% worsening of glucose tolerance.[27] This research suggests that women with diabetes who are otherwise healthy, nonsmokers, and younger than 35 years of age can safely use OCs.

Thromboembolism. Estrogen has been known to increase the risk of venous thromboembolism (VTE) by increasing prothrombin and decreasing antithrombin III.[44] In OC users, the incidence of VTE is increased by a factor of 3 to 5.[45] While several studies have compared high-dose estrogen (50 mcg) with low-dose (≤35 mcg) OCs,[46,47] there is no information about any differences in low (25-35 mcg) EE vs ultra-low doses (10 mcg).

Third-generation desogestrel-containing OCs have a slightly increased risk of VTE compared with second-generation pills[4] unexplained by bias and confounding factors.[49,50] It has been estimated that 25 additional cases of VTE occur every year among 100,000 women using third-generation OCs compared with 10 additional cases per 100,000 women using second-generation OCs.[51] A meta-analysis that included 9 case control and 3 cohort studies estimated an odds ratio for third- vs second-generation OCs of 1.7 (95% CI, 1.4-2.0).[52] A 2010 meta-analysis refutes these findings, showing no difference in OCs containing the third-generation progestin gestodene vs other formulations.[53] Because obesity (BMI >30 kg/m^2) is an independent risk factor for VTE, ACOG recommends a non-estrogen-containing hormonal method such as progestin-only pills or an IUD for obese women.[31]

Bone mineral density (BMD). A 2000 study compared 2 OCs with the same dose of progestin (gestodene 75 mcg) and 2 doses of EE (20 vs 30 mcg) to determine if there was a correlation between dose of estrogen and loss of BMD in young postadolescent women taking OCs. It concluded that pills with 20 and 30 mcg of estrogen were associated with the same reduction in BMD.[54]

However, a 2009 Cochrane review concluded that combined OCs do not affect bone health, ie, fracture rate, BMD, or biochemical markers of bone change. Thirteen RCTs were reviewed and researchers concluded that the relationship between OC use and fracture risk cannot be determined from the limited data currently available.[55]

Cancer. Research does not support the notion that OCs contribute to cancer. In fact, reduced endometrial and ovarian cancers have been shown among users of OCs containing 50 mcg EE.[56-58] Low-dose formulations (≤35 mcg EE) have been less studied but also confer a substantial risk reduction.[59]

Data are conflicting regarding a slight increase in risk for breast cancer in current or recent users of OCs from older, higher-estrogen doses; that risk returns to normal over time.[60] The World Health Organization recognizes this slight risk, but has concluded that the benefits of OCs outweigh the risks.[61]

Evidence-based guidelines are lacking

There is a paucity of RCTs with sufficient duration and sample size that compare different OC formulations to provide evidence-based guidance for physicians. While some pharmaceutical companies market their products for particular benefits, these findings too often come from noncomparative trials, ie, their product vs placebo.

So here's what we know…

No OC formulation is more effective at preventing pregnancy than any others. Cycle control, ie, less intermenstrual bleeding, is improved with 30 to 35 mcg EE formulations compared with ultra-low dose (20 mcg) EE. There are no advantages to choosing a multiphasic formulation over a monophasic OC. While extended-cycle formulations have more breakthrough bleeding than monthly cycles, overall they have fewer days of menstrual bleeding, which tend to decrease even further in successive cycles. Extended-cycle

formulations have decreased days of bloating and menstrual cramping.

There is no evidence that different doses of estrogen or progestin affect weight gain or total body water. DRSP leads to a more favorable lean body mass profile than LNG and desogestrel, which may be related to its antimineralocorticoid effect. While both second- and third-generation progestin formulations have been shown to improve acne, there is no evidence to indicate a preference.

There is also little evidence to recommend a particular OC to avoid adverse events such as CAD or VTE; in fact, the evidence is often contradictory. Epidemiologic studies confirm that venous thromboembolic disease is similar for 20 and 30 mcg EE. There may be an increase in VTE with desogestrel, but recent evidence finds no significant increase. The clinical significance that DRSP increases triglyceride levels while it decreases LDL and HDL, and the significance of LDL reduction by desogestrel, require further investigation.

There is no evidence that OCs affect bone health indices such as fracture rate, BMD, or biochemical markers of bone change. OC formulations with higher doses of estrogen have been shown to reduce ovarian and endometrial cancer, presumably due to fewer ovulatory cycles. However, similar reductions should therefore be observed with lower EE dose formulations, as well.

Clearly, the literature indicates that there is little evidence to recommend one OC formulation over another. All currently marketed OCs have low-dose EE. However, when counseling patients, keep in mind that extended cycle formulations decrease some side effects and generic formulations reduce costs. JFP

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While extended-cycle formulations have more breakthrough bleeding than monthly cycles, overall they have fewer days of menstrual bleeding.

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