The state of hormonal contraception today: benefits and risks of hormonal contraceptives: combined estrogen and progestin contraceptives

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Over the course of the past 50 years, modifications have been made to improve the effectiveness, acceptability, and tolerability of hormonal contraceptives. Initially, the doses of the estrogen and progestin components were lowered and formulations were developed containing only progestin. Subsequently, new progestins were developed to decrease androgenic side effects, and, more recently, alternative delivery systems were introduced to improve tolerability and continuance, and convenience of use.1 All combination hormonal contraceptives are highly effective in preventing pregnancy when used properly; the changes that have been made to pill regimens and components along the course of the past 50 years have been undertaken to improve tolerability and increase the likelihood of consistent and correct use to improve overall contraceptive effectiveness and maximize the noncontraceptive benefits associated with contraceptive use.

Benefits and risks of combination hormonal contraceptives

Understanding the benefits and risks of contraceptive methods and being able to communicate those to women are critical to improved acceptability and appropriate use of effective birth control. Providing detailed counseling to women at the outset that addresses the advantages, disadvantages, benefits, and risks of various contraceptive methods, invariably leads to better outcomes in the future. Frequently, misconceptions exist with regard to the safety of hormonal contraceptives. Clinicians must balance risks against the benefits of contraception in the context of a particular women’s health history. Unintended pregnancy is usually the result of a lack of contraceptive use or failure of the chosen contraceptive method. The impact of unintended pregnancy can be significant and encompasses health risks as well as adverse social and economic consequences. Health risks usually pertain to absent or poor prenatal care and include an increased risk of maternal and neonatal morbidity and mortality. Social and economic consequences include reduced maternal education and employment options, and an increased likelihood of welfare dependency. As such, unintended pregnancies place a substantial social, medical and economic burden on women and society.

In addition to preventing unintended pregnancy, hormonal contraceptives have been shown to provide numerous noncontraceptive benefits.2 Oral contraceptives have been shown to reduce the risk of ovarian epithelial cancer and endometrial cancer without increasing the risk for breast cancer.3 Combination hormonal contraceptives generally reduce androgenic symptoms, with several oral contraceptive regimens having been formally approved for the treatment of mild to moderate acne.2 Many women of childbearing age experience some degree of physical and emotional symptoms related to their impending menses. Some of these menstrual-related health issues include heavy menstrual bleeding, headache, dysmenorrhea and behavioral, emotional, and physical symptoms associated with premenstrual dysphoric disorder. Combination hormonal contraceptives have been shown to ameliorate or effectively treat these problems. Recently, in women choosing to use oral contraceptives for pregnancy prevention, the 20 mcg EE/3 mg drospirenone 24/4 regimen was approved by the US Food and Drug Administration (FDA) for the treatment of the symptoms of premenstrual dysphoric disorder4 and the multiphasic E2V/DNG regimen was approved in Europe for the treatment of heavy menstrual bleeding in women.5

As with any therapeutic agent, there is invariably an increased risk for side effects and adverse events that is concomitant with the benefits accrued by its use.

Discussion of effective birth control methods can be a challenging process for clinicians because the adoption and consistent use of contraception may be influenced by patients’ fears, myths, and misperceptions. Over the years, new progestins have been included in combination contraceptives or are used alone to provide effective contraception as well as to decrease androgenic side effects and ameliorate the symptoms of premenstrual dysphoric disorder. Alternative delivery systems and regimens have also been introduced to improve tolerability and continuance and convenience of use. This is a review of estrogen and progestin combinations and their effects.

Key words: androgenic effects, contraceptive side effects, menstrual cycle control, venous thromboembolism

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Clinicians are in the position to weigh the risks and benefits of hormonal contraceptives for each individual patient so as to empower that woman to decide which method, if any, to use to prevent pregnancy. The use of combination oral contraceptives is associated with an increased risk for thromboembolic events. In addition, other cardiovascular risks are increased especially among women who are smokers, are obese, or have personal or family histories of cardiovascular and other disease. However, many women believe that hormonal contraceptives are associated with great risk to their health and well-being. Much of this concern stems from women reading the lay press, which highlights women who have experienced considerable morbidity or even death while using such methods. Unfortunately, such reports rarely, if ever, present information as to the relative safety of such methods, especially in comparison to unintended pregnancy, which is characterized by profoundly higher rates of overall morbidity and mortality. Such fears have a powerful impact on women and all too often lead women either to choose less effective methods of contraception or to use no method at all, thus placing them at a much higher risk for pregnancy and its adverse outcomes.

Eliciting a woman’s choice for contraception during consultation is critical to the process of her finding a method of contraception that she can successfully incorporate into her lifestyle. Although some women may find the recommendations of her clinician to be important, it is the patient who best knows the type of contraceptive regimen that she is likely to use correctly and gain the maximal contraceptive and noncontraceptive benefits associated with her choice of contraception. Indeed, a study to determine factors associated with sustained use of contraceptives found that when the choice of birth control was denied by providing the patient with a popular method of oral contraception at the time of the study, about 72% of women discontinued its use within 12 months, whereas only 8.9% of those whose preferred choice was granted eventually discontinued the contraceptive (Figure 1).

Whereas the disparity between those who continued with their birth control and those who did not is impressive, the discontinuation rate among those denied a choice is even more remarkable. Adoption of effective birth control methods can be a challenging process for clinicians because of patient barriers—fears, myths, and misperceptions. These can include unrealistic expectations, media scares, and lack of awareness of numerous noncontraceptive benefits. Offering women choices, discussing benefits and risks, engaging women in birth-control decision making, and listening to women about their concerns and needs all support effective use.

**Nondaily, nonoral combination hormonal contraceptives**

Two nonoral, nondaily combination contraceptive methods are available, the vaginal ring and a transdermal patch. These methods have a number of characteristics that make them especially attractive to women: they are highly effective, convenient, and easy to use. Because these methods require less frequent attention to the method than other birth control, they are less likely to be subject to inconsistent use. In addition, these methods likely have the noncontraceptive benefits associated with other hormonal methods while not requiring daily administration.

**Vaginal ring**

The vaginal ring is a flexible transparent ring that is inserted like a tampon. It provides steady and continuous delivery of low-dose hormone (120 mcg/d of etonogestrel and 15 mcg/d of ethinyl estradiol) over 3 weeks, after which it is removed for a hormone-free week. Lower doses of estrogen afforded by vaginal administration may reduce the effects associated with higher doses of estrogen, such as breast tenderness, nausea, and headache. The pharmacokinetics of the ring show that contraceptive levels of etonogestrel and ethinyl estradiol are maintained for 35 days of use, suggesting that women can extend use and may experience lighter or even absent withdrawal bleeding during the ring-free week.

Efficacy, cycle control, and acceptability were studied in a population of 2322 women using the vaginal ring and followed for more than 23,000 cycles. Efficacy, measured by the Pearl Index, was 0.77 in the per-protocol population and 1.18 in the intent-to-treat group. This study found that the majority of completers (96%) were very satisfied with the ring and 90% of them indicated that they would recommend the ring to others. Contraceptive acceptability and continuance of use are influenced by many

**FIGURE 1**

Percent of women discontinuing a contraceptive based on choice offered

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<th>% Discontinuing at 1 Year</th>
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<tr>
<td>Choice Denied</td>
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<td>Choice Granted</td>
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factors, key among which is cycle control. The Dieben et al\textsuperscript{12} study reported good cycle control among the ring users. Almost all women experienced withdrawal bleeding, which did not generally occur outside the ring-free week, and, when it did, it was mainly spotting rather than bleeding.\textsuperscript{12} In another study, the profile of irregular bleeding was more favorable with the ring than with an oral levonorgestrel/ethinyl estradiol contraceptive.\textsuperscript{10} In this study and in clinical observation, the incidence of irregular bleeding in the combination oral contraceptive (COC) group was particularly high during the first cycle.\textsuperscript{10} This was not the experience among women using the ring, although this may be attributed to the fact that women starting the pill usually do so on day 1 of the cycle, whereas the ring users started on day 5.\textsuperscript{10}

\subsection*{Transdermal patch}

The transdermal patch contains 6.00 mg norelgestromin and 0.75 mg ethinyl estradiol and is a highly effective method of contraception, applied weekly for 3 weeks with a fourth week off.\textsuperscript{13} An analysis of pooled data from 3 open-label studies reported a Pearl Index of 0.88 and a low failure probability of 0.6\% with the patch.\textsuperscript{14}

The patch is also well accepted by women, and it may offer advantages over COCs, including convenience and better continuity of use. Using data pooled from 3 studies, researchers assessed compliance patterns of the patch compared with those of an established oral contraceptive.\textsuperscript{15} For all cycles, adherence to the weekly dosing schedule of the patch was significantly better than that of the oral contraceptive regardless of age of the women ($P < 0.001$) (Figure 2).\textsuperscript{15}

A pharmacokinetic study showed mean steady-state concentrations ranged from 0.305–1.53 ng/mL for the progestin component and from 11.2-137 pg/mL for the estrogen component of the patch.\textsuperscript{13} In a study that compared the patch with a COC containing 250 mcg norelgestromin and 35 mcg ethinyl estradiol, the overall exposure to these steroids (area under the curve) was greater with the patch.\textsuperscript{13} A study examining the pharmacokinetic properties of 3 hormonal contraceptive formulations (a vaginal ring, the transdermal patch, and a COC containing 30 mcg ethinyl estradiol) found that the maximal blood level of ethinyl estradiol with the patch was about 60\% less than that of the COC.\textsuperscript{16,17} A case-controlled study compared the risk of nonfatal venous thromboembolism (VTE) in women using the transdermal patch to that of women using a COC containing 35 mcg of ethinyl estradiol. The study found that the odds ratio for VTE for transdermal patch users was 0.9, representing no increased risk for VTE and similar to the risk observed in new users of the COC comparator.\textsuperscript{17} Another study found a 2-fold increased risk for VTE with the patch.\textsuperscript{18} Based on this negative information, the US FDA issued a warning concerning the possible increased risk of VTE with patch use. Since then, a third report of a case-controlled study using postmarketing data found that in women under 40 years of age, there was no increased risk of VTE with the transdermal patch, compared with a levonorgestrel-containing COC.\textsuperscript{19} The authors concluded that the risk of idiopathic VTE in users of the transdermal patch was not different from that of users of levonorgestrel-containing COCs in women 39 years of age or younger.

\subsection*{Combination oral contraceptives}

The daily COC remains the most commonly used nonbarrier method of reversible contraception. When properly used, it is more than 99\% effective.\textsuperscript{20} In reality, about half of women use COCs correctly and consistently,\textsuperscript{21} a study of use patterns showed that 37\% of women reported that they discontinued their COC because of side effects.\textsuperscript{21} Serious complications, like deep vein thrombosis or pulmonary embolism, are rare, and aside from a few persistent intolerable side effects—breast tenderness, spotting—the pill has few absolute contraindications and several noncontraceptive benefits. Refer to the package insert to review the complete list of contraindications and special considerations. Recent developments in OCs have focused on:

- The development of a pill or pill regimen that improves tolerability and acceptability.
- Lowering doses and altering delivery patterns of estrogen and progestins.
- The development of new progestins.

\subsection*{Drospirenone-containing COC}

Drospirenone is a novel progestin not derived from 19-nortestosterone but rather from 17alpha-spirolactone and has antimineralocorticoid and antiandrogenic properties. The Dieben et al\textsuperscript{12} study reported high during the first cycle.\textsuperscript{10} This was not the experience among women using the ring, although this may be attributed to the fact that women starting the pill usually do so on day 1 of the cycle, whereas the ring users started on day 5.\textsuperscript{10}
drogenic activity. Combined with ethinyl estradiol, it is an effective oral contraceptive and has favorable effects in women who have premenstrual dysphoric disorder (PMDD). In addition, its antimineralocorticoid properties have the potential to lower body weight (through water weight change and not loss of fat) and blood pressure.

Two prospective studies have been undertaken to examine the cardiovascular effects of the drospirenone-containing COC—one conducted in Europe and the other in an American population. Both studies found that deep vein thrombosis and pulmonary embolism occurred with equal frequency in the ethinyl estradiol/drospirenone COC and other COC users (Figure 3). The US study observed that a clinician can expect to find one case of thromboembolism among 769 women over the course of 1 year if they were prescribed the drospirenone-containing COC.

Two more-recent studies, both using European populations, have also examined thrombotic events in users of COCs. The Dutch study also found an increased risk, which differed by type of progestin, that decreased with duration of use and decreasing estrogen dose. All of the study results are now included in the prescribing information for the drospirenone-containing COCs; however, the FDA also added a statement that the results of the Dutch and Danish studies do not provide convincing evidence of an increased risk for VTE, given the relatively few number of VTE cases among drospirenone users in the Dutch study and a likelihood of ascertainment bias in the Danish study.

The rationale for shortening the hormone-free interval in women using COCs was improvement in ovarian suppression as well as reduction of adverse symptoms experienced during the hormone-free interval. An early study found that by adding 2 days to the COC regimen, ovarian suppression improved contraceptive efficacy. This was tested in the extended use of a low-dose 20-mcg ethinyl estradiol COC, and results showed that the efficacy of the 24-day low-dose COC improved efficacy.

The COCs of the future

Two COCs in development are a 26-day multiphasic regimen of estradiol valerate and dienogest and a COC containing 17 beta-estradiol and nomegestrol acetate. Although the use of estradiol valerate may have some advantages over ethinyl estradiol, there are no head-to-head studies of ethinyl estradiol and estradiol-containing pills to date. The 26-day multiphasic combination of estradiol valerate and dienogest offers reliable contraception and, with only 2 days off, may provide lighter withdrawal bleeding than does a traditional pill containing ethinyl estradiol and levonorgestrel.

The other new pill contains 17 beta-estradiol and nomegestrol acetate in a monophasic regimen. A recent pharmacologic and pharmacokinetic study indicates good ovulation suppression with this combination, with mean maximum follicular diameter decreased from 19.3 mm before treatment to between 6.9 and 8.2 mm during treatment. The findings from this study are consistent with ovulation inhibition produced by oral contraceptives containing ethinyl estradiol and drospirenone.

As the investigation of new compounds continues, it will add to the array of effective combination hormonal contraceptives available to women. The expansion of contraceptive choice can only improve the likelihood that a woman will find a method of contraception that she will successfully incorporate into her lifestyle and use consistently and correctly for as long as she chooses not to be pregnant. As many hormonal methods carry similar capabilities to prevent pregnancy, it will be the availability of methods with unique noncontraceptive benefits that will help women find a method that is right for them. It is important that research continues to improve tolerability and acceptability of contraceptive options, preserve efficacy, and delineate noncontraceptive benefits, while lowering hormone exposure and improving the safety profile.

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FIGURE 3
Comparison of risk for venous thromboembolism in 2 prospective trials comparing oral contraceptives with and without drospirenone

Drospirenone 3 mg/Ethinyl Estradiol 30 mcg* vs Other OCs Studied

EURAS18

In the EURAS study, other OCs included a levonorgestrel cohort and an other OCs cohort.

Ingenix19

In the Ingenix study, other OCs included initiators of other OCs; TE was defined as DVT only, PE only, and DVT and PE outcomes.

More than 125,000 OC users, with more than 150,000 woman-years, demonstrated that low-dose OC users studied had comparable VTE risk.18,19

*In a 21/7 regimen

CI, confidence interval; DVT, deep vein thrombosis; EURAS, European Active Surveillance Study; OC, oral contraceptive; PE, pulmonary embolism; TE, thromboembolism; VTE, venous thromboembolism.