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Combined Oral Contraception

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Combined oral contraceptives (COCs), oral contraceptives containing an estrogen and a progestin, are a common, effective, and generally well-tolerated form of contraception with a wide variety of noncontraceptive benefits. Combined oral contraceptives have been most limited by the potential severe adverse event of venous thromboembolism throughout their history and development. In recent years, natural-estrogen–containing COCs have emerged with an improved safety profile while maintaining high efficacy and should likely be recommended as first line for new-start patients. It is important for clinicians to understand the evolution of COC regimens and the specific hormones within each formulation to best optimize benefits while minimizing risks to patients.

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In the nearly seven decades since a combination estrogen–progestin oral medication was introduced for reproductive health, combined oral contraceptives (COCs) have been a mainstay of contraception, with a wide variety of noncontraceptive benefits. Oral contraceptive use appears to have peaked in the United States in 1973, with the National Survey for Family Growth reporting use by 36% of women, likely an underestimate because only married women could legally access prescription contraception until 1972.[1] Subsequently, the proportion of women using COCs has decreased, from about 21% of premenopausal females in the 1970s to about 15% in 2017,[2,3] likely related to increased use of alternative methods.[3] As of 2022–2023, 11.4% of female individuals aged 15–49 years (21.2% of those using contraception) used oral contraceptives.[4]

Combined oral contraceptive regimens have evolved primarily in response to venous thromboembolism (VTE) risk concerns and secondarily to improve tolerability. The primary estrogen used in COCs for decades, ethinyl estradiol (EE), induces hypercoagulability through hepatic effects that alter the coagulation system, although the exact changes responsible have been unclear until recently. For the first three decades of COC availability, therefore, decreasing the estrogen dose was the main alteration to improve safety. Combined oral contraceptives were referred to as high or low dose based on EE content, with those containing less than 50 micrograms EE considered low dose; in contemporary practice, this idea that continually lower EE doses are "safer" has not proved universally true. Subsequently, new progestins were introduced to address tolerability but were associated with increased VTE risk. Most recently, attention has focused on decreasing VTE risk with the introduction of natural-estrogen COCs. Given the wide array of hormones and combinations available, this update reviews the evolution and hormonal content of COCs, the importance of newer natural-estrogen–containing COCs on hepatic and renal metabolism, and their benefits compared with EE-containing COCs. Clinicians can use this information to gain a clearer understanding of COCs and how to best balance risks and benefits for their patients.

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COMBINED ORAL CONTRACEPTIVE HORMONES

Combined oral contraceptives contain an estrogen and a progestin. A multitude of commercially available COCs exist with different hormone types and combinations; all hormones used in COCs are synthesized from plant sources. Because generic formulations are given names and not simply prescribed according to the hormone content, it is challenging for clinicians to know the many different hormones that make up COCs.

Marketing concepts have muddied the understanding of the hormonal content of COCs. Some clinicians have become accustomed to using the term "generations" to describe COCs. This is a marketing term that does not accurately reflect benefits or risks[5]; we refrain from using it in this review.

In addition, androgenicity has been used to describe progestin actions based on in vitro studies of androgen receptor binding without clinical relevance[6] and a lack of consideration of the three compartments (peripheral, ovarian, and adrenal) that influence androgenic effects.[7] Although progestins can cause side effects such as acne or hair loss, this is attributable to overall effect in these three compartments, not just androgen receptor actions. In other words, none of the progestins used in COCs have significant action at the androgen receptor (eg, none of the contraceptive progestins are so androgenic that they are used for gender-affirming care), Accordingly, we refrain from using androgenicity in this review. Rather than androgenicity, the safety effect of these hormones is based on relative hepatic and renal neutrality. Because the progestin effects on the liver oppose those of the estrogen component (estrogen antagonist), a more liver-neutral progestin allows more estrogen effect to occur. Estrogen changes in the liver affect the coagulation system (thus, more hepatic neutral progestins allow more coagulation system changes that can lead to increased VTE occurrence) and angiotensinogen production, which, in the kidney, will eventually lead to water retention and the potential for hypertension (renal neutrality).

Most appropriately, especially given the wide variety of names and formulations of COCs on the market, it is important for clinicians to know the different estrogens and progestins, rather than product brand names, to help patients maximize safety, efficacy, and tolerability.

Estrogens

Estrogen is the overarching term encompassing natural and nonnatural steroid hormones with estrogen receptor activity. The estrogens available in COCs are summarized in Table 1. Natural estrogens in humans include estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4).[8] The numbers in the names reflect the number of hydroxy groups on the four-ring 18-carbon backbone similar to all estrogens. The primary estrogen of menopause is E1; a small amount (less than 10%) is converted to E2 through a reversible reduction reaction catalyzed by the enzyme 17β-hydroxysteroid dehydrogenase type 1.[9] The primary estrogen of the reproductive years, E2 is converted by 17β-hydroxysteroid dehydrogenase type 2 to E1. Estriol is produced by the placenta during pregnancy.[10] Estetrol is present in the embryo and fetus, produced only by the embryonic–fetal liver starting at about 9 weeks of duration.[10] Estrone, E3, and E4 are less potent than E2. When taken orally, E1, E2, and E3 undergo significant hepatic metabolism by the cytochrome P3a enzyme and are metabolized rapidly.[11] Estetrol does not interact with the cytochrome P450 system and has a longer half-life than the other natural estrogens.[9]

Until recently, the nonnatural E2 derivative EE has been the basis for all estrogen-containing COCs. Initial formulations in the 1950s contained mestranol, a prodrug for EE. Ethinyl estradiol–containing products appeared on the market in the 1960s with the eventual removal of mestranol in 1988. Although E2 and EE both undergo significant first-pass metabolism, E2 metabolites are much less potent, whereas the conjugated metabolite of EE is still potent and has a systemic bioavailability of 40–50%.[11] This feature, along with the long half-life of EE, made mestranol and EE ideal for use in a daily pill.

During the past two decades, COC regimens using natural estrogens have been introduced. Two E2-containing products are available worldwide, one of which, a quadriphasic E2 valerate–dienogest COC, has been marketed in the United States since 2010.[12] Micronization of E2 provides an extended-release formulation with a longer half-life than natural E2, although still much shorter than that of EE. Estetrol, with a half-life equal to or longer than that of EE, has been more recently marketed (2021) in combination with drospirenone.

Laboratory and clinical studies suggest health benefits of natural-estrogen COCs compared with EE-containing COCs. Ethinyl estradiol requires extensive hepatic cytochrome P450 system metabolism, passing through the liver multiple times during metabolism. Thus, the effect on protein synthesis and liver function is relatively extreme. Also metabolized by cytochrome P450, E2 is more easily metabolized

Table 1. Estrogens Used in Combined Oral Contraceptives in the United States

Estrogen	Type	Dose in COCs	Half-Life (h)	Metabolism	Conversion to Other Estrogens	Metabolized to Catechol Estrogens*
Estradiol†	Natural	2–3 mg	2	Cytochrome P450	Estrone, estriol	Yes
Estetrol	Natural	14.2 mg	28	UGT2B7 glucuronidation and sulfation	None	No
Ethinyl estradiol	Nonnatural	10–35 micrograms	14–16	Cytochrome P450	None	Yes

COC, combined oral contraceptive.
* Catechol estrogens are metabolites that are typically deactivated to neutral compounds through methylation. If the compounds are not deactivated, these metabolites can damage DNA in ways heavily linked to induction of breast and other estrogen-dependent cancers.
† Available as estradiol valerate.

by the liver.[11] Estetrol products have less effect on the liver because they are metabolized through cellular sulfation and glucuronidation, not the cytochrome P450 system, resulting in less effect on estrogen-sensitive hepatic globulins and coagulation factors compared with EE.[13,14] These differences have the potential to result in lower VTE risk and less other adverse events.

Progestins

Progestogen is the overarching term encompassing natural and nonnatural hormones that activate progesterone receptors. Progesterone is the naturally occurring progestogen; the term "progestin" refers to a synthetically derived progestogen. No marketed contraceptives contain progesterone. Broadly, progestins used in COCs are all derived from three main hormones: testosterone, progesterone, and spirolactone (Table 2). The progestin classes (families) used for COCs are estranes and gonanes (derived from testosterone), pregnanes and 19-norpregnanes (derived from progesterone), and spirolactones.[15] The progestin classes differ according to their chemical structures and therefore in their activity at other hormone receptors. Because COC use diminishes the body's progesterone production, the progestin component replaces those actions. Most progestins lack the same activity at estrogen, androgen, and mineralocorticoid receptors that occurs with progesterone other than drospirenone, the most biologically similar to progesterone (Fig. 1).[16]

The testosterone derivatives estranes and gonanes have similar structures; estranes have a methyl group at the 13-carbon position, and gonanes have an ethyl group. All estranes undergo metabolism to their parent compound, norethindrone, which, although derived from testosterone, has minimal androgenic effects.[17] Norethindrone undergoes minimal metabolism to EE that is clinically insignificant at the dose in COCs. This conversion has been best studied in reproductive-aged women using norethindrone acetate, which is metabolized to norethindrone at a rate of 88% (1 mg norethindrone acetate equals 0.88 mg norethindrone).[18] Norethindrone acetate 20 mg results in a peak concentration and area under the curve similar to those of an EE 30 micrograms COC.[19] Thus, the amount of EE generated with a norethindrone acetate dose used in COCs (1–1.5 mg) would be approximately 13–20 times less (estimated equivalence of EE 1.5–2.3 micrograms), a very small

Table 2. Progestins Used in Combined Oral Contraceptives

Parent Compound	Progesterone		Testosterone		Spirolactone
Parent compound derivative	19-norprogesterone	17-hydroxy-progesterone	19-nortestosterone	17α-spironolactone	
Class name	Norpregnanes	Pregnanes	Estranes	Gonanes	Spirolactone
Progestin name	Nomegestrol acetate		Norethindrone Norethindrone acetate Ethynodiol diacetate Norethynodrel Dienogest*	Norgestrel/ levonorgestrel Norgestimate Desogestrel Gestodene	Drospirenone

* Novel nonethinylated estrane (no ethinyl group at 17-carbon).

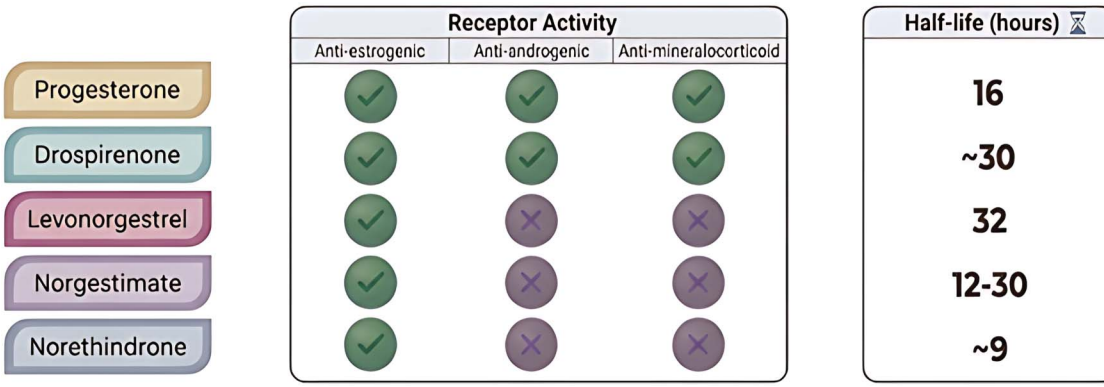

Fig. 1. Progesterone and progestin receptor activity and half-life. Data from Sitruk-Ware. New progestagens for contraceptive use. Hum Reprod Update 2006;12:169–78.[83]

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amount. Unlike estranes, gonanes are not metabolized into the same compound but into several related compounds. Some of the gonanes, gestodene and desogestrel, exhibit more liver neutrality than other progestins, leading to less dampening of the VTE risk of the estrogen component.[15]

The progesterone derivatives vary by whether they have a methyl group at the 10-carbon position (pregnanes) or lack it (norpregnanes). The norpregnanes have strong progestational (progesterone receptor) activity without androgenic, estrogenic, or glucocorticoid activity.[15] Drospirenone, the spirolactone available in COCs, is an analog of the potassium-sparing diuretic spironolactone, with comparatively more progesterone receptor activity and less antimineralocorticoid activity.[15] Drospirenone is the progestin most similar to natural progesterone and exhibits more liver neutrality than other progestins.[16,20]

COMBINED ORAL CONTRACEPTIVE HISTORY

Combined oral contraceptives have been in use in the United States since the U.S. Food and Drug Administration approved Enovid (mestranol 150 micrograms–norethynodrel 5 mg) for contraception in 1960; it was approved in 1957 for abnormal bleeding.[21] Mestranol is the prodrug of EE with loss of 30% of active hormone during metabolism; mestranol 150 micrograms is the equivalent of EE 105 micrograms, more than double the amount of EE in the highest-dose COCs available today.

Over the years, COC formulations have evolved significantly, including lowering the estrogen dose and introducing phased and extended cycle regimens, generics, and natural estrogens. Within 1 year after the introduction of COCs, their association with VTE was noted[22]; subsequently, the primary goal of manufacturers has been to decrease the estrogen dose to lower this risk. By the early 1970s, levonorgestrel-containing COCs entered the market, followed later in the 1970s by manufacturers primarily using EE instead of mestranol and decreasing the EE dose from 50 to 30–35 micrograms.[21]

The 1980s brought the introduction of triphasic regimens in 1984 as an attempt to lower overall hormone dose without evidence of clinical benefits.[23] Also in 1984, the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch–Waxman Act, established the current system of generic drug approval, which significantly changed COC availability and distribution.[24] As of 2007, more than 90 generic and brand-name COCs existed,[25] with many products coming on and off the market since.

After more than 30 years with two basic progestins (variations of norethindrone and levonorgestrel), the early 1990s brought new gonane progestins, desogestrel and gestodene, with marketing claims of fewer side effects and lower androgenicity. By 1995, studies suggested an increase in VTE risk for these formulations compared with EE-norethindrone and EE-levonorgestrel regimens, leading many European regulatory agencies to suggest that patients not receive them as first-line contraceptives. This public information release was confusing to clinicians and patients, did not include that the absolute VTE risk remained low for all COCs, and led to a rapid decline in all COC use (known as the pill scare) with an associated increase in unintended pregnancy, birth, and abortion rates.[26]

Another major change to COCs occurred in 2003 with extended cycles (fewer and shorter hormone-free intervals). Combined oral contraceptives had

historically been marketed as a regimen of 21 days of hormone and a 7-day hormone-free interval; extended-cycle regimens offered patients the option to take the hormone pills for months or longer without hormone-free intervals, leading to high efficacy and tolerability. Although extended cycle regimens result in a higher incidence of amenorrhea than cyclic use, some patients experience more unscheduled bleeding.[27,28] Shortly thereafter, in 2006, the first 24-day hormone, 4-day placebo regimen, EE 20 micrograms–drospirenone 3 mg, was introduced.[29] The original modification was designed to improve bleeding outcomes. It is important to note that subsequent studies demonstrated lower pregnancy rates with 24–4 than 21–7 pill regimens and that 24–4 regimens may decrease symptoms during the hormone-free interval.[30,31]

The most recent changes have been the addition of natural-estrogen formulations. In 2010, an E2–nomegestrol acetate formulation was approved in Europe followed in the United States by an E2 valerate–dienogest multiphasic COC.[32] This multiphasic COC has four combinations of hormones across 26 days with 2 days of placebo, designed to improve the bleeding profile, although the regimen still results in high rates of unscheduled bleeding.[33] The newest natural estrogen to be approved by the U.S. Food and Drug Administration for COCs is E4, approved in 2021 in combination with drospirenone.[34] Natural estrogens have a more favorable safety profile than EE because of lower hepatic metabolism and decreased effects on anticoagulants. Estetrol–containing COCs provide a good bleeding and side-effect profile as a result of the longer half-life and high bioavailability of E4.[35,36]

CONTRACEPTIVE EFFICACY

Contraceptive efficacy is typically reported with the Pearl index (unintended pregnancies per 100 person-years of exposure). This measure works well to approximate true efficacy over 1 year for methods with very high efficacy or very low discontinuation rates, two conditions not met by COCs. Therefore, the Pearl Index can overestimate efficacy, primarily because it does not account for fewer users over the course of 1 year as participants discontinue from a clinical trial. A better calculation of contraceptive efficacy uses survival analysis, or life table estimation, accounting for discontinuations during each cycle. Although life table measures are more exact, the Pearl index is required by regulatory agencies.[37]

There is no single efficacy rate for COCs; these rates will vary by population, and clinical trial efficacy rates may not be generalizable to real-life users. As an approximation, COCs have a perfect-use failure rate of 0.3% in the first year of use (identified from clinical trials) and a typical use failure rate of 7% in the first year of use.[15] Pearl indices from COC clinical trials have increased over time. This does not reflect a true efficacy decrease but likely results from changes in study design for regulatory approval. Contemporary studies have more frequent, highly sensitive pregnancy testing; enroll a broader range of participants to correlate more with real-life users; and exclude cycles in which participants did not have intercourse.[38] This concept, known as the "creeping Pearl," shows how changing study population characteristics and methodology affect outcomes.

A newer way to evaluate COC efficacy focuses on patient-reported adherence to eliminate other population-based influences. A secondary analysis of 2,837 patients in two phase 3 trials of E4 15 mg–drospirenone 3 mg COCs showed an increase in pregnancy rates correlating with the number of patient-reported missed pills per cycle: Patients missing zero, one, two, or more than two pills per cycle had pregnancy rates per cycle of 0.09%, 0.25%, 0.83%, and 1.6% respectively.[39] This methodology may be a more clinically applicable way to assess efficacy because it can be generalized to individual patient's behavior.

CONTRAINDICATIONS (RISKS AND ADVERSE EVENTS)

Contraindications to COCs generally relate to three main aspects of COC use that encompass many health conditions: thromboembolic–cardiovascular risk, cancer risk, and medication interactions.

Venous Thromboembolism and Cardiovascular Risk

Risk of VTE represents the largest source of contraindications and safety concerns for COC users. Concerns about liver effects (eg, liver failure, postpartum state) are primarily about increasing VTE risk. Only recently have we gained a better understanding of why and how COCs increase VTE risk; understanding these issues is critical for all clinicians. Although the overall absolute risk of VTE with COCs in a healthy user is low, VTE risk does approximately double with COC use, to a rate of almost 1 in 1,000 contraceptive users per year; this risk increases with increasing EE dose, age, and body weight.[40] Ethinyl estradiol has significant effects on the hematologic system regardless of route of administration as a result of multiple passes through the liver required for metabolism; nonoral EE delivery does not lessen the

effect on hepatic protein synthesis. Studies evaluating drospirenone-, gestodene-, and desogestrel-containing COCs show a higher VTE risk than COCs containing other progestins because they are more liver neutral and less likely to dampen the effects of EE than levonorgestrel and norethindrone.[15,41] Drospirenone, the most liver-neutral progestin, when combined with EE, has the highest VTE risk rate. However, when drospirenone is combined with E4, a very low VTE risk is realized, demonstrating that the estrogen drives VTE risk.[42]

Several recent studies underscore the importance of the association of different estrogens with VTE risk. A meta-analysis with approximately 72,000 E2 valerate–dienogest and 488,000 EE–levonorgestrel users demonstrated a 33% reduction of VTE risk with E2-containing pills.[43] Both European and U.S. pharmacovigilance database analyses demonstrated significantly lower proportional reporting of VTE events with E2 and E4 compared with EE pills.[44,45] Coagulation factor studies comparing EE–drospirenone and E4–drospirenone pills provide important insight into the mechanism of this improved safety profile. Only since the introduction of E4-drospirenone regimens have studies been performed comparing different estrogens (EE and E4) with the same progestin, allowing a better understanding of the effect of the estrogen on outcomes.[46] The differences in most procoagulant factors and anticoagulant proteins are considerable between EE–drospirenone and E4–drospirenone regimens, suggesting a potential clinical differentiation. The findings have helped us understand the mechanisms whereby EE-containing COCs have increased VTE risk, demonstrating that more liver-neutral progestins do not counteract the effect of EE on hepatic coagulation factor production, whereas less liver-neutral progestins do. In turn, EE–levonorgestrel regimens have a lower VTE risk than EE–drospirenone regimens, but not because drospirenone is thrombogenic; rather, with an EE–drospirenone pill, the full effect of EE occurs. With E4–drospirenone, less effect is seen because E4 has relatively minimal effect on coagulation factors.

Contraindications related to VTE risk can broadly be divided into two categories: impaired hepatic metabolism and conditions that increase baseline cardiovascular risk. Impaired hepatic metabolism generally occurs in the setting of decompensated cirrhosis, acute liver toxicity, or acute severe hepatitis. Combined oral contraceptives are contraindicated in these scenarios because of decreased ability to metabolize estrogen, resulting in unacceptably high estrogen levels and VTE risk.[47] The remainder of contraindications to COCs fit broadly into the category of conditions that increase baseline stroke or VTE risk, including poorly controlled hypertension, smoking, personal VTE history, cardiac disease, active cancer, multiple atherosclerotic risk factors, thrombophilia, and migraines with aura.[47] Aside from diagnosed thrombophilia, the majority of these do not represent absolute contraindications but factors that increase risk; a spectrum of risk exists, and the number and severity of factors must be considered.

The most common inherited thrombophilia is factor V Leiden mutation, or hereditary resistance to protein C. Patients with this mutation have a baseline sixfold to eightfold increase in VTE risk for heterozygotes and a baseline 80-fold increase in VTE risk for homozygotes.[15] For heterozygous factor V Leiden EE-containing COC users, their VTE risk may be up to 30 times that of a non-COC user without the mutation.[48] The second most common inherited thrombophilia is the prothrombin gene 20210A mutation; other inherited thrombophilias include antithrombin, protein C, and protein S deficiencies, as well as antiphospholipid antibody syndrome.[15] Although numbers needed to screen are not known, expert opinion does not support routine screening for thrombophilias before COC initiation but supports screening only in patients with family history.[49]

The association between hypertension and adverse cardiovascular events in COC users has been noted since the 1960s and is multidirectional; patients with hypertension have baseline elevated risk for stroke and VTE, but COCs can also contribute to worsening hypertension.[50] Several studies have shown an association between EE-containing COC use and blood pressure elevation,[51–53] likely occurring through EE-driven effects on the renin–angiotensin–aldosterone system.[54] Thus, patients with well-controlled or mild hypertension do not have the same risk profile with COCs as patients with severe, treatment-resistant hypertension and multiple cardiovascular risk factors. Risk factors like hypertension also put patients at risk for other adverse events such as stroke and myocardial infarction; contemporary studies show that COC users who develop these outcomes are typically those with hypertension or who are smokers.[55] Thus, although individual cardiovascular risk factors may not represent absolute COC contraindications, it is important to consider the existence of multiple risk factors. An analysis of 1,410 E4–drospirenone users found that hypertension developed in only three (0.2%), all of whom had high–normal blood pressure and at least one other cardiovascular risk factor at baseline.[56]

Another example of a vascular risk factor is migraines with aura, traditionally treated as an absolute contraindication. Most studies from which this recommendation comes used older COC formulations; more recent data suggest that lower-dose estrogen-containing COCs may be safe for use in some patients with migraines with aura.[57–59] That said, migraines with aura are a risk factor for stroke, especially in patients with other risk factors. Given the significant morbidity of stroke, it is reasonable to avoid estrogen as a first-line option in these patients.

The procoagulant effects of estrogen represent the most serious side effects limiting COC use and mechanistically appear to occur through lowering of natural anticoagulation factors. Because of the hepatic effects of EE, naturally occurring estrogens have a lower VTE risk. Future research should address whether natural-estrogen COCs can be used in patients for whom EE pills are contraindicated.

Cancer Risk

Except for some hormone-positive cancers, development of new cancers is not associated with COC use. Several large cohort studies have demonstrated an increase in breast cancer diagnosis with current or recent COC use that goes away after discontinuing COCs,[60,61] suggesting that COC use speeds the growth and diagnosis of preexisting small cancers (promoter effect) but lacks an inducer effect for causing new breast cancers.[62] In addition, the increased risk of diagnosis is only 1.2–1.3-fold; the risk of diagnosis goes from 0.49% to 0.64% at age 30 years and from 1.55% to 2.42% at age 40 years.[63] The increase in risk before age 40 years is still less than the risk without COC use at age 40 years, the age at which routine mammography screening would be indicated. The risk from age 40 to 49 years is equal to the risk without COC use at age 50 years.[63] In other words, breast cancer diagnosis goes from very, very rare to very rare with COC use and is still similar to age-based risks in non-COC users. These are likely cases diagnosed sooner than they would be without, not cases resulting from, COC use.

Medication Interactions

Medication interactions relate to use of cytochrome P450 inducers, which speed hepatic metabolism of COCs, decreasing their efficacy. All hormones used in COCs are metabolized by the cytochrome P450 enzymes other than E4. However, because the progestin (drospirenone) in E4-containing COCs is still metabolized by these enzymes, patients should be counseled on decreased contraceptive efficacy and avoid all COC use with strong cytochrome P450 inducers. A nonexhaustive list of cytochrome P450 inducers includes the antiepileptics phenytoin, carbamazepine, barbiturates, primidone, topiramate, and oxcarbazepine; the antiretroviral efavirenz; and the herbal supplement St. John's Wort.[47] For patients taking mild inducers who do choose COCs, we suggest pills containing progestins with minimal liver metabolism (levonorgestrel and drospirenone). Patients using cytochrome P450 inducers can still use COCs primarily for noncontraceptive indications if that is their preferred option.

NONCONTRACEPTIVE BENEFITS

Combined oral contraceptives have a wide variety of noncontraceptive uses and benefits, including management of menstrual complaints (including both abnormal bleeding and other aspects of menstruation), cancer prevention, and nongynecologic uses.

Menstrual Management

Combined oral contraceptives can be used to manage abnormal bleeding from a variety of structural and functional causes, including fibroids, adenomyosis, and anovulation.[64] Contraceptive regulatory approval studies are performed in participants with normal bleeding patterns, so bleeding outcomes from these studies are not helpful to predict the efficacy of COCs for abnormal bleeding. Extended-cycle regimens can also be used to increase the likelihood of amenorrhea in patients without abnormal bleeding, although unscheduled bleeding rates vary by regimen.[65]

By thinning the endometrial lining, leading to decreased prostaglandin production, COCs are useful treatments for dysmenorrhea, whether primary or caused by endometriosis.[66,67] A systematic review of 21 studies including 3,723 patients with primary dysmenorrhea demonstrated a 37–60% chance of symptom improvement with COCs compared with a 28% chance of improvement with placebo.[68] For endometriosis, a systematic review of 404 patients in three trials showed a mean difference in self-reported dysmenorrhea of 1.3 points on a 10-point scale; E2-containing COCs may have a small benefit for endometriosis, but it is not as well demonstrated as the benefit for primary dysmenorrhea.[69] A randomized trial comparing E4–drospirenone with placebo showed a significant reduction in both primary and secondary dysmenorrhea[70]; another trial showed a similar benefit for endometriosis.[71] Combined oral contraceptives can also be used to improve other conditions related to hormonal fluctuations such as

premenstrual dysphoric disorder[72] and menstrual migraines.[58]

Cancer Prevention

Combined oral contraceptive use is also associated with a decrease in development of endometrial and ovarian cancer. Combined oral contraceptives suppress unopposed estrogen that leads to anovulation and endometrial hyperplasia, protecting the endometrium and decreasing the odds of developing endometrial cancer, with a dose-dependent inverse relationship with duration of use.[73] Ovarian cancer is associated with factors that suggest more ovulation, including early menarche and late menopause; COC use, which suppresses ovulation, is associated with a decreased risk of ovarian cancer.[15] Altogether, COCs provide a net lifetime benefit of reduction of ovarian and endometrial cancer, outweighing the small promoter effect on breast cancer.[74] Studies also show a possible protective effect of COCs against a variety of nongynecologic cancers, including colorectal, esophageal, kidney, and thyroid.[62]

Nongynecologic Benefits

Suppression of the hypothalamic–pituitary–ovarian axis by COCs, as well as their differential androgenic effects in the peripheral, ovarian, and adrenal compartments, yields several other nongynecologic benefits. Although the American Academy of Dermatology recommends topical acne treatments as first line, COCs are a recommended acne treatment in patients without contraindications[75]; there is some minimal variation by progestin type.[76] Combined oral contraceptives also can treat hirsutism, especially in patients with polyendocrine metabolic ovarian syndrome.[77] Individual patients may benefit from actions in one or more compartments, so different pills may work better for different patients. Combined oral contraceptives additionally are associated with higher bone density in long-term users, which may decrease the development of osteoporosis.[78] Given the wide range of noncontraceptive uses for COCs, physicians who are not obstetrician–gynecologists should also be familiar with the hormones and contraindications.

SIDE-EFFECT MANAGEMENT

Management of side effects requires understanding the effects of the different hormones. For breakthrough bleeding, we suggest switching to a higher-dose EE-containing pill, an E4-containing pill, an extended-cycle regimen, or a 24-4 rather than 21-7 regimen. For estrogen-related side effects such as bloating, headache, mastalgia, and nausea, the EE dose can be decreased or the estrogen type changed. Although weight gain is a common concern for patients, multiple randomized trials have not demonstrated a causal relationship between COCs and weight gain; fluid retention is an estrogen-related side effect that can be addressed by changing the dose or type.[79] For progestin side effects such as mood changes or acne, we suggest switching to a pill containing a progestin from a different class (Table 2).

STARTING COMBINED ORAL CONTRACEPTIVES

Conventionally, COCs were recommended to start with menses, which ensured immediate efficacy (based on when they were initiated in reference to expected ovulation in that cycle) and low likelihood of pregnancy at the time of initiation. However, contemporary data show that neither the risk of pregnancy after COC initiation nor the risk of starting COCs while inadvertently pregnant is affected by the cycle day of initiation.[80] "Quick start" (starting on the day of the health care visit) can lead to increased rates of initiation and continuation, at least initially.[80] Current Selective Practice Recommendations from the Centers for Disease Control and Prevention state that COCs can be initiated at any time if the clinician can be reasonably sure the patient is not pregnant, with a backup method or abstinence recommended for 7 days if the patient is more than 5 days from the start of menses.[81] Combined oral contraceptives can be initiated immediately after abortion or miscarriage but, after a delivery at 20 weeks or more gestational duration, should be delayed until 6 weeks postpartum because of increased VTE risk during this period.[82]

Choosing which COC to start is a balance of prior experience, patient goals, and financial issues. For patients who have successfully used a specific COC in the past (effective and good tolerability), starting the same proven COC is very reasonable. Otherwise, when balancing overall population-based risk and benefit, starting with a natural-estrogen COC is most appropriate, although insurance coverage and individual cost may limit their use. Population-level absolute risk of VTE is still low, so for patients who have previously tolerated EE or for whom insurance does not cover a natural-estrogen COC, it is reasonable to use EE-containing COCs with the lowest tolerable EE dose. It is important to note that a 24-4, extended cycle, or continuous regimen should be considered given their higher efficacy and better bleeding profile. From a population health standpoint, 21-7 pill

use will result in more unintended pregnancies and should not be considered first line.

CONCLUSION

Combined oral contraceptives remain the most commonly used reversible contraceptive method in the United States, with even higher use in Europe. They represent an effective and overall well-tolerated form of contraception with significant noncontraceptive benefits. Although efficacy can be high, as a user-controlled method, it varies by population. As a preventive treatment provided to healthy users for contraception, their most significant risk and limitation is VTE risk; the aim to minimize this potentially severe adverse event has been a long and important goal throughout their history.

Given the wide array of available COCs, clinicians need to know the hormonal content of specific COCs rather than just the regimen names. In today's world, it is clear that VTE risk can be mitigated by the use of natural-estrogen–containing COCs. If natural-estrogen COCs had been on the market for years and an EE pill were newly developed today, the EE pill would be unlikely to be approved because of the higher VTE risk. As a medical community, we face cost issues within our health care systems that make safer products less accessible. We need to be fully aware of the benefits of natural-estrogen products and should consider them first line, including advocating for insurance coverage and broader availability.

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