

The ABCs of COCs: A Guide for Dermatology Residents on Combined Oral Contraceptives



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RESIDENT PEARLS

- Screen for contraindications to combined oral contraceptives (COCs) by taking a medical history, measuring a baseline blood pressure, and excluding pregnancy. A baseline pelvic examination is unnecessary.
- Characteristics to consider when selecting a COC include the formulation, hormone-free interval, estrogen dose, and progestin type.
- Combined oral contraceptives can be initiated on any day of the menstrual cycle, with the need for backup contraception based on the number of days since the first day of the patient's most recent period.
- Management of risks and side effects includes simple lifestyle changes, skipping the hormone-free interval, switching the COC, and referring to an obstetrician/gynecologist.

Despite the number of on-label and off-label uses for combined oral contraceptives (COCs) in dermatology, research suggests that dermatologists underprescribe COCs. With the intention of familiarizing dermatology residents with COCs, this article discusses ways to assess patient eligibility, select a COC, counsel on use, and manage risks and side effects.

Cutis. 2019;104:E10-E14.

The American Academy of Dermatology confers combined oral contraceptives (COCs) a strength A recommendation for the treatment

of acne based on level I evidence, and 4 COCs are approved for the treatment of acne by the US Food and Drug Administration (FDA).¹ Furthermore, when dermatologists prescribe isotretinoin and thalidomide to women of reproductive potential, the iPLEDGE and THALOMID Risk Evaluation and Mitigation Strategy (REMS) programs require 2 concurrent methods of contraception, one of which may be a COC. In addition, COCs have several potential off-label indications in dermatology including idiopathic hirsutism, female pattern hair loss, hidradenitis suppurativa, and autoimmune progesterone dermatitis.

Despite this evidence and opportunity, research suggests that dermatologists underprescribe COCs. The National Ambulatory Medical Care Survey found that between 1993 and 2008, dermatologists in the United States prescribed COCs to only 2.03% of women presenting for acne treatment, which was less often than obstetricians/gynecologists (36.03%) and internists (10.76%).² More recently, in a survey of 130 US dermatologists conducted from 2014 to 2015, only 55.4% reported prescribing COCs. This survey also found that only 45.8% of dermatologists who prescribed COCs felt very comfortable counseling on how to begin taking them, only 48.6% felt very comfortable counseling patients on side effects, and only 22.2% felt very comfortable managing side effects.³

In light of these data, this article reviews the basics of COCs for dermatology residents, from assessing patient eligibility and selecting a COC to counseling on use and managing risks and side effects. Because there are different approaches to prescribing COCs, readers are

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The author reports no conflict of interest.

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encouraged to integrate the information in this article with what they have learned from other sources.

Assess Patient Eligibility

In general, patients should be at least 14 years of age and have waited 2 years after menarche to start COCs. They can be taken until menopause.^{1,4} Contraindications can be screened for by taking a medical history and measuring a baseline blood pressure (Tables 1 and 2).⁵ In addition, pregnancy should be excluded with a urine or serum pregnancy test or criteria provided in Box 2 of the 2016 US Selected Practice Recommendations for Contraceptive Use from the Centers for Disease Control and Prevention (CDC).⁴ Although important for women's overall health, a pelvic examination is not required to start

COCs according to the CDC and the American Academy of Dermatology.^{1,4}

Select the COC

Combined oral contraceptives combine estrogen, usually in the form of ethinyl estradiol, with a progestin. Data suggest that all COCs effectively treat acne, but 4 are specifically FDA approved for acne: ethinyl estradiol–norethindrone acetate–ferrous fumarate, ethinyl estradiol–norgestimate, ethinyl estradiol–drospirenone, and ethinyl estradiol–drospirenone–levomefolate.¹ Ethinyl estradiol–desogestrel and ethinyl estradiol–drospirenone are 2 go-to COCs for some of the attending physicians at my residency program. All COCs are FDA approved for contraception.

TABLE 1. Conditions That Represent an Unacceptable Health Risk if COCs Are Used (Category 4)

Personal characteristics and reproductive history

- <21 days postpartum regardless of breastfeeding
- Age \geq 35 years and smoking \geq 15 cigarettes per day

Cardiovascular disease

- Systolic blood pressure \geq 160 mm Hg or diastolic blood pressure \geq 100 mm Hg
- VTE with \geq 1 risk factor for recurrence^a
- Major surgery with prolonged immobilization
- Known thrombogenic mutations^b
- Multiple risk factors for atherosclerosis^c
- Ischemic heart disease
- Cerebrovascular accident
- Vascular disease
- Valvular heart disease complicated by pulmonary hypertension, risk for atrial fibrillation, or subacute bacterial endocarditis
- Peripartum cardiomyopathy with normal or mildly impaired cardiac function for <6 months or moderately or severely impaired cardiac function

Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies

Migraine with aura

Current breast cancer

Diabetes mellitus with nephropathy, retinopathy, neuropathy, other vascular disease, or of >20 years' duration

Gastrointestinal conditions

- Acute or flare of viral hepatitis
- Severe/decompensated cirrhosis
- Hepatocellular adenoma
- Malignant liver tumor (hepatoma)

Solid organ transplantation complicated by acute or chronic graft failure, rejection, or cardiac allograft vasculopathy

Abbreviations: COC, combined oral contraceptive; VTE, venous thromboembolism; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aEstrogen-associated VTE, pregnancy-associated VTE, idiopathic VTE, known thrombophilia, active cancer (metastatic, receiving therapy, or within 6 months after clinical remission) excluding nonmelanoma skin cancer, and history of recurrent VTE.

^bIncludes factor V Leiden, prothrombin mutation, protein S deficiency, protein C deficiency, and antithrombin deficiency.

^cIncludes older age, smoking, diabetes mellitus, hypertension, low HDL, high LDL, and high triglycerides.

Data from Curtis et al.⁵

TABLE 2. Conditions for Which the Theoretical or Proven Risks Outweigh the Advantages of COCs

Personal characteristics and reproductive history

- Breastfeeding 21 to <30 days postpartum with or without other VTE risk factors^a
- Breastfeeding 30–42 days postpartum with other VTE risk factors^a
- Not breastfeeding 21–42 days postpartum with other VTE risk factors^a
- Age ≥35 years and smoking <15 cigarettes per day
- History of malabsorptive procedures (Roux-en-Y gastric bypass or biliopancreatic diversion)

Cardiovascular disease

- Adequately controlled hypertension
- Systolic blood pressure 140–159 mm Hg or diastolic blood pressure 90–99 mm Hg
- VTE with no risk factors for recurrence
- Superficial venous thrombosis
- Peripartum cardiomyopathy with normal or mildly impaired cardiac function for ≥6 months

Multiple sclerosis with prolonged immobility

History of breast cancer without evidence of current disease for 5 years

Gastrointestinal conditions

- Ulcerative colitis or Crohn disease with increased risk for VTE^b
- Untreated or medically treated symptomatic gallbladder disease
- COC-related cholestasis

Drug interactions

- Fosamprenavir
- Lamotrigine monotherapy, phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine
- Rifampin, rifabutin

Abbreviations: COC, combined oral contraceptive; VTE, venous thromboembolism; BMI, body mass index.

^aAge ≥35 years, previous VTE, thrombophilia, immobility, transfusion at delivery, peripartum cardiomyopathy, BMI ≥30 kg/m², postpartum hemorrhage, post-cesarean delivery, preeclampsia, and smoking.

^bActive or extensive disease, surgery, immobilization, corticosteroid use, vitamin deficiencies, and fluid depletion.

Data from Curtis et al.⁵

When selecting a COC, one approach is to start with the patient's drug formulary, then consider the following characteristics.

Monophasic vs Multiphasic—All the hormonally active pills in a monophasic formulation contain the same dose of estrogen and progestin; however, these doses change per pill in a multiphasic formulation, which requires that patients take the pills in a specific order. Given this greater complexity and the fact that multiphasic formulations often are more expensive and lack evidence of superiority, a 2011 Cochrane review recommended monophasic formulations as first line.⁶ In addition, monophasic formulations are preferred for autoimmune progesterone dermatitis because of the stable progestin dose.

Hormone-Free Interval—Some COCs include placebo pills during which hormone withdrawal symptoms such as bleeding, pelvic pain, mood changes, and headache may occur. If a patient is concerned about these symptoms, choose a COC with no or fewer placebo pills, or have the patient skip the hormone-free interval altogether and start the next pack early⁷; in this case, the

prescription should be written with instructions to allow the patient to get earlier refills from the pharmacy.

Estrogen Dose—To minimize estrogen-related side effects, the lowest possible dose of ethinyl estradiol that is effective and tolerable should be prescribed^{7,8}; 20 µg of ethinyl estradiol generally is the lowest dose available, but it may be associated with more frequent breakthrough bleeding.⁹ The International Planned Parenthood Federation recommends starting with COCs that contain 30 to 35 µg of estrogen.¹⁰ Synthesizing this information, one option is to start with 20 µg of ethinyl estradiol and increase the dose if breakthrough bleeding persists after 3 cycles.

Progestin Type—First-generation progestins (eg, norethindrone), second-generation progestins (eg, norgestrel, levonorgestrel), and third-generation progestins (eg, norgestimate, desogestrel) are derived from testosterone and therefore are variably androgenic; second-generation progestins are the most androgenic, and third-generation progestins are the least. On the other hand, drospirenone, the fourth-generation progestin available in the United States, is derived from

17 α -spironolactone and thus is mildly antiandrogenic (3 mg of drospirenone is considered equivalent to 25 mg of spironolactone).

Although COCs with less androgenic progestins should theoretically treat acne better, a 2012 Cochrane review of COCs and acne concluded that “differences in the comparative effectiveness of COCs containing varying progestin types and dosages were less clear, and data were limited for any particular comparison.”¹¹ As a result, regardless of the progestin, all COCs are believed to have a net antiandrogenic effect due to their estrogen component.¹

Counsel on Use

Combined oral contraceptives can be started on any day of the menstrual cycle, including the day the prescription is given. If a patient begins a COC within 5 days of the first day of her most recent period, backup contraception is not needed.⁴ If she begins the COC more than 5 days after the first day of her most recent period, she needs to use backup contraception or abstain from sexual intercourse for the next 7 days.⁴ In general, at least 3 months of therapy are required to evaluate the effectiveness of COCs for acne.¹

Manage Risks and Side Effects

Breakthrough Bleeding—The most common side effect of breakthrough bleeding can be minimized by taking COCs at approximately the same time every day and avoiding missed pills. If breakthrough bleeding does not stop after 3 cycles, consider increasing the estrogen dose to 30 to 35 μ g and/or referring to an obstetrician/gynecologist to rule out other etiologies of bleeding.^{7,8}

Nausea, Headache, Bloating, and Breast Tenderness—These symptoms typically resolve after the first 3 months. To minimize nausea, patients should take COCs in the early evening and eat breakfast the next morning.^{7,8} For headaches that occur during the hormone-free interval, consider skipping the placebo pills and starting the next pack early. Switching the progestin to drospirenone, which has a mild diuretic effect, can help with bloating as well as breast tenderness.⁷ For persistent symptoms, consider a lower estrogen dose.^{7,8}

Changes in Libido—In a systemic review including 8422 COC users, 64% reported no change in libido, 22% reported an increase, and 15% reported a decrease.¹²

Weight Gain—Although patients may be concerned that COCs cause weight gain, a 2014 Cochrane review concluded that “available evidence is insufficient to determine the effect of combination contraceptives on weight, but no large effect is evident.”¹³ If weight gain does occur, anecdotal evidence suggests it tends to be not more than 5 pounds. If weight gain is an issue, consider a less androgenic progestin.⁸

Venous Thromboembolism—Use the 3-6-9-12 model to contextualize venous thromboembolism (VTE) risk: a woman’s annual VTE risk is 3 per 10,000 women at baseline, 6 per 10,000 women with nondrospirenone COCs,

9 per 10,000 women with drospirenone-containing COCs, and 12 per 10,000 women when pregnant.¹⁴ Patients should be counseled on the signs and symptoms of VTE such as unilateral or bilateral leg or arm swelling, pain, warmth, redness, and/or shortness of breath. The British Society for Haematology recommends maintaining mobility as a reasonable precaution when traveling for more than 3 hours.¹⁵

Cardiovascular Disease—A 2015 Cochrane review found that the risk for myocardial infarction or ischemic stroke is increased 1.6-fold in COC users.¹⁶ Despite this increased relative risk, the increased absolute annual risk of myocardial infarction in nonsmoking women remains low: increased from 0.83 to 3.53 per 10,000,000 women younger than 35 years and from 9.45 to 40.4 per 10,000,000 women 35 years and older.¹⁷

Breast Cancer and Cervical Cancer—Data are mixed on the effect of COCs on the risk for breast cancer and cervical cancer.¹ According to the CDC, COC use for 5 or more years might increase the risk of cervical carcinoma in situ and invasive cervical carcinoma in women with persistent human papillomavirus infection.⁵ Regardless of COC use, women should undergo age-appropriate screening for breast cancer and cervical cancer.

Melasma—Melasma is an estrogen-mediated side effect of COCs.⁸ A study from 1967 found that 29% of COC users (N=212) developed melasma; however, they were taking COCs with much higher ethinyl estradiol doses (50–100 μ g) than typically used today.¹⁸ Nevertheless, as part of an overall skin care regimen, photoprotection should be encouraged with a broad-spectrum, water-resistant sunscreen that has a sun protection factor of at least 30. In addition, sunscreens with iron oxides have been shown to better prevent melasma relapse by protecting against the shorter wavelengths of visible light.¹⁹

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